GROUP B STREPTOCOCCUS

This application incorporates by reference the contents of each of two duplicate CD-ROMs which contain an identical 90.1 MB file labeled "PP28007 PCT sequence listing.txt," which is the sequence listing for this application. The CD-ROMs were created on December 21, 2005. This application also incorporates by reference the contents of each of two duplicate CD-ROMs which contain an identical 681 KB file labeled "Table I.txt" and containing Table I. The CD-ROMs were created on December 20, 2005.

All documents cited herein are incorporated by reference in their entirety.

TECHNICAL FIELD

This invention is in the field of *Streptococcus* biology, and in particular relates to *S.agalactiae*, also known as 'group B streptococcus' (GBS).

BACKGROUND ART

Once thought to infect only cows, the Gram-positive bacterium *Streptococcus agalactiae* (or "group B streptococcus", abbreviated to "GBS") is now known to cause serious disease, bacteremia and meningitis, in immunocompromised individuals and in neonates. There are two types of neonatal infection. The first (early onset, usually within 5 days of birth) is manifested by bacteremia and pneumonia. It is contracted vertically as a baby passes through the birth canal. GBS colonises the vagina of about 25% of young women, and approximately 1% of infants born via a vaginal birth to colonised mothers will become infected. Mortality is between 50-70%. The second is a meningitis that occurs 10 to 60 days after birth. If pregnant women are vaccinated with type III capsule so that the infants are passively immunised, the incidence of the late onset meningitis is reduced but is not entirely eliminated.

The "B" in "GBS" refers to the Lancefield classification, which is based on the antigenicity of a carbohydrate which is soluble in dilute acid and called the C carbohydrate. Lancefield identified 13 types of C carbohydrate, designated A to O, that could be serologically differentiated. The organisms that most commonly infect humans are found in groups A, B, D, and G. Within group B, strains can be divided into 8 serotypes (Ia, Ib, Ia/c, II, III, IV, V, and VI) based on the structure of their polysaccharide capsule. The genome sequence of a serotype V strain of GBS has been published and analysed [1,2], including a comparative genome hybridization analysis of 19 disease-causing isolates of the same type V strain 2603V/R. The genome sequence of a serotype III strain is also known [3].

Current GBS vaccines are based on polysaccharide antigens, although these suffer from poor immunogenicity. Anti-idiotypic approaches have also been used (*e.g.* ref. 4). There remains a need, however, for effective adult vaccines against *S.agalactiae* infection.

It is an object of the invention to provide proteins which can be used in the development of such vaccines. The proteins may also be useful for diagnostic purposes, and as targets for antibiotics.

DISCLOSURE OF THE INVENTION

Polypeptides

The invention provides polypeptides comprising the GBS amino acid sequences disclosed in the examples. These amino acid sequences are the even SEQ ID NOs between 2 and 22740. There are thus 11370 amino acid sequences. The polypeptides encoded by sequences listed in Table IV have not previously been seen in GBS strains.

The invention also provides polypeptides comprising amino acid sequences that have sequence identity to the GBS amino acid sequences disclosed in the examples. Depending on the particular sequence, the degree of sequence identity is preferably greater than 50% (*e.g.* 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more). These polypeptides include homologs, orthologs, allelic variants and functional mutants. Typically, 50% identity or more between two polypeptide sequences is considered to be an indication of functional equivalence. Identity between polypeptides is preferably determined by the Smith-Waterman homology search algorithm as implemented in the MPSRCH program (Oxford Molecular), using an affine gap search with parameters *gap open penalty=12* and *gap extension penalty=1*.

These polypeptide may, compared to the GBS sequences of the examples, include one or more (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, *etc.*) conservative amino acid replacements *i.e.* replacements of one amino acid with another which has a related side chain. Genetically-encoded amino acids are generally divided into four families: (1) acidic *i.e.* aspartate, glutamate; (2) basic *i.e.* lysine, arginine, histidine; (3) non-polar *i.e.* alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan; and (4) uncharged polar *i.e.* glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. In general, substitution of single amino acids within these families does not have a major effect on the biological activity. The polypeptides may have one or more (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, *etc.*) single amino acid deletions relative to the GBS sequences of the examples. The polypeptides may also include one or more (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, *etc.*) insertions (*e.g.* each of 1, 2, 3, 4 or 5 amino acids) relative to the GBS sequences of the examples. Some of these deletions, insertions or substitutions may convert one sequence of the invention to another sequence of the invention *e.g.* amino acids 180-230 of SEQ ID NO: 8614 (identical to amino acids 173-223 of SEQ ID NO: 14060 and amino acids 4-54 of SEQ ID NO: 3916) become amino acids 180-230 of SEQ ID NO: 12908 by conservative substitution of Ile-185 for Val.

Preferred polypeptides of the invention are listed below, including polypeptides that are lipidated, that are located in the outer membrane, that are located in the inner membrane, or that are located in the periplasm. Particularly preferred polypeptides are those that fall into more than one of these categories *e.g.* lipidated polypeptides that are located in the outer membrane. Lipoproteins may have a N-terminal cysteine to which lipid is covalently attached, following post-translational processing of the signal peptide.

The invention further provides polypeptides comprising fragments of the GBS amino acid sequences disclosed in the examples. The fragments should comprise at least *n* consecutive amino acids from the sequences and, depending on the particular sequence, *n* is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100 or more).

The fragment may comprise at least one T-cell or, preferably, a B-cell epitope of the sequence. T- and B-cell epitopes can be identified empirically (*e.g.* using PEPSCAN [5,6] or similar methods), or they can be predicted (*e.g.* using the Jameson-Wolf antigenic index [7], matrix-based approaches [8], TEPITOPE [9], neural networks [10], OptiMer & EpiMer [11,12], ADEPT [13], Tsites [14], hydrophilicity [15], antigenic index [16] or the methods disclosed in reference 17, *etc.*). Other preferred fragments are (a) the N-terminal signal peptides of the GBS polypeptides of the invention, (b) the GBS polypeptides, but without their N-terminal signal peptides, (c) the GBS polypeptides, but without their N-terminal amino acid residue.

Further preferred fragments are those common to at least two (*e.g.* 2, 3, 4 or 5) homologous coding sequences, and in particular those common to homologous coding sequences within the sequence listing. Table II shows homologous SEQ ID numbers for nucleic acids within the sequence listing *e.g.* SEQ ID NOs: 88, 4374, 8834, 13214 and 17994 are homologous within the sequence listing, and are also homologous with prior art GI sequences 22533036 and 23094457. Simple alignments show that amino acids 1-131 of these five SEQ ID NOs are common, as are amino acids 133-176, 178-182, 184-190, 192-217, 219-250, 252-278, 280-322, 324-366, 368-373 and 375-434. Similarly, 1-176 are common to SEQ ID NOs: 88, 4374, 8834 and 13214, but not to 17994. Thus fragments 1-131, 1-176 and 133-176 are all preferred fragments of the invention. In some cases, where homologous sequences are 100% identical between strains along their complete lengths (*e.g.* SEQ ID NOs: 2, 8616, 12910, 14062 and 22384), the common 'fragment' will in fact be the complete sequence.

Other preferred fragments are those that begin with an amino acid encoded by a potential start codon (ATG, GTG, TTG). Fragments starting at the methionine encoded by a start codon downstream of the indicated start codon are polypeptides of the invention.

Polypeptides of the invention can be prepared in many ways *e.g.* by chemical synthesis (in whole or in part), by digesting longer polypeptides using proteases, by translation from RNA, by purification from cell culture (*e.g.* from recombinant expression), from the organism itself (*e.g.* after bacterial culture, or direct from patients), *etc.* A preferred method for production of peptides <40 amino acids long involves *in vitro* chemical synthesis [18,19]. Solid-phase peptide synthesis is particularly preferred, such as methods based on tBoc or Fmoc [20] chemistry. Enzymatic synthesis [21] may also be used in part or in full. As an alternative to chemical synthesis, biological synthesis may be used *e.g.* the polypeptides may be produced by translation. This may be carried out *in vitro* or *in vivo*. Biological methods are in general restricted to the production of polypeptides based on L-amino acids, but manipulation of translation machinery (*e.g.* of aminoacyl tRNA molecules) can be used to allow the introduction of D-amino acids (or of other non natural amino acids, such as iodotyrosine or

methylphenylalanine, azidohomoalanine, etc.) [22]. Where D-amino acids are included, however, it is preferred to use chemical synthesis. Polypeptides of the invention may have covalent modifications at the C-terminus and/or N-terminus.

Polypeptides of the invention can take various forms (*e.g.* native, fusions, glycosylated, non-glycosylated, lipidated, non-lipidated, phosphorylated, non-phosphorylated, myristoylated, non-myristoylated, monomeric, multimeric, particulate, denatured, *etc.*).

Polypeptides of the invention are preferably provided in purified or substantially purified form *i.e.* substantially free from other polypeptides (*e.g.* free from naturally-occurring polypeptides), particularly from other streptococcal or host cell polypeptides, and are generally at least about 50% pure (by weight), and usually at least about 90% pure *i.e.* less than about 50%, and more preferably less than about 10% (*e.g.* 5%) of a composition is made up of other expressed polypeptides. Polypeptides of the invention are preferably GBS polypeptides. Polypeptides of the invention preferably have the function indicated in Table I for the relevant sequence.

Polypeptides of the invention may be attached to a solid support. Polypeptides of the invention may comprise a detectable label (*e.g.* a radioactive or fluorescent label, or a biotin label).

The term "polypeptide" refers to amino acid polymers of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, *etc.*), as well as other modifications known in the art. Polypeptides can occur as single chains or associated chains. Polypeptides of the invention can be naturally or non-naturally glycosylated (*i.e.* the polypeptide has a glycosylation pattern that differs from the glycosylation pattern found in the corresponding naturally occurring polypeptide).

Polypeptides of the invention may be at least 40 amino acids long (*e.g.* at least 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 350, 400, 450, 500 or more). Polypeptides of the invention may be shorter than 500 amino acids (*e.g.* no longer than 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280, 300, 350, 400 or 450 amino acids).

The invention provides polypeptides comprising a sequence -X-Y- or -Y-X-, wherein: -X- is an amino acid sequence as defined above and -Y- is not a sequence as defined above *i.e.* the invention provides fusion proteins. Where the N-terminus codon of a polypeptide-coding sequence is not ATG then that codon will be translated as the standard amino acid for that codon rather than as a Met, which occurs when the codon is translated as a start codon.

The invention provides a process for producing polypeptides of the invention, comprising the step of culturing a host cell of to the invention under conditions which induce polypeptide expression.

The invention provides a process for producing a polypeptide of the invention, wherein the polypeptide is synthesised in part or in whole using chemical means.

The invention provides a composition comprising two or more polypeptides of the invention.

The invention also provides a hybrid polypeptide represented by the formula NH_2-A-[-X-L-]$_n$-B-COOH, wherein X is a polypeptide of the invention as defined above, L is an optional linker amino acid sequence, A is an optional N-terminal amino acid sequence, B is an optional C-terminal amino acid sequence, and n is an integer greater than 1. The value of n is between 2 and x, and the value of x is typically 3, 4, 5, 6, 7, 8, 9 or 10. Preferably n is 2, 3 or 4; it is more preferably 2 or 3; most preferably, n = 2. For each n instances, -X- may be the same or different. For each n instances of [-X-L-], linker amino acid sequence -L- may be present or absent. For instance, when n=2 the hybrid may be NH_2-X_1-L_1-X_2-L_2-COOH, NH_2-X_1-X_2-COOH, NH_2-X_1-L_1-X_2-COOH, NH_2-X_1-X_2-L_2-COOH, *etc.* Linker amino acid sequence(s) -L- will typically be short (*e.g.* 20 or fewer amino acids *i.e.* 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include short peptide sequences which facilitate cloning, poly-glycine linkers (*i.e.* Gly_n where n = 2, 3, 4, 5, 6, 7, 8, 9, 10 or more), and histidine tags (*i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable linker amino acid sequences will be apparent to those skilled in the art. -A- and -B- are optional sequences which will typically be short (*e.g.* 40 or fewer amino acids *i.e.* 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1). Examples include leader sequences to direct polypeptide trafficking, or short peptide sequences which facilitate cloning or purification (*e.g.* histidine tags *i.e.* His_n where n = 3, 4, 5, 6, 7, 8, 9, 10 or more). Other suitable N-terminal and C-terminal amino acid sequences will be apparent to those skilled in the art.

Various tests can be used to assess the *in vivo* immunogenicity of polypeptides of the invention. For example, polypeptides can be expressed recombinantly and used to screen patient sera by immunoblot. A positive reaction between the polypeptide and patient serum indicates that the patient has previously mounted an immune response to the protein in question *i.e.* the protein is an immunogen. This method can also be used to identify immunodominant proteins.

Antibodies

The invention provides antibodies that bind to polypeptides of the invention. These may be polyclonal or monoclonal and may be produced by any suitable means (*e.g.* by recombinant expression). To increase compatibility with the human immune system, the antibodies may be chimeric or humanised [*e.g.* refs. 23 & 24], or fully human antibodies may be used. The antibodies may include a detectable label (*e.g.* for diagnostic assays). Antibodies of the invention may be attached to a solid support. Antibodies of the invention are preferably neutralising antibodies.

Monoclonal antibodies are particularly useful in identification and purification of the individual polypeptides against which they are directed. Monoclonal antibodies of the invention may also be

employed as reagents in immunoassays, radioimmunoassays (RIA) or enzyme-linked immunosorbent assays (ELISA), *etc.*. In these applications, the antibodies can be labelled with an analytically-detectable reagent such as a radioisotope, a fluorescent molecule or an enzyme. The monoclonal antibodies produced by the above method may also be used for the molecular identification and characterization (epitope mapping) of polypeptides of the invention.

Antibodies of the invention are preferably specific to *Streptococci i.e.* they bind preferentially to *Streptococci* bacteria relative to non-*Streptococci* bacteria. More preferably, the antibodies are specific to GBS *i.e.* they bind preferentially to GBS bacteria relative to non-type-b streptococci.

Antibodies of the invention are preferably provided in purified or substantially purified form. Typically, the antibody will be present in a composition that is substantially free of other polypeptides *e.g.* where less than 90% (by weight), usually less than 60% and more usually less than 50% of the composition is made up of other polypeptides.

Antibodies of the invention can be of any isotype (*e.g.* IgA, IgG, IgM *i.e.* an α, γ or μ heavy chain), but will generally be IgG. Within the IgG isotype, antibodies may be IgG1, IgG2, IgG3 or IgG4 subclass. Antibodies of the invention may have a κ or a λ light chain.

Antibodies of the invention can take various forms, including whole antibodies, antibody fragments such as $F(ab')_2$ and F(ab) fragments, Fv fragments (non-covalent heterodimers), single-chain antibodies such as single chain Fv molecules (scFv), minibodies, oligobodies, *etc.* The term "antibody" does not imply any particular origin, and includes antibodies obtained through non-conventional processes, such as phage display.

The invention provides a process for detecting polypeptides of the invention, comprising the steps of: (a) contacting an antibody of the invention with a biological sample under conditions suitable for the formation of an antibody-antigen complexes; and (b) detecting said complexes.

The invention provides a process for detecting antibodies of the invention, comprising the steps of: (a) contacting a polypeptide of the invention with a biological sample (*e.g.* a blood or serum sample) under conditions suitable for the formation of an antibody-antigen complexes; and (b) detecting said complexes.

For good cross-reactivity, preferred antibodies of the invention bind to epitopes within fragments that are common to at least two (*e.g.* 2, 3, 4 or 5) homologous coding sequences, as described in more detail above. Conversely, for good specificity, other preferred antibodies of the invention bind to epitopes that include an amino acid that differs between homologous coding sequences *e.g.* binds to Phe-132 in SEQ ID NO: 17994 to distinguish from SEQ ID NOs: 88, 4374, 8834 and 13214, all of which have a Serine residue at position 132.

Nucleic acids

The invention provides nucleic acid comprising the GBS nucleotide sequences disclosed in the examples. These nucleic acid sequences are the odd SEQ ID NOs between 1 and 22739.

The invention also provides nucleic acid comprising nucleotide sequences having sequence identity to the GBS nucleotide sequences disclosed in the examples. Identity between sequences is preferably determined by the Smith-Waterman homology search algorithm as described above.

The invention also provides nucleic acid which can hybridize to the GBS nucleic acid disclosed in the examples. Hybridization reactions can be performed under conditions of different "stringency". Conditions that increase stringency of a hybridization reaction of widely known and published in the art [*e.g.* page 7.52 of reference 25]. Examples of relevant conditions include (in order of increasing stringency): incubation temperatures of 25°C, 37°C, 50°C, 55°C and 68°C; buffer concentrations of 10 x SSC, 6 x SSC, 1 x SSC, 0.1 x SSC (where SSC is 0.15 M NaCl and 15 mM citrate buffer) and their equivalents using other buffer systems; formamide concentrations of 0%, 25%, 50%, and 75%; incubation times from 5 minutes to 24 hours; 1, 2, or more washing steps; wash incubation times of 1, 2, or 15 minutes; and wash solutions of 6 x SSC, 1 x SSC, 0.1 x SSC, or de-ionized water. Hybridization techniques and their optimization are well known in the art [*e.g.* see refs 25-28, *etc.*].

In some embodiments, nucleic acid of the invention hybridizes to a target of the invention under low stringency conditions; in other embodiments it hybridizes under intermediate stringency conditions; in preferred embodiments, it hybridizes under high stringency conditions. An exemplary set of low stringency hybridization conditions is 50°C and 10 x SSC. An exemplary set of intermediate stringency hybridization conditions is 55°C and 1 x SSC. An exemplary set of high stringency hybridization conditions is 68°C and 0.1 x SSC.

Nucleic acid comprising fragments of these sequences are also provided. These should comprise at least *n* consecutive nucleotides from the GBS sequences and, depending on the particular sequence, *n* is 10 or more (*e.g.* 12, 14, 15, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more).

The invention provides nucleic acid of formula 5'-X-Y-Z-3', wherein: -X- is a nucleotide sequence consisting of *x* nucleotides; -Z- is a nucleotide sequence consisting of *z* nucleotides; -Y- is a nucleotide sequence consisting of either (a) a fragment of one of the odd-numbered SEQ ID NOs: 1 to 22739, or (b) the complement of (a); and said nucleic acid 5'-X-Y-Z-3' is neither (i) a fragment of one of the odd-numbered SEQ ID NOs: 1 to 22739 nor (ii) the complement of (i). The -X- and/or -Z- moieties may comprise a promoter sequence (or its complement).

The invention also provides nucleic acid encoding the polypeptides and polypeptide fragments of the invention.

The invention includes nucleic acid comprising sequences complementary to the sequences disclosed in the sequence listing (*e.g.* for antisense or probing, or for use as primers), as well as the sequences in the orientation actually shown.

Nucleic acids of the invention can be used in hybridisation reactions (*e.g.* Northern or Southern blots, or in nucleic acid microarrays or 'gene chips') and amplification reactions (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA, *etc.*) and other nucleic acid techniques.

Nucleic acid according to the invention can take various forms (*e.g.* single-stranded, double-stranded, vectors, primers, probes, labelled *etc.*). Nucleic acids of the invention may be circular or branched, but will generally be linear. Unless otherwise specified or required, any embodiment of the invention that utilizes a nucleic acid may utilize both the double-stranded form and each of two complementary single-stranded forms which make up the double-stranded form. Primers and probes are generally single-stranded, as are antisense nucleic acids.

Nucleic acids of the invention are preferably provided in purified or substantially purified form *i.e.* substantially free from other nucleic acids (*e.g.* free from naturally-occurring nucleic acids), particularly from other streptococcal or host cell nucleic acids, generally being at least about 50% pure (by weight), and usually at least about 90% pure. Nucleic acids of the invention are preferably GBS nucleic acids.

Nucleic acids of the invention may be prepared in many ways *e.g.* by chemical synthesis (*e.g.* phosphoramidite synthesis of DNA) in whole or in part, by digesting longer nucleic acids using nucleases (*e.g.* restriction enzymes), by joining shorter nucleic acids or nucleotides (*e.g.* using ligases or polymerases), from genomic or cDNA libraries, *etc.*

Nucleic acid of the invention may be attached to a solid support (*e.g.* a bead, plate, filter, film, slide, microarray support, resin, *etc.*). Nucleic acid of the invention may be labelled *e.g.* with a radioactive or fluorescent label, or a biotin label. This is particularly useful where the nucleic acid is to be used in detection techniques *e.g.* where the nucleic acid is a primer or as a probe.

The term "nucleic acid" includes in general means a polymeric form of nucleotides of any length, which contain deoxyribonucleotides, ribonucleotides, and/or their analogs. It includes DNA, RNA, DNA/RNA hybrids. It also includes DNA or RNA analogs, such as those containing modified backbones (*e.g.* peptide nucleic acids (PNAs) or phosphorothioates) or modified bases. Thus the invention includes mRNA, tRNA, rRNA, ribozymes, DNA, cDNA, recombinant nucleic acids, branched nucleic acids, plasmids, vectors, probes, primers, *etc.*. Where nucleic acid of the invention takes the form of RNA, it may or may not have a 5' cap.

Nucleic acids of the invention comprise GBS sequences, but they may also comprise non-GBS sequences (*e.g.* in nucleic acids of formula 5'-X-Y-Z-3', as defined above). This is particularly useful for primers, which may thus comprise a first sequence complementary to a GBS nucleic acid target and a second sequence which is not complementary to the nucleic acid target. Any such non-complementary sequences in the primer are preferably 5' to the complementary sequences. Typical non-complementary sequences comprise restriction sites or promoter sequences.

Nucleic acids of the invention can be prepared in many ways *e.g.* by chemical synthesis (at least in part), by digesting longer nucleic acids using nucleases (*e.g.* restriction enzymes), by joining shorter nucleic acids (*e.g.* using ligases or polymerases), from genomic or cDNA libraries, *etc.*

Nucleic acids of the invention may be part of a vector *i.e.* part of a nucleic acid construct designed for transduction/transfection of one or more cell types. Vectors may be, for example, "cloning vectors" which are designed for isolation, propagation and replication of inserted nucleotides, "expression vectors" which are designed for expression of a nucleotide sequence in a host cell, "viral vectors" which is designed to result in the production of a recombinant virus or virus-like particle, or "shuttle vectors", which comprise the attributes of more than one type of vector. Preferred vectors are plasmids. A "host cell" includes an individual cell or cell culture which can be or has been a recipient of exogenous nucleic acid. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in total DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. Host cells include cells transfected or infected *in vivo* or *in vitro* with nucleic acid of the invention.

Where a nucleic acid is DNA, it will be appreciated that "U" in a RNA sequence will be replaced by "T" in the DNA. Similarly, where a nucleic acid is RNA, it will be appreciated that "T" in a DNA sequence will be replaced by "U" in the RNA.

The term "complement" or "complementary" when used in relation to nucleic acids refers to Watson-Crick base pairing. Thus the complement of C is G, the complement of G is C, the complement of A is T (or U), and the complement of T (or U) is A. It is also possible to use bases such as I (the purine inosine) *e.g.* to complement pyrimidines (C or T). The terms also imply a direction – the complement of 5'-ACAGT-3' is 5'-ACTGT-3' rather than 5'-TGTCA-3'.

Nucleic acids of the invention can be used, for example: to produce polypeptides; as hybridization probes for the detection of nucleic acid in biological samples; to generate additional copies of the nucleic acids; to generate ribozymes or antisense oligonucleotides; as single-stranded DNA primers or probes; or as triple-strand forming oligonucleotides.

The invention provides a process for producing nucleic acid of the invention, wherein the nucleic acid is synthesised in part or in whole using chemical means.

The invention provides vectors comprising nucleotide sequences of the invention (*e.g.* cloning or expression vectors) and host cells transformed with such vectors.

The invention also provides a kit comprising primers (*e.g.* PCR primers) for amplifying a template sequence contained within a streptococcus bacterium (*e.g.* GBS) nucleic acid sequence, the kit comprising a first primer and a second primer, wherein the first primer is substantially complementary to said template sequence and the second primer is substantially complementary to a complement of said template sequence, wherein the parts of said primers which have substantial complementarity define the termini of the template sequence to be amplified. The first primer and/or the second primer may include a detectable label (*e.g.* a fluorescent label).

The invention also provides a kit comprising first and second single-stranded oligonucleotides which allow amplification of a streptococcal template nucleic acid sequence contained in a single- or

double-stranded nucleic acid (or mixture thereof), wherein: (a) the first oligonucleotide comprises a primer sequence which is substantially complementary to said template nucleic acid sequence; (b) the second oligonucleotide comprises a primer sequence which is substantially complementary to the complement of said template nucleic acid sequence; (c) the first oligonucleotide and/or the second oligonucleotide comprise(s) sequence which is not complementary to said template nucleic acid; and (d) said primer sequences define the termini of the template sequence to be amplified. The non-complementary sequence(s) of feature (c) are preferably upstream of (*i.e.* 5' to) the primer sequences. One or both of these (c) sequences may comprise a restriction site [*e.g.* ref. 29] or a promoter sequence [*e.g.* 30]. The first oligonucleotide and/or the second oligonucleotide may include a detectable label (*e.g.* a fluorescent label).

The invention provides a process for detecting nucleic acid of the invention, comprising the steps of: (a) contacting a nucleic probe according to the invention with a biological sample under hybridising conditions to form duplexes; and (b) detecting said duplexes.

The invention provides a process for detecting GBS in a biological sample (*e.g.* blood), comprising the step of contacting nucleic acid according to the invention with the biological sample under hybridising conditions. The process may involve nucleic acid amplification (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA, *etc.*) or hybridisation (*e.g.* microarrays, blots, hybridisation with a probe in solution *etc.*). PCR detection of GBS in clinical samples has been reported [*e.g.* see refs. 31 to 34]. Clinical assays based on nucleic acid are described in general in ref. 35.

The invention provides a process for preparing a fragment of a target sequence, wherein the fragment is prepared by extension of a nucleic acid primer. The target sequence and/or the primer are nucleic acids of the invention. The primer extension reaction may involve nucleic acid amplification (*e.g.* PCR, SDA, SSSR, LCR, TMA, NASBA, *etc.*).

Nucleic acid amplification according to the invention may be quantitative and/or real-time.

For certain embodiments of the invention, nucleic acids are preferably at least 7 nucleotides in length (*e.g.* 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 225, 250, 275, 300 nucleotides or longer).

For certain embodiments of the invention, nucleic acids are preferably at most 500 nucleotides in length (*e.g.* 450, 400, 350, 300, 250, 200, 150, 140, 130, 120, 110, 100, 90, 80, 75, 70, 65, 60, 55, 50, 45, 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15 nucleotides or shorter).

Primers and probes of the invention, and other nucleic acids used for hybridization, are preferably between 10 and 30 nucleotides in length (*e.g.* 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 nucleotides).

Pharmaceutical compositions

The invention provides compositions comprising: (a) polypeptide, antibody, and/or nucleic acid of the invention; and (b) a pharmaceutically acceptable carrier. These compositions may be suitable as immunogenic compositions, for instance, or as diagnostic reagents, or as vaccines. Vaccines according to the invention may either be prophylactic (*i.e.* to prevent infection) or therapeutic (*i.e.* to treat infection), but will typically be prophylactic.

A 'pharmaceutically acceptable carrier' includes any carrier that does not itself induce the production of antibodies harmful to the individual receiving the composition. Suitable carriers are typically large, slowly metabolised macromolecules such as proteins, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers, sucrose, trehalose, lactose, and lipid aggregates (such as oil droplets or liposomes). Such carriers are well known to those of ordinary skill in the art. The vaccines may also contain diluents, such as water, saline, glycerol, *etc.* Additionally, auxiliary substances, such as wetting or emulsifying agents, pH buffering substances, and the like, may be present. Sterile pyrogen-free, phosphate-buffered physiologic saline is a typical carrier. A thorough discussion of pharmaceutically acceptable excipients is available in ref. 155.

Compositions of the invention may include an antimicrobial, particularly if packaged in a multiple dose format.

Compositions of the invention may comprise detergent *e.g.* a Tween (polysorbate), such as Tween 80. Detergents are generally present at low levels *e.g.* <0.01%.

Compositions of the invention may include sodium salts (*e.g.* sodium chloride) to give tonicity. A concentration of 10±2mg/ml NaCl is typical.

Compositions of the invention will generally include a buffer. A phosphate buffer is typical.

Compositions of the invention may comprise a sugar alcohol (*e.g.* mannitol) or a disaccharide (*e.g.* sucrose or trehalose) *e.g.* at around 15-30mg/ml (*e.g.* 25 mg/ml), particularly if they are to be lyophilised or if they include material which has been reconstituted from lyophilised material. The pH of a composition for lyophilisation may be adjusted to around 6.1 prior to lyophilisation.

Polypeptides of the invention may be administered in conjunction with other immunoregulatory agents. In particular, compositions will usually include a vaccine adjuvant. Adjuvants which may be used in compositions of the invention include, but are not limited to:

A. Mineral-containing compositions

Mineral containing compositions suitable for use as adjuvants in the invention include mineral salts, such as aluminium salts and calcium salts. The invention includes mineral salts such as hydroxides (*e.g.* oxyhydroxides), phosphates (*e.g.* hydroxyphosphates, orthophosphates), sulphates, *etc.* [*e.g.* see chapters 8 & 9 of ref. 36], or mixtures of different mineral compounds (*e.g.* a mixture of a phosphate and a hydroxide adjuvant, optionally with an excess of the phosphate), with the compounds taking

any suitable form (e.g. gel, crystalline, amorphous, *etc.*), and with adsorption to the salt(s) being preferred. Mineral containing compositions may also be formulated as a particle of metal salt [37].

Aluminum salts may be included in vaccines of the invention such that the dose of Al^{3+} is between 0.2 and 1.0 mg per dose.

A typical aluminium phosphate adjuvant is amorphous aluminium hydroxyphosphate with PO_4/Al molar ratio between 0.84 and 0.92, included at 0.6mg Al^{3+}/ml. Adsorption with a low dose of aluminium phosphate may be used *e.g.* between 50 and 100μg Al^{3+} per conjugate per dose. Where an aluminium phosphate it used and it is desired not to adsorb an antigen to the adjuvant, this is favoured by including free phosphate ions in solution (*e.g.* by the use of a phosphate buffer).

B. Oil Emulsions

Oil emulsion compositions suitable for use as adjuvants in the invention include squalene-water emulsions, such as MF59 (5% Squalene, 0.5% Tween 80, and 0.5% Span 85, formulated into submicron particles using a microfluidizer) [Chapter 10 of ref. 36; see also refs. 38-40]. MF59 is used as the adjuvant in the FLUAD™ influenza virus trivalent subunit vaccine.

Particularly preferred adjuvants for use in the compositions are submicron oil-in-water emulsions. Preferred submicron oil-in-water emulsions for use herein are squalene/water emulsions optionally containing varying amounts of MTP-PE, such as a submicron oil-in-water emulsion containing 4-5% w/v squalene, 0.25-1.0% w/v Tween 80 (polyoxyethylenesorbitan monooleate), and/or 0.25-1.0% Span 85 (sorbitan trioleate), and, optionally, N-acetylmuramyl-L-alanyl-D-isogluatminyl-L-alanine-2-(1'-2'-dipalmitoyl-sn-glycero-3-hydroxyphosphophoryloxy)-ethylamine (MTP-PE). Submicron oil-in-water emulsions, methods of making the same and immunostimulating agents, such as muramyl peptides, for use in the compositions, are described in detail in references 38 & 41-42.

Complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) may also be used as adjuvants in the invention.

C. Saponin formulations [chapter 22 of ref. 36]

Saponin formulations may also be used as adjuvants in the invention. Saponins are a heterologous group of sterol glycosides and triterpenoid glycosides that are found in the bark, leaves, stems, roots and even flowers of a wide range of plant species. Saponins isolated from the bark of the *Quillaja saponaria* Molina tree have been widely studied as adjuvants. Saponin can also be commercially obtained from *Smilax ornata* (sarsaprilla), *Gypsophilla paniculata* (brides veil), and *Saponaria officianalis* (soap root). Saponin adjuvant formulations include purified formulations, such as QS21, as well as lipid formulations, such as ISCOMs.

Saponin compositions have been purified using HPLC and RP-HPLC. Specific purified fractions using these techniques have been identified, including QS7, QS17, QS18, QS21, QH-A, QH-B and QH-C. Preferably, the saponin is QS21. A method of production of QS21 is disclosed in ref. 43. Saponin formulations may also comprise a sterol, such as cholesterol [44].

Combinations of saponins and cholesterols can be used to form unique particles called immunostimulating complexes (ISCOMs) [chapter 23 of ref. 36]. ISCOMs typically also include a phospholipid such as phosphatidylethanolamine or phosphatidylcholine. Any known saponin can be used in ISCOMs. Preferably, the ISCOM includes one or more of QuilA, QHA and QHC. ISCOMs are further described in refs. 44-46. Optionally, the ISCOMs may be devoid of additional detergent(s) [47].

A review of the development of saponin based adjuvants can be found in refs. 48 & 49.

D. Virosomes and virus-like particles

Virosomes and virus-like particles (VLPs) can also be used as adjuvants in the invention. These structures generally contain one or more proteins from a virus optionally combined or formulated with a phospholipid. They are generally non-pathogenic, non-replicating and generally do not contain any of the native viral genome. The viral proteins may be recombinantly produced or isolated from whole viruses. These viral proteins suitable for use in virosomes or VLPs include proteins derived from influenza virus (such as HA or NA), Hepatitis B virus (such as core or capsid proteins), Hepatitis E virus, measles virus, Sindbis virus, Rotavirus, Foot-and-Mouth Disease virus, Retrovirus, Norwalk virus, human Papilloma virus, HIV, RNA-phages, Qß-phage (such as coat proteins), GA-phage, fr-phage, AP205 phage, and Ty (such as retrotransposon Ty protein p1). VLPs are discussed further in refs. 50-55. Virosomes are discussed further in, for example, ref. 56

E. Bacterial or microbial derivatives

Adjuvants suitable for use in the invention include bacterial or microbial derivatives such as non-toxic derivatives of enterobacterial lipopolysaccharide (LPS), Lipid A derivatives, immunostimulatory oligonucleotides and ADP-ribosylating toxins and detoxified derivatives thereof.

Non-toxic derivatives of LPS include monophosphoryl lipid A (MPL) and 3-O-deacylated MPL (3dMPL). 3dMPL is a mixture of 3 de-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains. A preferred "small particle" form of 3 De-O-acylated monophosphoryl lipid A is disclosed in ref. 57. Such "small particles" of 3dMPL are small enough to be sterile filtered through a 0.22μm membrane [57]. Other non-toxic LPS derivatives include monophosphoryl lipid A mimics, such as aminoalkyl glucosaminide phosphate derivatives *e.g.* RC-529 [58,59].

Lipid A derivatives include derivatives of lipid A from *Escherichia coli* such as OM-174. OM-174 is described for example in refs. 60 & 61.

Immunostimulatory oligonucleotides suitable for use as adjuvants in the invention include nucleotide sequences containing a CpG motif (a dinucleotide sequence containing an unmethylated cytosine linked by a phosphate bond to a guanosine). Double-stranded RNAs and oligonucleotides containing palindromic or poly(dG) sequences have also been shown to be immunostimulatory.

The CpG's can include nucleotide modifications/analogs such as phosphorothioate modifications and can be double-stranded or single-stranded. References 62, 63 and 64 disclose possible analog

substitutions *e.g.* replacement of guanosine with 2'-deoxy-7-deazaguanosine. The adjuvant effect of CpG oligonucleotides is further discussed in refs. 65-70.

The CpG sequence may be directed to TLR9, such as the motif GTCGTT or TTCGTT [71]. The CpG sequence may be specific for inducing a Th1 immune response, such as a CpG-A ODN, or it may be more specific for inducing a B cell response, such a CpG-B ODN. CpG-A and CpG-B ODNs are discussed in refs. 72-74. Preferably, the CpG is a CpG-A ODN.

Preferably, the CpG oligonucleotide is constructed so that the 5' end is accessible for receptor recognition. Optionally, two CpG oligonucleotide sequences may be attached at their 3' ends to form "immunomers". See, for example, refs. 71 & 75-77.

Bacterial ADP-ribosylating toxins and detoxified derivatives thereof may be used as adjuvants in the invention. Preferably, the protein is derived from *E.coli* (*E.coli* heat labile enterotoxin "LT"), cholera ("CT"), or pertussis ("PT"). The use of detoxified ADP-ribosylating toxins as mucosal adjuvants is described in ref. 78 and as parenteral adjuvants in ref. 79. The toxin or toxoid is preferably in the form of a holotoxin, comprising both A and B subunits. Preferably, the A subunit contains a detoxifying mutation; preferably the B subunit is not mutated. Preferably, the adjuvant is a detoxified LT mutant such as LT-K63, LT-R72, and LT-G192. The use of ADP-ribosylating toxins and detoxified derivatives thereof, particularly LT-K63 and LT-R72, as adjuvants can be found in refs. 80-87. Numerical reference for amino acid substitutions is preferably based on the alignments of the A and B subunits of ADP-ribosylating toxins set forth in ref. 88, specifically incorporated herein by reference in its entirety.

F. Human immunomodulators

Human immunomodulators suitable for use as adjuvants in the invention include cytokines, such as interleukins (*e.g.* IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-12 [89], *etc.*) [90], interferons (*e.g.* interferon-γ), macrophage colony stimulating factor, and tumor necrosis factor.

G. Bioadhesives and Mucoadhesives

Bioadhesives and mucoadhesives may also be used as adjuvants in the invention. Suitable bioadhesives include esterified hyaluronic acid microspheres [91] or mucoadhesives such as cross-linked derivatives of poly(acrylic acid), polyvinyl alcohol, polyvinyl pyrollidone, polysaccharides and carboxymethylcellulose. Chitosan and derivatives thereof may also be used as adjuvants in the invention [92].

H. Microparticles

Microparticles may also be used as adjuvants in the invention. Microparticles (*i.e.* a particle of ~100nm to ~150μm in diameter, more preferably ~200nm to ~30μm in diameter, and most preferably ~500nm to ~10μm in diameter) formed from materials that are biodegradable and non-toxic (*e.g.* a poly(α-hydroxy acid), a polyhydroxybutyric acid, a polyorthoester, a polyanhydride, a polycaprolactone, *etc.*), with poly(lactide-co-glycolide) are preferred, optionally treated to have a

negatively-charged surface (*e.g.* with SDS) or a positively-charged surface (*e.g.* with a cationic detergent, such as CTAB).

I. Liposomes (Chapters 13 & 14 of ref. 36)

Examples of liposome formulations suitable for use as adjuvants are described in refs. 93-95.

J. Polyoxyethylene ether and polyoxyethylene ester formulations

Adjuvants suitable for use in the invention include polyoxyethylene ethers and polyoxyethylene esters [96]. Such formulations further include polyoxyethylene sorbitan ester surfactants in combination with an octoxynol [97] as well as polyoxyethylene alkyl ethers or ester surfactants in combination with at least one additional non-ionic surfactant such as an octoxynol [98]. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether (laureth 9), polyoxyethylene-9-steoryl ether, polyoxytheylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether.

K. Polyphosphazene (PCPP)

PCPP formulations are described, for example, in refs. 99 and 100.

L. Muramyl peptides

Examples of muramyl peptides suitable for use as adjuvants in the invention include N-acetyl-muramyl-L-threonyl-D-isoglutamine (thr-MDP), N-acetyl-normuramyl-L-alanyl-D-isoglutamine (nor-MDP), and N-acetylmuramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1'-2'-dipalmitoyl-*sn*-glycero-3-hydroxyphosphoryloxy)-ethylamine MTP-PE).

M. Imidazoquinolone Compounds.

Examples of imidazoquinolone compounds suitable for use adjuvants in the invention include Imiquamod and its homologues (*e,g.* "Resiquimod 3M"), described further in refs. 101 and 102.

N. Thiosemicarbazone Compounds.

Examples of thiosemicarbazone compounds, as well as methods of formulating, manufacturing, and screening for compounds all suitable for use as adjuvants in the invention include those described in ref. 103. The thiosemicarbazones are particularly effective in the stimulation of human peripheral blood mononuclear cells for the production of cytokines, such as TNF-α.

O. Tryptanthrin Compounds.

Examples of tryptanthrin compounds, as well as methods of formulating, manufacturing, and screening for compounds all suitable for use as adjuvants in the invention include those described in ref. 104. The tryptanthrin compounds are particularly effective in the stimulation of human peripheral blood mononuclear cells for the production of cytokines, such as TNF-α.

The invention may also comprise combinations of aspects of one or more of the adjuvants identified above. For example, the following combinations may be used as adjuvant compositions in the invention: (1) a saponin and an oil-in-water emulsion [105]; (2) a saponin (*e.g.* QS21) + a non-toxic

LPS derivative (*e.g.* 3dMPL) [106]; (3) a saponin (*e.g.* QS21) + a non-toxic LPS derivative (*e.g.* 3dMPL) + a cholesterol; (4) a saponin (*e.g.* QS21) + 3dMPL + IL-12 (optionally + a sterol) [107]; (5) combinations of 3dMPL with, for example, QS21 and/or oil-in-water emulsions [108]; (6) SAF, containing 10% squalane, 0.4% Tween 80™, 5% pluronic-block polymer L121, and thr-MDP, either microfluidized into a submicron emulsion or vortexed to generate a larger particle size emulsion. (7) Ribi™ adjuvant system (RAS), (Ribi Immunochem) containing 2% squalene, 0.2% Tween 80, and one or more bacterial cell wall components from the group consisting of monophosphorylipid A (MPL), trehalose dimycolate (TDM), and cell wall skeleton (CWS), preferably MPL + CWS (Detox™); (8) one or more mineral salts (such as an aluminum salt) + a non-toxic derivative of LPS (such as 3dMPL); and (9) one or more mineral salts (such as an aluminum salt) + an immunostimulatory oligonucleotide (such as a nucleotide sequence including a CpG motif).

Other substances that act as immunostimulating agents are disclosed in chapter 7 of ref. 36.

The use of an aluminium hydroxide or aluminium phosphate adjuvant is particularly preferred, and antigens are generally adsorbed to these salts. Calcium phosphate is another preferred adjuvant.

The pH of compositions of the invention is preferably between 6 and 8, preferably about 7. Stable pH may be maintained by the use of a buffer. Where a composition comprises an aluminium hydroxide salt, it is preferred to use a histidine buffer [109]. The composition may be sterile and/or pyrogen-free. Compositions of the invention may be isotonic with respect to humans.

Compositions may be presented in vials, or they may be presented in ready-filled syringes. The syringes may be supplied with or without needles. A syringe will include a single dose of the composition, whereas a vial may include a single dose or multiple doses. Injectable compositions will usually be liquid solutions or suspensions. Alternatively, they may be presented in solid form (*e.g.* freeze-dried) for solution or suspension in liquid vehicles prior to injection.

Compositions of the invention may be packaged in unit dose form or in multiple dose form. For multiple dose forms, vials are preferred to pre-filled syringes. Effective dosage volumes can be routinely established, but a typical human dose of the composition for injection has a volume of 0.5ml.

Where a composition of the invention is to be prepared extemporaneously prior to use (*e.g.* where a component is presented in lyophilised form) and is presented as a kit, the kit may comprise two vials, or it may comprise one ready-filled syringe and one vial, with the contents of the syringe being used to reactivate the contents of the vial prior to injection.

Immunogenic compositions used as vaccines comprise an immunologically effective amount of antigen(s), as well as any other components, as needed. By 'immunologically effective amount', it is meant that the administration of that amount to an individual, either in a single dose or as part of a series, is effective for treatment or prevention. This amount varies depending upon the health and physical condition of the individual to be treated, age, the taxonomic group of individual to be treated

(*e.g.* non-human primate, primate, *etc.*), the capacity of the individual's immune system to synthesise antibodies, the degree of protection desired, the formulation of the vaccine, the treating doctor's assessment of the medical situation, and other relevant factors. It is expected that the amount will fall in a relatively broad range that can be determined through routine trials, and a typical quantity of each meningococcal saccharide antigen per dose is between 1μg and 10mg per antigen.

Pharmaceutical uses

The invention also provides a method of treating a patient, comprising administering to the patient a therapeutically effective amount of a composition of the invention. The patient may either be at risk from the disease themselves or may be a pregnant woman ('maternal immunisation' [110]).

The invention provides nucleic acid, polypeptide, or antibody of the invention for use as medicaments (*e.g.* as immunogenic compositions or as vaccines) or as diagnostic reagents. It also provides the use of nucleic acid, polypeptide, or antibody of the invention in the manufacture of: (i) a medicament for treating or preventing disease and/or infection caused by GBS; (ii) a diagnostic reagent for detecting the presence of GBS or of antibodies raised against GBS; and/or (iii) a reagent which can raise antibodies against GBS. Said GBS can be of any serotype or strain. Said disease may be, for instance, bacteremia, meningitis, puerperal fever, scarlet fever, erysipelas, pharyngitis, impetigo, necrotising fasciitis, myositis or toxic shock syndrome.

The patient is preferably a human. Where the vaccine is for prophylactic use, the human is preferably an adolescent (*e.g.* aged between 10 and 20 years); where the vaccine is for therapeutic use, the human is preferably an adult. A vaccine intended for children or adolescents may also be administered to adults *e.g.* to assess safety, dosage, immunogenicity, *etc.*

One way of checking efficacy of therapeutic treatment involves monitoring GBS infection after administration of the composition of the invention. One way of checking efficacy of prophylactic treatment involves monitoring immune responses against an administered polypeptide after administration. Immunogenicity of compositions of the invention can be determined by administering them to test subjects (*e.g.* children 12-16 months age, or animal models *e.g.* a mouse model) and then determining standard parameters including ELISA titres (GMT) of IgG. These immune responses will generally be determined around 4 weeks after administration of the composition, and compared to values determined before administration of the composition. Where more than one dose of the composition is administered, more than one post-administration determination may be made. A mouse neonatal sepsis model for protective efficacy against GBS infection is known *e.g.* see ref. 111.

Administration of polypeptide antigens is a preferred method of treatment for inducing immunity. Administration of antibodies of the invention is another preferred method of treatment. This method of passive immunisation is particularly useful for newborn children or for pregnant women. This method will typically use monoclonal antibodies, which will be humanised or fully human.

Preferred compositions for use in immunisation include more than one GBS polypeptide. Multiple antigens can be included as separate admixed polypeptides in a single composition, and/or can be part of a hybrid polypeptide as described above. Preferred combinations of antigens include at least one (*e.g.* 1, 2, 3, 4, 5, 6 or more) 'core' polypeptide (as described below; Table V) and at least one (*e.g.* 1, 2, 3, 4, 5, 6 or more) 'variable' polypeptide (as described below; Table VI). Mixtures of one core polypeptide with more than one variable polypeptides are preferred. Examples of these combinations, using the nomenclature of reference 2, include (a) GBS322 (a core antigen) plus GBS80, GBS104 & GBS67 (all variable antigens); and (b) GBS322 plus GBS80 & GBS104. In some embodiments, this specific 3-valent combination [112] and this specific 4-valent combination [113] are excluded from the invention, although they illustrate the principle of combining core and variable antigens.

Compositions of the invention will generally be administered directly to a patient. Direct delivery may be accomplished by parenteral injection (*e.g.* subcutaneously, intraperitoneally, intravenously, intramuscularly, or to the interstitial space of a tissue), or by rectal, oral, vaginal, topical, transdermal, intranasal, sublingual, ocular, aural, pulmonary or other mucosal administration. Intramuscular administration to the thigh or the upper arm is preferred. Injection may be via a needle (*e.g.* a hypodermic needle), but needle-free injection may alternatively be used. A typical intramuscular dose is 0.5 ml.

The invention may be used to elicit systemic and/or mucosal immunity.

Dosage treatment can be a single dose schedule or a multiple dose schedule. Multiple doses may be used in a primary immunisation schedule and/or in a booster immunisation schedule. A primary dose schedule may be followed by a booster dose schedule. Suitable timing between priming doses (*e.g.* between 4-16 weeks), and between priming and boosting, can be routinely determined.

Bacterial infections affect various areas of the body and so compositions may be prepared in various forms. For example, the compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared (*e.g.* a lyophilised composition). The composition may be prepared for topical administration *e.g.* as an ointment, cream or powder. The composition be prepared for oral administration *e.g.* as a tablet or capsule, or as a syrup (optionally flavoured). The composition may be prepared for pulmonary administration *e.g.* as an inhaler, using a fine powder or a spray. The composition may be prepared as a suppository or pessary. The composition may be prepared for nasal, aural or ocular administration *e.g.* as spray, drops, gel or powder [*e.g.* refs 114 & 115].

Further antigenic components of compositions of the invention

The invention also provides a composition comprising a polypeptide or the invention and one or more of the following further antigens:

- a saccharide antigen from *N.meningitidis* serogroup A, C, W135 and/or Y (preferably all four), such as the oligosaccharide disclosed in ref. 116 from serogroup C [see also ref. 117] or the oligosaccharides of ref. 118.
- a saccharide antigen from *Streptococcus pneumoniae* [*e.g.* 119, 120, 121].
- an antigen from hepatitis A virus, such as inactivated virus [*e.g.* 122, 123].
- an antigen from hepatitis B virus, such as the surface and/or core antigens [*e.g.* 123, 124].
- a diphtheria antigen, such as a diphtheria toxoid [*e.g.* chapter 3 of ref. 125] *e.g.* the CRM_{197} mutant [*e.g.* 126].
- a tetanus antigen, such as a tetanus toxoid [*e.g.* chapter 4 of ref. 125].
- an antigen from *Bordetella pertussis*, such as pertussis holotoxin (PT) and filamentous haemagglutinin (FHA) from *B.pertussis*, optionally also in combination with pertactin and/or agglutinogens 2 and 3 [*e.g.* refs. 127 & 128].
- a saccharide antigen from *Haemophilus influenzae* B [*e.g.* 117].
- polio antigen(s) [*e.g.* 129, 130] such as IPV.
- measles, mumps and/or rubella antigens [*e.g.* chapters 9, 10 & 11 of ref. 125].
- influenza antigen(s) [*e.g.* chapter 19 of ref. 125], such as the haemagglutinin and/or neuraminidase surface proteins.
- an antigen from *Moraxella catarrhalis* [*e.g.* 131].
- a saccharide antigen from *Streptococcus agalactiae* (group B streptococcus).
- an antigen from *Streptococcus pyogenes* (group A streptococcus) [*e.g.* 132, 133, 134].
- an antigen from *Staphylococcus aureus* [*e.g.* 135].

The composition may comprise one or more of these further antigens.

In another embodiment, the GBS antigens of the invention are combined with one or more additional, non-GBS antigens suitable for use in a vaccine designed to protect elderly or immunocompromised individuals. For example, the GBS antigens may be combined with an antigen derived from the group consisting of *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermis, Pseudomonas aeruginosa, Legionella pneumophila, Listeria monocytogenes, Neisseria meningitides,* influenza, and Parainfluenza virus ('PIV').

Toxic protein antigens may be detoxified where necessary (*e.g.* detoxification of pertussis toxin by chemical and/or genetic means [128]).

Where a diphtheria antigen is included in the composition it is preferred also to include tetanus antigen and pertussis antigens. Similarly, where a tetanus antigen is included it is preferred also to include diphtheria and pertussis antigens. Similarly, where a pertussis antigen is included it is preferred also to include diphtheria and tetanus antigens. DTP combinations are thus preferred.

Saccharide antigens are preferably in the form of conjugates. Carrier proteins for the conjugates include bacterial toxins (such as diphtheria toxoid or tetanus toxoid), the *N.meningitidis* outer membrane protein [136], synthetic peptides [137,138], heat shock proteins [139,140], pertussis

proteins [141,142], protein D from *H.influenzae* [143,144], cytokines [145], lymphokines [145], *H. influenzae* proteins, hormones [145], growth factors [145], toxin A or B from *C.difficile* [146], iron-uptake proteins [147], artificial proteins comprising multiple human CD4+ T cell epitopes from various pathogen-derived antigens [148] such as the N19 protein [149], pneumococcal surface protein PspA [150], pneumolysin [151], *etc.* A preferred carrier protein is the CRM197 protein [152].

Antigens in the composition will typically be present at a concentration of at least 1μg/ml each. In general, the concentration of any given antigen will be sufficient to elicit an immune response against that antigen.

As an alternative to using proteins antigens in the immunogenic compositions of the invention, nucleic acid (preferably DNA *e.g.* in the form of a plasmid) encoding the antigen may be used.

Antigens are preferably adsorbed to an aluminium salt.

Screening methods

The invention provides a process for determining whether a test compound binds to a polypeptide of the invention. If a test compound binds to a polypeptide of the invention and this binding inhibits the life cycle of the GBS bacterium, then the test compound can be used as an antibiotic or as a lead compound for the design of antibiotics. The process will typically comprise the steps of contacting a test compound with a polypeptide of the invention, and determining whether the test compound binds to said polypeptide. Preferred polypeptides of the invention for use in these processes are enzymes (*e.g.* tRNA synthetases), membrane transporters and ribosomal polypeptides. Suitable test compounds include polypeptides, polypeptides, carbohydrates, lipids, nucleic acids (*e.g.* DNA, RNA, and modified forms thereof), as well as small organic compounds (*e.g.* MW between 200 and 2000 Da). The test compounds may be provided individually, but will typically be part of a library (*e.g.* a combinatorial library). Methods for detecting a binding interaction include NMR, filter-binding assays, gel-retardation assays, displacement assays, surface plasmon resonance, reverse two-hybrid *etc.* A compound which binds to a polypeptide of the invention can be tested for antibiotic activity by contacting the compound with GBS bacteria and then monitoring for inhibition of growth. The invention also provides a compound identified using these methods.

Preferably, the process comprises the steps of: (a) contacting a polypeptide of the invention with one or more candidate compounds to give a mixture; (b) incubating the mixture to allow polypeptide and the candidate compound(s) to interact; and (c) assessing whether the candidate compound binds to the polypeptide or modulates its activity.

Once a candidate compound has been identified *in vitro* as a compound that binds to a polypeptide of the invention then it may be desirable to perform further experiments to confirm the *in vivo* function of the compound in inhibiting bacterial growth and/or survival. Thus the method comprise the further step of contacting the compound with a GBS bacterium and assessing its effect.

The polypeptide used in the screening process may be free in solution, affixed to a solid support, located on a cell surface or located intracellularly. Preferably, the binding of a candidate compound to the polypeptide is detected by means of a label directly or indirectly associated with the candidate compound. The label may be a fluorophore, radioisotope, or other detectable label.

Preferred polypeptides for use in these screening methods are the 'core' sequences identified below.

General

The invention provides a computer-readable medium (*e.g.* a floppy disk, a hard disk, a CD-ROM, a DVD *etc.*) and/or a computer memory and/or a computer database containing one or more of the sequences in the sequence listing.

The term "comprising" encompasses "including" as well as "consisting" *e.g.* a composition "comprising" X may consist exclusively of X or may include something additional *e.g.* X + Y.

The term "about" in relation to a numerical value *x* means, for example, $x \pm 10\%$.

The word "substantially" does not exclude "completely" *e.g.* a composition which is "substantially free" from Y may be completely free from Y. Where necessary, the word "substantially" may be omitted from the definition of the invention.

The N-terminus residues in the amino acid sequences in the sequence listing are given as the amino acid encoded by the first codon in the corresponding nucleotide sequence. Where the first codon is not ATG, it will be understood that it will be translated as methionine when the codon is a start codon, but will be translated as the indicated non-Met amino acid when the sequence is at the C-terminus of a fusion partner. The invention specifically discloses and encompasses each of the amino acid sequences of the sequence listing having a N-terminus methionine residue (*e.g.* a formyl-methionine residue) in place of any indicated non-Met residue. It also specifically discloses and encompasses each of the amino acid sequences of the sequence listing starting at any internal methionine residues in the sequences.

As indicated in the above text, nucleic acids and polypeptides of the invention may include sequences that:

(a) are identical (*i.e.* 100% identical) to the sequences disclosed in the sequence listing;

(b) share sequence identity with the sequences disclosed in the sequence listing;

(c) have 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 single nucleotide or amino acid alterations (deletions, insertions, substitutions), which may be at separate locations or may be contiguous, as compared to the sequences of (a) or (b); and

(d) when aligned with a particular sequence from the sequence listing using a pairwise alignment algorithm, a moving window of *x* monomers (amino acids or nucleotides) moving from start (N-terminus or 5') to end (C-terminus of 3'), such that for an alignment that extends to *p* monomers (where $p>x$) there are $p-x+1$ such windows, each window has at least $x \cdot y$ identical

aligned monomers, where: x is selected from 20, 25, 30, 35, 40, 45, 50, 60, 70, 80, 90, 100, 150, 200; y is selected from 0.50, 0.60, 0.70, 0.75, 0.80, 0.85, 0.90, 0.91, 0.92, 0.93, 0.94, 0.95, 0.96, 0.97, 0.98, 0.99; and if $x \cdot y$ is not an integer then it is rounded up to the nearest integer. The preferred pairwise alignment algorithm is the Needleman-Wunsch global alignment algorithm [153], using default parameters (*e.g.* with Gap opening penalty = 10.0, and with Gap extension penalty = 0.5, using the EBLOSUM62 scoring matrix). This algorithm is conveniently implemented in the *needle* tool in the EMBOSS package [154].

The nucleic acids and polypeptides of the invention may additionally have further sequences to the N-terminus/5' and/or C-terminus/3' of these sequences (a) to (d).

The practice of the present invention will employ, unless otherwise indicated, conventional methods of chemistry, biochemistry, molecular biology, immunology and pharmacology, within the skill of the art. Such techniques are explained fully in the literature. See, *e.g.*, references 155-162, *etc.*

BRIEF DESCRIPTION OF DRAWINGS

There are no drawings.

MODES FOR CARRYING OUT THE INVENTION

Genome sequencing has been carried out on five strains of GBS from different serotypes: '18RS21' (type II; MLST type ST19), '515' (type Ia; MLST type ST23), 'CJB111' (type V; MLST type ST1), 'COH1' (type III; MLST type ST17) and 'H36B' (type Ib; MLST type ST6). Different numbers of coding sequences were identified in the five genomes:

Strain	18RS21	515	CJB111	COH1	H36B
Coding seqs	2151	2249	2167	2410	2393

These 11370 coding sequences are given in the sequence listing together with their inferred translation products. Annotation of these polypeptide sequences is given in Table I.

The sequence listing gives sequences in pairs, such that an odd-numbered sequence 'n' is a DNA coding sequence and the even-numbered sequence 'n+1' is the corresponding amino acid sequence:

Strain	18RS21	515	CJB111	COH1	H36B
SEQ ID NO^S	1-4302	4303-8800	8801-13134	13135-17954	17955-22740

The polypeptides and their epitopes can be used as antigens *e.g.* in vaccines or diagnostic tests.

Homologous coding sequences between strains are shown in Table II (listing SEQ ID numbers). For comparison, Table II also includes the 'gi' (GenInfo Identifier) accession numbers for strains 2603V/R (serotype V; MLST type ST106) [1] and NEM316 (serotype III; MLST type ST23) [3]. A single row in Table II includes all homologs and, where applicable, paralogs within a single strain.

In contrast to Table II, coding sequences without homologs in any of the other six sequenced genomes (*i.e.* unique to one strain within the six strains) are listed in Table III. These are preferred coding sequences of the invention *e.g.* when strain-specificity is desired. Each of the seven

sequenced genomes contains between 13 and 61 sequences not present in any of the other strains. This variability exceeds that seen in the comparative genome hybridization analysis of reference 1.

Table IV lists coding sequences in the five new sequenced genomes that do not have any homologs in strains 2603V/R [1] or NEM316 [3]. These are preferred coding sequences of the invention *e.g.* when sequences not known in the prior art are desired.

Table V lists 'core' GBS genes, namely those that are found in all seven sequenced genomes. These 'universal' GBS coding sequences are preferred for use with the invention *e.g.* when strain-specificity is not desired, such as when designing a diagnostic test with high inter-strain cross-reactivity, or when preparing a composition which will elicit antibodies with high inter-strain cross-reactivity, or when screening for broad-range anti-GBS antibiotics. Table VI lists variable GBS genes, namely those that are found in at least two sequenced genomes, but not in all seven. The format of Tables V and VI follows that of Table II.

The GBS "pan-genome" can thus be divided in three parts: a core-genome, strain-specific sequences, and "dispensable genes" shared only by some of the strains. The core genes describe the basic aspects of GBS biology and major phenotypic traits, whereas dispensable and strain-specific genes contribute to the observed genetic diversity of the species and might confer selective advantages, such as adaptation to different niches, antibiotic resistance, and increased invasive capabilities.

The vast majority of genes making up the core genome belong to the groups of housekeeping functions, cell envelope, regulatory functions, and transport and binding proteins. However, about one third of the shared genes fall into the annotation class of hypothetical proteins and proteins of unknown function, thus suggesting that many aspects of basic GBS biology still need to be explored. Because of their 'core' nature, however, these sequences still have utility as they can be used in situations where inter-strain cross-reactivity is needed, without needing to know their true underlying biological function. Hypothetical genes and genes of unknown function are much more represented among the dispensable genes, probably due to the fact that more functions have been ascribed to better known (*i.e.* more frequently found) genes. This view is also supported by the strain-specific genes being predominantly of unknown function. Furthermore, genes associated with mobile and extrachromosomal elements are particularly abundant in this group, supporting the hypothesis that the majority of specific traits depend upon phenomena of lateral gene transfer. On the other hand, this class of genes is very poorly represented within the core genome, indicating that only a few of these rearrangements have remained stable during evolution of GBS.

The core shared by all isolates (Table V) accounts for only about 80% of any single genome, with the remaining 20% being absent in at least one other strain (Table VI). Approximately 1800 coding sequences are shared by the sequenced GBS strains. The criteria for gene identity between genomes was set low so that coding sequences were considered shared even if they were quite divergent in sequence. The size of the core is thus likely to be an overestimated, but it substantially defines the basic characteristics of the GBS species. As further GBS genome sequences become available then

this "core" may decrease (by analogy, a coding sequence would move from Table V to Table VI), but for the purposes of the present invention the "core" is the group given in Table V. Even using the sequences herein, the core decreases with the addition of each new genome, but extrapolation of the curve indicates that the core stabilizes at around 1800 coding sequences and will remain constant even as many more genomes are added.

One mechanism by which bacteria can modulate their lifestyle and virulence in response to variable stimuli, stress conditions and adaptation to different niches is phase variation [163,164]. Such variation occurs by altering the length of short repeated DNA tracts within or immediately upstream of coding regions (contingency genes), thus causing frame-shifts and affecting protein synthesis. At least one important virulence-associated gene in GBS is regulated in this way [165], and so identification of further phase variable genes can identify new virulence factors. Virulence factors are particularly useful for vaccination, antibiotic targets, *etc.* Table VII shows such phase variable genes, and these are preferred polypeptides for use with the invention.

It will be understood that the invention has been described by way of example only and modifications may be made whilst remaining within the scope and spirit of the invention.

TABLE II — Homologs and paralogs

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22535220	1, 3919	8615	12909	14061	22383	24413708
22535221	3	8617	12911	14063	22385, 22427	24413709
22535222	5	8619, 8703	12913	14065	22387	24413710
22535223	7	8621	12915	14067	22389	24413711
22535224	9	8623	12917	14069	22391	24413712
22535225	11	8625	12919	14071	22393	24413713
22533003	13	8627	12921	14073	22395	23094427
22533004	15	4303, 8629	12923	14075	22397	23094428
22533005	17	4305, 8631	12925, 12927	14077	22399	23094429
22533006,22535061	19, 3631	4307, 8305, 8323, 8325, 8327, 8329, 8787	-	14079, 17271	22401	23094430
22533007	21	4309	9607	14081	22403	23094431
22533008	23	4311	9609	14083	22405	23094432
22533009	25	4313	9611	14085	22407	23094433
22533010	27, 29	4315	9613	14087	22409, 22663	23094434
22533012	31	4317	9615	14089	22413	23094435
22533013	33	4319	9617	14091	22415	23094436
22533014	35	4321	9619	14093	22417	23094437
22533015	37	4323	9621	13135, 14095	22419	23094438
22533016,22534732	39	4325	9623, 12021	13137, 14097, 16681	21493, 22421	23094439
22533017	41	4327	9625	13139, 13143, 14099	22423	23094440
22533018	43	4329	9627	13145, 13147, 13149, 14101	22425, 22623	23094441
22533020	45, 47, 49, 51	4331	8801	13181	17963	23094442
22533021	53	4333, 4335	8803	13183	17965	23094443
22533022	55	4337	8805	13185	17967	23094444
22533023	57	4339, 4341	8807	13187, 13189	17969	23094445
22533024	59	4343	8809	13191	17971	23094446
22533025	61	4345	8811	13193	17973	23094447
22533026	63	4347	8813, 8815	13195	17975	23094448
22533027	65	4349	8817	13197	17977, 18033, 18035	23094449
22533028	67	4351	8819	13199, 13245, 13247, 17811, 17821, 17859	17979, 18037, 22555	23094450
22533029	69, 71, 3965, 4017, 4061	4353	8821	13201, 17803, 17891	17981	23094451
22533030	73, 75, 3963	4355	8823	13203	17983	23094452
22533032	77	4357, 4365	8825	13205	17985	23094453
22533033	79	-	8827	13207	17987	23094454
22533034	81	4361, 4369, 8707	8829	13209	17989, 22505	23094455
22533035	83, 85	4371	8831	13211, 13249, 13251, 13253	17991	23094456
22533036	87	4373	8833	13213	17993	23094457
22533037	89	4375	8835	13215, 17895	17995	23094458
22533038	91	4377, 4413, 4415, 4417	8837	13217, 13255, 17893	17997	23094459

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533039	93	4379	8839	13219, 13257	17999	23094460
22533040	95	4381, 4419, 4421	8841	13221, 13259	18001	23094461
22533041	97	4383	8843	13223, 13261	18003	23094462
22533042	99	4385	8845	13225	18005	23094463
22533043	101	4387	8847	13227	18007	23094464
22533044	103	4389	8849	13229	18009	23094465
22533045	105	4391	8851	13231	18011	23094466
22533046	107	4393	8853	13233	18013	23094467
22533047	109	4395	8855	13235, 17875, 17941	18015, 18039, 18041, 22631	23094468
22533048	111	4397	8857, 13023	13237	18017	23094469
22533049	113, 115, 117, 3949	4399	8859	13239	18019	23094470
22533050	119	-	8861	-	18021	-
22533051	121	4405	8863	13265	18023	23094473
22533053	123	4407	8865	13267	-	23094474
22533054	125	4409	8867	13269	18027	23094475
22533055	127	4411	8869	13271	18029	23094476
22533056	129	4423	8871	13273	18031	23094477
22533057	131	4425, 4427	8873	13275	18043	23094478
22533058	133	4429, 4431, 4433	8875	13277, 13279	18045, 18047, 18049, 18051	23094479
22533059	135	4435, 4437	8877	13281	18053	23094480
22533060	137	4439	8879	17759	18055	23094481
22533061	139	4441	8881	13283	18057	23094482
22533062	141	-	8883	-	18059	23094483
22533063	143	4443	8885	13285	18061	23094484
22533064	145	4445	8887	13287, 13289	18063, 18071	23094485
22533065	147	4447	8889	13291	18065, 18073	23094486
22533066	149	4449	8891	13293	18067, 18069, 18075	23094487
22533067	151	4451	8893	13295	18077	23094488
22533068	153	4453	8895	13297	18079	23094489
22533069	155	4455	8897	13299	18081	23094490
22533070	157	4457	8899	13301	18083	23094491
22533071	159	4461	8903	13155, 13305, 17925	18087	23094492
22533072	161	4463	8905	13307	18089	23094493
22533073	163	4465	8907	13309	18091	23094494
22533074	165	4467	8909	13311	18093	23094495
22533075	167	4469	8911	13313	18095	23094496
22533076,22534790	169, 3205	6299	12167	16801	21615	23094497,24413378
22533077	171	4471	8913	13315	18097	23094498
22533078	173	4473	8915	13317	18099	23094499
22533080	175	4475	8917	13319	18101	23094500
22533081	177	4477	8919	13321, 17737	18103	23094501
22533082	179	4481	8923	13325	18107	23094502
22533083	181	4483	8925	13327	18109	23094503
22533084	183	4485	8927	13329	18111	23094504
22533085	185	4487	8929, 8931	13331	18113	23094505
22533086	187	4489	8933	-	18115	23094506

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533088	189	4491	8935	-	18117	23094508
22533089	191	4493	8937	-	18119	23094509
22533090	193	4495	8939	13333, 13335	18121, 18123	23094510
22533091	195	4497	8941	13337	18125	23094511
22533092,22533093,22533257,22533270	199, 201, 503	4499, 4875	8943, 8945, 9475, 9497	13341, 13345, 13663, 13681, 13685	18127, 18135, 18437, 18451	23094512
22533094,22533258,22533260	203, 505	4501	8947, 9477	13343, 13347, 13665, 13687, 17743	18129, 18137	23094513
22533095	205	4503	8949	13349	18139	23094514
22533096	207	4505	8951	13339, 13351	18141	23094515
22533097	209	4507	8953	13353	18143	23094516
22533098	211	4509	8955	13355, 13357	18145	23094517
22533099	213	4511	8957	13359	18147	23094518
22533100	215	4513	8959	13361	18149	23094519
22533101	217	4515	8961	13363	18151, 18171	23094520
22533102	219	4517	8963	13365	18153	23094521
22533104	221	4519	8965	13367	18155	23094522
22533105	223	4521	8967	13369	18157	23094523
22533106	225	4523	8969	13371	18159	23094524
22533107	227	4525	8971	13373	18161	23094525
22533108	229	4527	8973	13375, 13385	18163	23094526
22533116	231	4549	8991	13399	18183	23094534
22533117	233	4551	8993	13401, 13403	18185	23094535
22533118	235	4553	8995	13405	18187	23094536
22533119	237	4555	8997	13407	18189	23094537
22533120	239	4557	8999	13413	18193	23094538
22533121	241	4559, 4561, 4563	9001	13415	18195	23094539
22533122	243	4565	9003	13417, 13443	18197	23094540
22533123	245	4567	9005	13419, 13445	18199	23094541
22533124	247	4569	9007	13421	18201	23094542
22533125	249, 251, 253, 4055	4571	9009	13423	18203	23094543
22533126	255	4573	9011	13425	18205	23094544
22533128	257	4577	9015	13429	18209	23094545
22533133	259, 261	4585	9023	13437	18217	23094549
22533134	263, 265, 267	4587	9025	13439	18219	23094550
22533139	269, 271	4591	9035	13451, 13487	18227	23094555
22533140	273	4593	9037	13453	18229	23094556
22533141,22533904,22534480	275, 1701, 2693, 4111	4595, 6149, 7287, 8771	9039, 10563, 11555	13455, 15055, 16017	18231, 19849, 20993, 20995	23095333,24413101
22533142	277	4597, 4599	9041	13457	22175	-
22533143	281, 285, 4051	4603	9045	13461	22173	23094558
-	283	4601	9043	13459	-	-
22533144	287, 4053	4605	9047	13463	22169, 22171	23094559
22533145	289, 4163	4607, 4609	9049	13465	22165, 22167	23094560
22533146	291	4611	9051	13467	22163	23094561
22533147	293	4613	9053	13469	22161	23094562
22533148	295, 297	4615	9055	13471	22159	23094563
22533149	299	4617	9057	13473, 17949	22157, 22647	23094564

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533150,22534271	301	4619	9059	13475	22155	23094565
22533151,22534154	303	4621, 6727, 6729, 6731	9061, 11015	13477, 13489, 15575	20309, 20311, 20313, 22153	23094566,23095668
22533152	305	4623	9063	13479	22151	23094567
22533154	307	4625	9065	13481	22149	23094568
22533155	309, 311	4627	9067	13483	22147	23094569
22533156	313	4629	9069	13485	22145	23094570
		4631	9071	13491		
22533158	315	4633	9073	13493	17955, 18239	23094572
22533159	317	4635	9075	13495	17957, 18241	23094573
22533160	319	4637	9077	13497	17959	23094574
22533161	321, 4077, 4101, 4113	4639, 8785	9079	13499	17961, 22541	23094575
22533162	323	4641	9081	13501, 13503	18243, 18253	23094576
22533163	325	4643	9087	13505	18245	23094577
22533164	327	4645	9089	13507	18247	23094578
22533165	329	4647	9091	13509	18249	23094579
-	331	4649	9093	13511	18251	23094580
22533167	333	4655, 4657	9095	13513	18255	23094581
22533168	335	4659	9097	13515, 13517	18257	23094582
22533169	337	4661	9099, 13081	13519	18259	23094583
22533170	339, 343	4663, 4729	9083, 9085, 9101	13521, 17817	18261, 18281, 18283, 18285	23094584
22533171	341, 345	4665	9103	13523	18263, 18287	23094585
22533172	347	4667	9105	13525, 13527	18265	23094586
22533173	349	4669	9107	13529	18267	23094587
22533174	351	4675	9115	13531	18269	23094591
22533175	353	4677	9117	-	18271	23094592
22533176	355	4679	9119	13533	18273	23094593
22533177	357	4681	9121	13535	18275	23094594
22533178	359	4683	9123	13537	18277	23094595
22533179	361	4685	9125	13539	18279	-
22533180	363	4687	9127	13541	-	23094596
22533181	365	4689	9129	13543	18289	23094597
22533182	367	4691	9131	13545	18291	23094598
22533183	369	4693	9133	13547, 13611, 13613	18293	23094599
22533186	371	4697	9137	13551	18297	23094601
22533187	373	4699	9139	13553	18299	23094602
22533188	375, 377	4701	9141	13555, 13615, 13617	18301	23094603
22533189	379	4703	9143	13557, 13619	18303	23094604
22533190,22533587,22534747,22534904	381, 3121	4705, 5537, 7833	9145, 12049	13559	18305, 19283	23094605,24413338
22533191	383	4707	9147	13561	18307	23094606
22533192	385	4709	9149	13563	18309	23094607
22533193	387	4711, 4731	9151	13565	18311	23094608
22533194	389	4713, 4733, 8679	9153	13567	18313	23094609
22533195	391, 393	4715	9155	13569	18315, 18319	23094610
22533196	395	4717	9157	13571	18317, 18321	-

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533197	397	4719	9159	13573, 13621, 13623, 13625	18323	23094611
22533198	399	4721	9161	13575, 13627, 13629	18325	23094612
22533199	401	4723	9163	13577, 13631	18327	23094613
22533200	403	4725	9165	13579, 13633, 13635	18329	23094614
22533201	405	4727, 4735	9167	13581	18331	23094615
22533202	407	4737, 4739	9169	13583	18333, 18693	23094616
22533203	409, 411	4741	9171	13585	18335, 18431	23094617
22533204,22533207	413	4745, 4749	9173	13587, 13637	18337	23094618
22533208	415	4747, 4751	9175	13589, 13639	18339	23094619
22533209	417	4753, 8715	9177	13591, 13641	18341	23094620
22533210	419	4755	9179	13593	18343	23094621
22533211	421	4757	9181	13595	18345	23094622
22533212	423, 425	4759	9183	13597	18347	23094623
22533213	427	4761	9185	13599	18349	23094624
22533214	429	4763, 8793	9187, 13129	13601, 13643	18351, 18433	23094625
22533215	431	4765	9189	13603	18353	23094626
22533216	433	4767	9191	13605	18355, 22597	23094627
22533217	435	4769	9193	13607	18357, 22595	23094628
22533218	437, 439	4771	9195	13609, 13645	18359	23094629
22533219	441	4773	9197	13647	18361	23094630
22533220	443	4775	9199	13649	18363, 18435, 22635	23094631
22533221	445	4777	9201	13651	18365	23094632
22533222	447	4779	9203	13653, 13655	18367	23094633
22533225	449	4787	9207	13659	18371	23094636
22533226	451	4789	9209	13661	18373	23094637
22533228	453	4791	9211	17729	18375	23094638
-	455	-	-	-	18377	23094639
22533230	457	-	9215	-	18379	23094640
22533231	459	4795	9217	17725	18381	23094641
22533234	461	-	9223	-	18385	23094643
22533235	463	-	9225	-	18387	23094644
22533236	465	-	9227	-	18389	23094645
22533238	467	-	9229	-	18391	23094646
22533239	469	-	9231	-	18393	23094647
22533240	471	-	9233	-	18395	23094648
22533241,22534994	473, 3519	8203	9235, 12471, 12939, 12941	17133	18397, 21891	23094649,24413519
22533242	475	4815	9241, 12547	-	18399, 21965, 22459	23094650,24413560
22533243	477	4817	9243	-	18401	23094651,23094652
22533244	479	4819	9245, 9247	-	18403	23094653
22533245	481	4821, 4823	9249, 12537, 12539, 12543	17327, 17331	18405, 18407, 21953, 21955, 21959, 21963	24413548,24413559
22533246	483	4825	9251	-	18409	23094654
22533247	485	4827	9253	-	18411	23094655
22533248	487	4829	9255	-	18413	-

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533249	489	4831	9257	13163	18415	-
22533251	491	4835	9261	13167, 13169	18419	23094656
22533252	493	4837, 4839, 4841, 6645	9263	13171	18421	23094657
22533253	495	4843	9265	13173	18423	23094658
22533254	497	4845	9267	13175	18425	23094659
22533255	499	4847	9269, 9271	13177	18427	23094660
22533256	501, 3975, 4215	4849	9273	13179, 17931	18429	23094661
22533261	507	-	9479	13667	18131	-
22533262	509	-	9481	13669, 13689	18133	-
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22533264	515	-	9485	-	18439	-
22533265	517	4865	9487	13671	18441	23094671
22533266	519	4867	9489	13673	18443	23094672
22533267	521	4869	9491	13675	18445	23094673
22533268	523	4871	9493	13677, 17877	18447	23094674
22533269	525	4873	9495	13679	18449	23094675
22533271	527	4877	9499	13683	18453	23094676
22533272	529	4879, 4881	9317, 9501	13691	18455, 18459	23094677
22533276	531	4885	9321	13695	18463	23094679
22533277	533	4887	9323	13697	18465, 18471	23094680
22533278	535	4889	9325	13699	18467	23094681
22533279	537	4891	9327	13701	18469	23094682
22533280	539	4893	9329, 9331	13703	18473, 22133	23094683
22533281	541	4895	9333	13705	18475	23094684
22533282	543	4897	9335	13707	18477	23094685
22533283	545	4899	9337	13709	18479, 18609, 18613	23094686
22533284	547	4901	9339	13711	18481, 18611, 18615	23094687
22533285	549	4903	9341	13713	18483, 18617	23094688
22533286	551	4905	9343	13715	18485	23094689
22533287	553	4907	9345	13717	18487	23094690
22533288	555	4909	9347	13719, 13781	18489	23094691
22533290	557	4911	9349	13721, 13783	18491	23094692
22533291	559	4913	9351	13723, 13785	18493	23094693
22533292	561, 563, 565, 4153, 4155	4915	9353, 12121	13725	18495, 21593, 22429	23094694
22533293	567	4917	9355	13727	18497	23094695
22533294	569, 571	4919	9357	13729	18499	23094696
22533295	573	4921	9359	13731	18501	23094697
22533296	575	4923, 4929	9361	13733, 13735, 13787, 13789	18503	23094698
22533297	577	4925, 4931	9363	13737	18505	23094699
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22533302	587	4941	9373	13747	18515	23094704
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22533310	603	4957	9387	13761	18529	23094711
22533311	605	4959	9389	13763	18531	23094712
22533312	607	4961	9391	13765, 13793	18533	23094713
22533313	609	4963	9393	13767	18535, 18537	23094714
22533314	611	4965	9395	13769	18539	23094715
22533315	613	4967	9397	13771	18541	23094716
22533317	615	4971	9401	13775	18545	23094717
22533318	617	4973	9403	13777, 13779	18547	23094718
22533319	619, 621	4975	9405	13795	18549	23094719
22533320	623	4977	9407	13797	18551	23094720
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22533323	627	4983	9413	13803	18557	23094722
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22533325	631	4985	9417	13807	18561	23094724
-	633	4987	9419	13809	18563	23094725
22533326	635	4989	9421	13811	18565	23094726
22533327	637	4991	9423	13813	18567	23094727
22533328	639	4993	9425	13815	18569	23094728
22533330	641	4995	9427	13817	18571	23094729
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22533332	645	4999	9431	13821	18575, 18621	23094731
22533333	647	5001	9433	13823, 13871	18577, 22673	23094732
22533334	649	5003	9435	13825, 13873	18579	23094733
22533335	651	5005	9437	13827, 13875	18581	23094734
22533336	653	5007	9439	13829, 13877, 13879, 13881	18583	23094735
22533337	655	5009, 5043	9441	13831	18585	23094736
22533338	657	5011	9443	13833	18587	23094737
22533339	659	5013	9445	13835	18589, 18623	23094738
22533340	661	5015	9447	13837	18591	23094739
22533341	663	5017	9449	13839	18593	23094740
22533342	665	5019	9451	13841	18595, 18625	23094741
22533343	667	5021	9453	13843	18597, 18627	23094742
22533344	669	5023	9455	13845	18599	23094743
22533345	671	5025	9457	13847	18601	23094744
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22533354	687	5041	9473	13863	18643	23094752
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22533356	691	5047	9277	13867	18649	23094754
22533358	693	5049, 5079	9279	13869, 13883	18651, 18653	23094755
22533359	695	5051	9281	13885, 13887	18655	23094756
22533360	697	5053	9283	13889	18657	23094757

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22533362	701, 4133, 4135	5057	9287	13893	18661	23094759
22533363	703	5059, 5081	9289	13895, 17153	18663	23094760
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22533365	707	5063	9293	13899	18667	23094762
22533366	709	5065	9295	13901	18669	23094763
22533367	711, 723, 4301	5067	9297	13903	18671, 18695	23094764
22533368	713, 725, 4299	5069	9299	13905	18673, 18697	23094765
22533369	715, 727, 4297	5071, 5087	9301	13907	18675, 18699, 18701	23094766
22533370,22534818	717, 729, 3261, 3263, 4165, 4167, 4295	5073, 5089, 5091, 7953	9303, 12225	13909, 16863, 16893, 17849	18677, 18703, 21667	23094767,24413404
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22533373	721, 733, 4291	5095	9307	13913	18681	23094769
22533374	735	5097	9309	13915	18683	23094770
22533375	737	5099, 5105	9311	13917	18685	23094771
22533376	739	5101, 5107, 5109	9313	13919	18687	23094772
22533377	741	5111	9315	13921	18705	23094773
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22533382	749	5121	9513	13931	18717	23094778
22533383	751	5123	9515	13933	18719	23094779
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22533385	755	5127	9519	13937	18723	23094781
22533386	757	5129	9521	13939	18725	23094782
22533387	759	5131	9523	13941	18727	23094783
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22533392	767	5141	9533	13951	18737	23094837
22533393	769	5143	9535	13953	18739	23094838
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22533396	775	5153	9541	13959	18745	23094841
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22533404	793	5171	9555	13973	18761	23094848
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22533407	799	5177	9561	13979	18767, 22527	23094851
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22533412	809	5187	9571	13989, 13991, 14011	18777	23094856
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22533414	813	5191	9575, 9577	13995	18781	23094858
22533415	815	5193	9579	13997	18785	23094859
22533416	817	5195	9581	13999	18787	23094860
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22533418	821	5199	9585	14005	18793	23094862
22533420	823	4651	9589	14007	18797	23094863
22533421	825	4653, 5209	9591	14009	18799	23094864
22533426	827	5217	9599	14019	18809	23094868
22533422	829	5211	9593	14013	18801	23094865
22533427	831	5219	9601	14021	18811	23094869
22533428	833	5221	9603	14023, 14025	18813	23094870
22533429	835	5223	9605	14027	18815	23094871
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22533431	839	4853	9631	14105	18819	23094873
22533432	841, 843	4855, 8777	9633	14107	18821	23094874
22533433	845	4857	9635	14109	18823	23094875
22533434	847	4859	9637	14111	18825	23094876
22533435	849	4861, 4863, 5225	9639	14113, 14115, 14117, 14159, 14161	18827, 18867, 18869	23094877
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22533438	853	5229	9643	14121	18831	23094879
22533439	855	5231	9645	14123	18833	23094880
22533440	857	5233	9647	14125	18835	23094881
22533441	859	5235	9649	14127	18837	23094882
22533442	861	5237	9651	14129	18839	23094883
22533443	863	5239	9653	14135	18841	23094884
22533444	865	5241	9655, 9657	14137	18843, 18845	23094885
22533445	867	5243	9659	14139	18847	23094886
22533446	869	5245	9661, 9663	14141	18849	23094887
22533447	871	5247	9665	14143	18851	23094888
22533448	873	5249, 5251	9667, 9669	14145, 14147	18853, 18855	23094889
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22533463	913	5287	9705	14187, 17695	18933	23094915
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22533469	925	5305	9719	14191	18949	23094921
22533470	927	5307	9721	14193	18951	23094922
22533471	929	5309	9723	14195	18953	23094923,23095104,23095466
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22533478	945	5323	9737	14209, 14269, 14271	18969	23094930
22533479	947	5325	9739	14211	18971	23094931
22533480	949	5327	9741	14213, 14273	18973	23094932
22533481	951	5329	9743	14215	18975	23094933
22533482	953	5331	9745	14217	18977	23094934
22533483	955	5333	9747	14219	18979	23094935
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22533486	961	5339	9753	14225	18985	23094937
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22533491	973	5349	9763	14235	18995	23094942
22533492	975	5351	9765	14237	18997	23094943
22533493	977	5353	9767	14239, 14275, 14277	18999	23094944
22533494	979	5355	9769	14241	19001	23094945
22533495	981	5357	9771	14243	19003	23094946
22533496	983	5359	9773	14245	19005	23094947
22533497	985	5361	9775	14247	19007	23094948
22533498	987	5363	9777	14249	19009	23094949
22533499	989	5365, 5371	9779	14251	19011	23094950
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22533501	993, 995	5373	9781	14253	19013, 19029	23094952
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22533504	999, 1001	5377	9785	14257, 14279, 14281, 14283, 14285	19017	23094954
22533505	1003	5379	9787	14259	19019	23094955
22533506	1005	5381	9789	14261	19021	23094956
22533507	1007	5383	9791	14263	19023	23094957
22533509	1009	8635	9793	14265	19031	23094958
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22533512	1013	5387	9799, 9801	14291	19037	23094962
22533513	1015	5389	9803	14293	19039	23094963
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22533517	1023	5397	9811	14301	19047	23094967
22533518	1025	5399	9813	14303	19049	23094968
22533519	1027	5401	9815	14305	19051	23094969
22533520	1029	5403	9817	14307	19053	23094970
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22533522	1033	5407	9823	14311	19057	23094972
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22533535	1057	5433	9845	14333, 14335	19191	23094984
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22533540	1069	5445	9857	14351	19203	23094990
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22533542	1073	5449	9861	14355, 14357, 14359	19207	23094992
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22533545	1079	5453	9865	14363	19211	23094994
22533546	1081	5455	9867	14365	19213	23094995
22533547	1083, 4257	5457	9869	14367, 14443	19215	23094996
22533548	1085, 1087, 4259	5459	9871	14369, 14445	19217	23094997
22533550	1089, 1093	5461	9873	14371	19219	23094998
22533551	1091, 1095	5463	9875	14373	19221	23094999
22533552	1097	5465	9877	14375	19223	23095000
22533553	1099	5467	9879	14377	19225	23095001
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22533555	1103, 1105	5471	9883, 12785	14381	19231	23095003
22533556	1107	5473	9885	14383	19233	23095004
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22533645	1165	5669	9951	14441	19315	23095025
22533646	1167	5671	9953	14455	19317	23095026
22533647	1169	5673	9955	14457	19319, 19321	23095027
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22533809	1497	5953	10385	14859	19649, 19651	23095246
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22533818	1513	5969	10401	14875	19669	23095254
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22533826	1517	5987	10415, 10417	14901	19683	23095261
22533827	1519	5989	10419	14903	19685	23095262
22533828	1521	5991	10421	14905, 14951	19687, 19689	23095263
22533829	1523	5993	10423	14907	19691	23095264
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22533833	1527	5997, 5999	10427	14911	19695	23095266
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22533875	1629	6089	10509	14999	19789	23095308
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22533880	1641	6097	10517	15007	19797	23095312
22533881	1643	6099	10519	15009	19799	23095313
22533882	1645	6101	10521	15011	19801, 19813, 19815	23095314
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22533887	1657	6111	10529	15019	19809	23095318
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22533889	1661	6115, 6119	10533	15023	19821	23095320
22533890	1663	6117, 6121	10535	15025, 15027	19823	23095321
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22533895	1683	6133	10547	15037	19833	23095325
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22533898	1687	6137	10551	15041, 15085	19837	23095327
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22533903	1699	6147	10561	15051	19847	23095332
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22533907	1705	6155	10569, 10573	15061	19855	23095336
22533908	1707, 1709	6157	10575	15063	19857	23095337
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22533914	1719	6169	10587	15075	19869	23095343
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22533916	1725	6173	10591	15079, 15089	19873	23095345
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22533918	1729	6177	10595	15093	19877	23095347
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22533928	1735	6187	10601	15099	19883	23095371
22533929	1737	6189, 6225	10603, 10605	15101, 15103	19885	23095372
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22533962	1761	6251	10633	15129	19913	23095385
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22533968	1769	6259	10641	15137	19921	23095388
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22533971	1775	6265	10647	15145	19927	23095391
22533972	1777	6267	10649	15147	19929	23095392
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22533980	1791	6283	10665	15163, 15167	19945	23095400
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22533984	1799	6291	10673	15173	19955	23095404
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22533995	1823	6341	10695, 10697	15245	19977	23095413
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22534010	1851	6371	10725	15281	20009, 20043	23095475
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22534012	1855	6375	10729	15285	20013	23095477
22534013	1857	6377	10731	15287	20015	23095478
22534014	1859	6379	10733	15289	20017, 20045	23095479
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22534118	2057	6647	10945	15491	20223	23095634
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22534408	2579	7153	11411	16035	20857	24413030
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22534548	2791	7431	11675	16295	21113	24413158
22534549	2793	7433	11677	16297	21115	24413159
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22534724	3087	7781	12009	16669	21475, 21481	24413314
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22534726	3091	7783, 7787	12013	16673	21485	24413316
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22534774	3177, 3179, 3683, 4067	7885, 7893	12103	16765	21569	24413364
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-	-	-	-	17621	22281	-

TABLE III — Unique coding sequences

2603V/R	22533205, 22533568, 22533571, 22533574, 22533576, 22533597, 22533706, 22533776, 22533967, 22534356, 22534614, 22534650, 22534875, 22534876, 22534877, 22534880, 22534882, 22534885, 22534886, 22534887, 22534889, 22534891, 22534892, 22534894, 22534895, 22534898, 22534900, 22534901, 22534903, 22534906, 22534907, 22534908, 22534911, 22534912, 22534915, 22534916, 22534917, 22534919, 22534924, 22535035, 22535159, 22535160, 22535163, 22535164, 22535165, 22535166, 22535167
18RS21	1749, 3623, 3981, 3985, 3989, 3991, 3999, 4057, 4059, 4081, 4203, 4205, 4207
515	4359, 4367, 4803, 4805, 4807, 4809, 4811, 4813, 5289, 5295, 5493, 5497, 5499, 5505, 5507, 5511, 5513, 5515, 5563, 6887, 8267, 8269, 8647, 8683, 8685, 8695, 8725, 8727, 8783, 8789, 8797
CJB11	9213, 9237, 9239, 10005, 10681, 10809, 10811, 12795, 12823, 12827, 12949, 12951, 12967, 12997, 13043, 13047, 13087, 13091, 13093, 13105
COH1	13153, 13157, 13159, 13241, 13243, 13263, 15187, 15201, 15227, 15819, 15821, 15823, 15825, 15827, 15829, 16015, 16019, 16021, 16023, 16539, 16561, 16565, 17319, 17321, 17693, 17705, 17707, 17719, 17753, 17785, 17797, 17819, 17897, 17921, 17933
H36B	18691, 19065, 19067, 19071, 19073, 19075, 19085, 19087, 19089, 19091, 19093, 19095, 19099, 19103, 19111, 19113, 19115, 19117, 19119, 19123, 19125, 19127, 19129, 19131, 19133, 19135, 19139, 19141, 19143, 19145, 19149, 19165, 20099, 20401, 22529, 22531, 22533, 22535, 22545, 22547, 22557, 22559, 22561, 22565, 22571, 22585, 22589, 22621, 22641, 22667, 22671, 22679, 22695, 22699, 22705, 22715, 22717, 22721, 22723, 22725, 22733
NEM316	23094662, 23094664, 23094667, 23094668, 23094669, 23094670, 23094794, 23094796, 23094797, 23094798, 23094799, 23094802, 23094803, 23094806, 23094808, 23094809, 23094810, 23094811, 23094812, 23094813, 23094814, 23094815, 23094816, 23094818, 23094820, 23094821, 23094822, 23094823, 23094824, 23094825, 23094827, 23094828, 23094829, 23094830, 23094831, 23094832, 23094833, 23094835, 23095107, 23095109, 23095110, 23095111, 23095112, 23095115, 23095116, 23095119, 23095121, 23095122, 23095123, 23095124, 23095125, 23095126, 23095127, 23095128, 23095129, 23095131, 23095133, 23095134, 23095135, 23095136, 23095137, 23095138, 23095140, 23095141, 23095142, 23095143, 23095144, 23095145, 23095146, 23095148, 23095423, 23095425, 23095426, 23095427, 23095428, 23095429, 23095430, 23095431, 23095433, 23095434, 23095435, 23095436, 23095437, 23095438, 23095440, 23095442, 23095443, 23095444, 23095445, 23095446, 23095447, 23095448, 23095449, 23095450, 23095452, 23095455, 23095456, 23095459, 23095460, 23095461, 23095462, 23095463, 23095569, 23095570, 23095571, 23095572, 23095573, 23095574, 23095575, 23095576, 23095577, 23095578, 23095579, 23095580, 23095581, 23095582, 23095583, 23095584, 23095585, 23095586, 23095587, 23095614, 23095615, 23095617, 23095623, 23095624, 23095626, 23095627, 24412909, 24412910, 24412911, 24412912, 24412921, 24412922, 24412923, 24412924, 24413555

TABLE IV – Sequences without homologs in 2603V/R or NEM316

18RS21	283, 1123, 1127, 1129, 1273, 1275, 1731, 2321, 2367, 3839, 3841, 3843, 3845, 3917, 4047, 4099, 4131, 4139, 4141, 4159, 4181, 4219, 4221, 4223, 4225, 4227, 4229, 4231, 4233, 4235, 4237, 4239, 4241, 4243, 4245, 4247, 4249, 4251, 4253, 4255, 4263, 4265, 4267, 4269, 4271, 4273, 4275, 4277, 4287
515	4459, 4479, 4601, 4793, 4797, 4801, 5285, 5291, 5293, 5559, 5561, 5565, 5567, 5569, 5573, 5575, 5577, 5579, 5581, 5585, 5587, 5589, 5591, 5593, 5595, 5621, 5625, 5627, 5629, 5687, 5753, 6179, 6181, 6209, 6211, 6821, 6957, 8315, 8317, 8319, 8321, 8331, 8333, 8335, 8665, 8667, 8673, 8791
CJB11	8901, 8921, 9043, 9897, 9911, 9915, 9917, 9919, 9981, 9985, 10009, 10017, 10019, 10097, 10143, 10145, 10185, 10597, 10799, 10827, 10831, 11227, 12117, 12119, 12125, 12127, 12129, 12131, 12133, 12135, 12137, 12139, 12141, 12143, 12145, 12147, 12149, 12481, 12551, 12605, 12793, 12797, 12799, 12803, 12805, 12807, 12809, 12813, 12815, 12817, 12819, 12821, 12831, 12929, 12953, 13045
COH1	13161, 13303, 13323, 13459, 14397, 14401, 14403, 14405, 14507, 14557, 14559, 14619, 15211, 15375, 15785, 15803, 15817, 16085, 16093, 17143, 17213, 17281, 17283, 17285, 17287, 17289, 17291, 17389, 17605, 17607, 17611, 17615, 17617, 17619, 17621, 17623, 17625, 17627, 17629, 17631, 17641, 17643, 17645, 17647, 17691, 17721, 17723, 17727, 17805, 17825, 17881, 17929, 17939, 17947
H36B	18085, 18105, 18237, 18873, 18893, 18895, 18931, 19255, 19259, 19261, 19263, 19333, 19381, 19383, 19385, 19429, 19879, 20105, 20109, 20367, 20405, 20537, 20595, 21587, 21589, 21599, 21903, 21951, 22031, 22135, 22269, 22271, 22275, 22277, 22279, 22281, 22283, 22285, 22287, 22293, 22299, 22301, 22433, 22435, 22437, 22439, 22441, 22443, 22445, 22447, 22449, 22451, 22453, 22455, 22457, 22467, 22507, 22509, 22643

TABLE V — 'Core' coding sequences

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22535220	1,3919	8615	12909	14061	22383	24413708
22535221	3	8617	12911	14063	22385,22427	24413709
22535222	5	8619,8703	12913	14065	22387	24413710
22535223	7	8621	12915	14067	22389	24413711
22535224	9	8623	12917	14069	22391	24413712
22535225	11	8625	12919	14071	22393	24413713
22533003	13	8627	12921	14073	22395	23094427
22533004	15	4303,8629	12923	14075	22397	23094428
22533005	17	4305,8631	12925,12927	14077	22399	23094429
22533007	21	4309	9607	14081	22403	23094431
22533008	23	4311	9609	14083	22405	23094432
22533009	25	4313	9611	14085	22407	23094433
22533010	27,29	4315	9613	14087	22409,22663	23094434
22533012	31	4317	9615	14089	22413	23094435
22533013	33	4319	9617	14091	22415	23094436
22533014	35	4321	9619	14093	22417	23094437
22533015	37	4323	9621	13135,14095	22419	23094438
22533016,22534732	39	4325	9623,12021	13137,14097,16681	21493,22421	23094439
22533017	41	4327	9625	13139,13143,14099	22423	23094440
22533018	43	4329	9627	13145,13147,13149,14101	22425,22623	23094441
22533020	45,47,49,51	4331	8801	13181	17963	23094442
22533021	53	4333,4335	8803	13183	17965	23094443
22533022	55	4337	8805	13185	17967	23094444
22533023	57	4339,4341	8807	13187,13189	17969	23094445
22533024	59	4343	8809	13191	17971	23094446
22533025	61	4345	8811	13193	17973	23094447
22533026	63	4347	8813,8815	13195	17975	23094448
22533027	65	4349	8817	13197	17977,18033,18035	23094449
22533028	67	4351	8819	13199,13245,13247,17811,17821,17859	17979,18037,22555	23094450
22533029	69,71,3965,4017,4061	4353	8821	13201,17803,17891	17981	23094451
22533030	73,75,3963	4355	8823	13203	17983	23094452
22533032	77	4357,4365	8825	13205	17985	23094453
22533034	81	4361,4369,8707	8829	13209	17989,22505	23094455
22533035	83,85	4371	8831	13211,13249,13251,13253	17991	23094456
22533036	87	4373	8833	13213	17993	23094457
22533037	89	4375	8835	13215,17895	17995	23094458
22533038	91	4377,4413,4415,4417	8837	13217,13255,17893	17997	23094459
22533039	93	4379	8839	13219,13257	17999	23094460
22533040	95	4381,4419,44	8841	13221,13259	18001	23094461

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
		21				
22533041	97	4383	8843	13223,13261	18003	23094462
22533042	99	4385	8845	13225	18005	23094463
22533043	101	4387	8847	13227	18007	23094464
22533044	103	4389	8849	13229	18009	23094465
22533045	105	4391	8851	13231	18011	23094466
22533046	107	4393	8853	13233	18013	23094467
22533047	109	4395	8855	13235,17875, 17941	18015,18039, 18041,22631	23094468
22533048	111	4397	8857,13023	13237	18017	23094469
22533049	113,115,117,3 949	4399	8859	13239	18019	23094470
22533051	121	4405	8863	13265	18023	23094473
22533054	125	4409	8867	13269	18027	23094475
22533055	127	4411	8869	13271	18029	23094476
22533056	129	4423	8871	13273	18031	23094477
22533057	131	4425,4427	8873	13275	18043	23094478
22533058	133	4429,4431,44 33	8875	13277,13279	18045,18047, 18049,18051	23094479
22533059	135	4435,4437	8877	13281	18053	23094480
22533060	137	4439	8879	17759	18055	23094481
22533061	139	4441	8881	13283	18057	23094482
22533063	143	4443	8885	13285	18061	23094484
22533064	145	4445	8887	13287,13289	18063,18071	23094485
22533065	147	4447	8889	13291	18065,18073	23094486
22533066	149	4449	8891	13293	18067,18069, 18075	23094487
22533067	151	4451	8893	13295	18077	23094488
22533068	153	4453	8895	13297	18079	23094489
22533069	155	4455	8897	13299	18081	23094490
22533070	157	4457	8899	13301	18083	23094491
22533071	159	4461	8903	13155,13305, 17925	18087	23094492
22533072	161	4463	8905	13307	18089	23094493
22533073	163	4465	8907	13309	18091	23094494
22533074	165	4467	8909	13311	18093	23094495
22533075	167	4469	8911	13313	18095	23094496
22533076,225 34790	169,3205	6299	12167	16801	21615	23094497,244 13378
22533077	171	4471	8913	13315	18097	23094498
22533078	173	4473	8915	13317	18099	23094499
22533080	175	4475	8917	13319	18101	23094500
22533081	177	4477	8919	13321,17737	18103	23094501
22533082	179	4481	8923	13325	18107	23094502
22533083	181	4483	8925	13327	18109	23094503
22533084	183	4485	8927	13329	18111	23094504
22533085	185	4487	8929,8931	13331	18113	23094505
22533090	193	4495	8939	13333,13335	18121,18123	23094510
22533091	195	4497	8941	13337	18125	23094511
22533092,225	199,201,503	4499,4875	8943,8945,94	13341,13345,	18127,18135,	23094512

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
33093,22533257,22533270			75,9497	13663,13681,13685	18437,18451	
22533094,22533258,22533260	203,505	4501	8947,9477	13343,13347,13665,13687,17743	18129,18137	23094513
22533095	205	4503	8949	13349	18139	23094514
22533096	207	4505	8951	13339,13351	18141	23094515
22533097	209	4507	8953	13353	18143	23094516
22533098	211	4509	8955	13355,13357	18145	23094517
22533099	213	4511	8957	13359	18147	23094518
22533100	215	4513	8959	13361	18149	23094519
22533101	217	4515	8961	13363	18151,18171	23094520
22533102	219	4517	8963	13365	18153	23094521
22533104	221	4519	8965	13367	18155	23094522
22533105	223	4521	8967	13369	18157	23094523
22533106	225	4523	8969	13371	18159	23094524
22533107	227	4525	8971	13373	18161	23094525
22533108	229	4527	8973	13375,13385	18163	23094526
22533116	231	4549	8991	13399	18183	23094534
22533117	233	4551	8993	13401,13403	18185	23094535
22533118	235	4553	8995	13405	18187	23094536
22533119	237	4555	8997	13407	18189	23094537
22533120	239	4557	8999	13413	18193	23094538
22533121	241	4559,4561,4563	9001	13415	18195	23094539
22533122	243	4565	9003	13417,13443	18197	23094540
22533123	245	4567	9005	13419,13445	18199	23094541
22533124	247	4569	9007	13421	18201	23094542
22533125	249,251,253,4055	4571	9009	13423	18203	23094543
22533126	255	4573	9011	13425	18205	23094544
22533128	257	4577	9015	13429	18209	23094545
22533133	259,261	4585	9023	13437	18217	23094549
22533134	263,265,267	4587	9025	13439	18219	23094550
22533139	269,271	4591	9035	13451,13487	18227	23094555
22533140	273	4593	9037	13453	18229	23094556
22533141,22533904,22534480	275,1701,2693,4111	4595,6149,7287,8771	9039,10563,11555	13455,15055,16017	18231,19849,20993,20995	23095333,24413101
22533143	281,285,4051	4603	9045	13461	22173	23094558
22533144	287,4053	4605	9047	13463	22169,22171	23094559
22533145	289,4163	4607,4609	9049	13465	22165,22167	23094560
22533146	291	4611	9051	13467	22163	23094561
22533147	293	4613	9053	13469	22161	23094562
22533148	295,297	4615	9055	13471	22159	23094563
22533149	299	4617	9057	13473,17949	22157,22647	23094564
22533150,22534271	301	4619	9059	13475	22155	23094565
22533151,22534154	303	4621,6727,6729,6731	9061,11015	13477,13489,15575	20309,20311,20313,22153	23094566,23095668

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533152	305	4623	9063	13479	22151	23094567
22533154	307	4625	9065	13481	22149	23094568
22533155	309,311	4627	9067	13483	22147	23094569
22533156	313	4629	9069	13485	22145	23094570
22533158	315	4633	9073	13493	17955,18239	23094572
22533159	317	4635	9075	13495	17957,18241	23094573
22533160	319	4637	9077	13497	17959	23094574
22533161	321,4077,4101,4113	4639,8785	9079	13499	17961,22541	23094575
22533162	323	4641	9081	13501,13503	18243,18253	23094576
22533163	325	4643	9087	13505	18245	23094577
22533164	327	4645	9089	13507	18247	23094578
22533165	329	4647	9091	13509	18249	23094579
22533167	333	4655,4657	9095	13513	18255	23094581
22533168	335	4659	9097	13515,13517	18257	23094582
22533169	337	4661	9099,13081	13519	18259	23094583
22533170	339,343	4663,4729	9083,9085,9101	13521,17817	18261,18281,18283,18285	23094584
22533171	341,345	4665	9103	13523	18263,18287	23094585
22533172	347	4667	9105	13525,13527	18265	23094586
22533173	349	4669	9107	13529	18267	23094587
22533174	351	4675	9115	13531	18269	23094591
22533176	355	4679	9119	13533	18273	23094593
22533177	357	4681	9121	13535	18275	23094594
22533178	359	4683	9123	13537	18277	23094595
22533181	365	4689	9129	13543	18289	23094597
22533182	367	4691	9131	13545	18291	23094598
22533183	369	4693	9133	13547,13611,13613	18293	23094599
22533186	371	4697	9137	13551	18297	23094601
22533187	373	4699	9139	13553	18299	23094602
22533188	375,377	4701	9141	13555,13615,13617	18301	23094603
22533189	379	4703	9143	13557,13619	18303	23094604
22533190,22533587,22534747,22534904	381,3121	4705,5537,7833	9145,12049	13559	18305,19283	23094605,24413338
22533191	383	4707	9147	13561	18307	23094606
22533192	385	4709	9149	13563	18309	23094607
22533193	387	4711,4731	9151	13565	18311	23094608
22533194	389	4713,4733,8679	9153	13567	18313	23094609
22533195	391,393	4715	9155	13569	18315,18319	23094610
22533197	397	4719	9159	13573,13621,13623,13625	18323	23094611
22533198	399	4721	9161	13575,13627,13629	18325	23094612
22533199	401	4723	9163	13577,13631	18327	23094613
22533200	403	4725	9165	13579,13633,13635	18329	23094614

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533201	405	4727,4735	9167	13581	18331	23094615
22533202	407	4737,4739	9169	13583	18333,18693	23094616
22533203	409,411	4741	9171	13585	18335,18431	23094617
22533204,22533207	413	4745,4749	9173	13587,13637	18337	23094618
22533208	415	4747,4751	9175	13589,13639	18339	23094619
22533209	417	4753,8715	9177	13591,13641	18341	23094620
22533210	419	4755	9179	13593	18343	23094621
22533211	421	4757	9181	13595	18345	23094622
22533212	423,425	4759	9183	13597	18347	23094623
22533213	427	4761	9185	13599	18349	23094624
22533214	429	4763,8793	9187,13129	13601,13643	18351,18433	23094625
22533215	431	4765	9189	13603	18353	23094626
22533216	433	4767	9191	13605	18355,22597	23094627
22533217	435	4769	9193	13607	18357,22595	23094628
22533218	437,439	4771	9195	13609,13645	18359	23094629
22533219	441	4773	9197	13647	18361	23094630
22533220	443	4775	9199	13649	18363,18435,22635	23094631
22533221	445	4777	9201	13651	18365	23094632
22533222	447	4779	9203	13653,13655	18367	23094633
22533225	449	4787	9207	13659	18371	23094636
22533226	451	4789	9209	13661	18373	23094637
22533228	453	4791	9211	17729	18375	23094638
22533231	459	4795	9217	17725	18381	23094641
22533241,22534994	473,3519	8203	9235,12471,12939,12941	17133	18397,21891	23094649,24413519
22533245	481	4821,4823	9249,12537,12539,12543	17327,17331	18405,18407,21953,21955,21959,21963	24413548,24413559
22533251	491	4835	9261	13167,13169	18419	23094656
22533252	493	4837,4839,4841,6645	9263	13171	18421	23094657
22533253	495	4843	9265	13173	18423	23094658
22533254	497	4845	9267	13175	18425	23094659
22533255	499	4847	9269,9271	13177	18427	23094660
22533256	501,3975,4215	4849	9273	13179,17931	18429	23094661
22533265	517	4865	9487	13671	18441	23094671
22533266	519	4867	9489	13673	18443	23094672
22533267	521	4869	9491	13675	18445	23094673
22533268	523	4871	9493	13677,17877	18447	23094674
22533269	525	4873	9495	13679	18449	23094675
22533271	527	4877	9499	13683	18453	23094676
22533272	529	4879,4881	9317,9501	13691	18455,18459	23094677
22533276	531	4885	9321	13695	18463	23094679
22533277	533	4887	9323	13697	18465,18471	23094680
22533278	535	4889	9325	13699	18467	23094681
22533279	537	4891	9327	13701	18469	23094682
22533280	539	4893	9329,9331	13703	18473,22133	23094683

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533281	541	4895	9333	13705	18475	23094684
22533282	543	4897	9335	13707	18477	23094685
22533283	545	4899	9337	13709	18479,18609, 18613	23094686
22533284	547	4901	9339	13711	18481,18611, 18615	23094687
22533285	549	4903	9341	13713	18483,18617	23094688
22533286	551	4905	9343	13715	18485	23094689
22533287	553	4907	9345	13717	18487	23094690
22533288	555	4909	9347	13719,13781	18489	23094691
22533290	557	4911	9349	13721,13783	18491	23094692
22533291	559	4913	9351	13723,13785	18493	23094693
22533292	561,563,565,4153,4155	4915	9353,12121	13725	18495,21593, 22429	23094694
22533293	567	4917	9355	13727	18497	23094695
22533294	569,571	4919	9357	13729	18499	23094696
22533295	573	4921	9359	13731	18501	23094697
22533296	575	4923,4929	9361	13733,13735, 13787,13789	18503	23094698
22533297	577	4925,4931	9363	13737	18505	23094699
22533298	579	4927,4933	9365	13739	18507	23094700
22533299	581	4935	9367	13741	18509	23094701
22533300	583	4937	9369	13743	18511	23094702
22533301	585	4939	9371	13745,13791	18513	23094703
22533302	587	4941	9373	13747	18515	23094704
22533303	589,591	4943,4945,8721	9375	13749	18517	23094705
22533304	593	4947	9377	13751	18519	23094706
22533305	595	4949	9379	13753	18521	23094707
22533306	597	4951	9381	13755	18523	23094708
22533308	599	4953	9383	13757	18525	23094709
22533309	601	4955	9385	13759	18527	23094710
22533310	603	4957	9387	13761	18529	23094711
22533311	605	4959	9389	13763	18531	23094712
22533312	607	4961	9391	13765,13793	18533	23094713
22533313	609	4963	9393	13767	18535,18537	23094714
22533314	611	4965	9395	13769	18539	23094715
22533315	613	4967	9397	13771	18541	23094716
22533317	615	4971	9401	13775	18545	23094717
22533318	617	4973	9403	13777,13779	18547	23094718
22533319	619,621	4975	9405	13795	18549	23094719
22533320	623	4977	9407	13797	18551	23094720
22533321	625	4979	9409	13799	18553,18619	23094721
22533323	627	4983	9413	13803	18557	23094722
22533325	631	4985	9417	13807	18561	23094724
22533326	635	4989	9421	13811	18565	23094726
22533327	637	4991	9423	13813	18567	23094727
22533328	639	4993	9425	13815	18569	23094728
22533330	641	4995	9427	13817	18571	23094729
22533331	643	4997	9429	13819	18573	23094730

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22533332	645	4999	9431	13821	18575,18621	23094731
22533333	647	5001	9433	13823,13871	18577,22673	23094732
22533334	649	5003	9435	13825,13873	18579	23094733
22533335	651	5005	9437	13827,13875	18581	23094734
22533336	653	5007	9439	13829,13877, 13879,13881	18583	23094735
22533337	655	5009,5043	9441	13831	18585	23094736
22533338	657	5011	9443	13833	18587	23094737
22533339	659	5013	9445	13835	18589,18623	23094738
22533340	661	5015	9447	13837	18591	23094739
22533341	663	5017	9449	13839	18593	23094740
22533342	665	5019	9451	13841	18595,18625	23094741
22533343	667	5021	9453	13843	18597,18627	23094742
22533344	669	5023	9455	13845	18599	23094743
22533345	671	5025	9457	13847	18601	23094744
22533346	673	5027	9459	13849	18603	23094745
22533347	675	5029	9461	13851	18605,18629	23094746
22533348	677	5031	9463	13853,17831	18607,18631, 18633	23094747
22533350	679	5033	9465,9503	13855	18635,18645	23094748
22533351	681	5035	9467	13857	18637	23094749
22533352	683	5037	9469	13859,17911	18639	23094750
22533353	685	5039	9471	13861	18641	23094751
22533354	687	5041	9473	13863	18643	23094752
22533355	689,3921	5045	9275	13865	18647	23094753
22533356	691	5047	9277	13867	18649	23094754
22533358	693	5049,5079	9279	13869,13883	18651,18653	23094755
22533359	695	5051	9281	13885,13887	18655	23094756
22533360	697	5053	9283	13889	18657	23094757
22533361	699	5055	9285	13891	18659	23094758
22533362	701,4133,4135	5057	9287	13893	18661	23094759
22533363	703	5059,5081	9289	13895,17153	18663	23094760
22533364	705	5061,5083	9291	13897	18665	23094761
22533365	707	5063	9293	13899	18667	23094762
22533366	709	5065	9295	13901	18669	23094763
22533367	711,723,4301	5067	9297	13903	18671,18695	23094764
22533368	713,725,4299	5069	9299	13905	18673,18697	23094765
22533369	715,727,4297	5071,5087	9301	13907	18675,18699, 18701	23094766
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22533373	721,733,4291	5095	9307	13913	18681	23094769
22533374	735	5097	9309	13915	18683	23094770
22533375	737	5099,5105	9311	13917	18685	23094771
22533376	739	5101,5107,5109	9313	13919	18687	23094772
22533377	741	5111	9315	13921	18705	23094773

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22533380	745	5117,5149	9509	13927	18713	23094776
22533381	747	5119,5151	9511	13929	18715	23094777
22533382	749	5121	9513	13931	18717	23094778
22533383	751	5123	9515	13933	18719	23094779
22533384	753	5125	9517	13935	18721	23094780
22533385	755	5127	9519	13937	18723	23094781
22533386	757	5129	9521	13939	18725	23094782
22533387	759	5131	9523	13941	18727	23094783
22533388	761	5133	9525	13943	18729	23094785
22533390	763	5137	9529	13947	18733	23094786
22533391	765	5139	9531	13949	18735	23094787
22533392	767	5141	9533	13951	18737	23094837
22533393	769	5143	9535	13953	18739	23094838
22533394	771	5145	9537	13955	18741	23094839
22533395	773	5147	9539	13957	18743	23094840
22533396	775	5153	9541	13959	18745	23094841
22533397	777	5155	9543	13961	18747	23094842
22533398	779,781,783	5157,5159,5161	9545	13963	18749,18751	23094843
22533400	785	5163	9547	13965	18753	23094844
22533401	787	5165	9549	13967	18755	23094845
22533402	789	5167,5201	9551	13969	18757	23094846
22533403	791,2369,4147,4149,4179	5169	9553	13971	18759,18783,20597	23094847
22533404	793	5171	9555	13973	18761	23094848
22533405	795	5173	9557	13975	18763	23094849
22533406	797	5175	9559	13977	18765	23094850
22533407	799	5177	9561	13979	18767,22527	23094851
22533408	801	5179	9563	13981	18769,22525	23094852
22533409	803	5181	9565	13983	18771	23094853
22533410	805	5183,5203,5205	9567	13985,17809	18773	23094854
22533411	807	5185	9569	13987	18775	23094855
22533412	809	5187	9571	13989,13991,14011	18777	23094856
22533413,22534328	811	5189	9573	13993	18779	23094857
22533414	813	5191	9575,9577	13995	18781	23094858
22533415	815	5193	9579	13997	18785	23094859
22533416	817	5195	9581	13999	18787	23094860
22533417	819	5197	9583	14001,14003	18789,18791	23094861
22533418	821	5199	9585	14005	18793	23094862
22533420	823	4651	9589	14007	18797	23094863
22533421	825	4653,5209	9591	14009	18799	23094864
22533426	827	5217	9599	14019	18809	23094868
22533422	829	5211	9593	14013	18801	23094865
22533427	831	5219	9601	14021	18811	23094869
22533428	833	5221	9603	14023,14025	18813	23094870
22533429	835	5223	9605	14027	18815	23094871

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22533430	837,4049	4851	9629	14103	18817	23094872
22533431	839	4853	9631	14105	18819	23094873
22533432	841,843	4855,8777	9633	14107	18821	23094874
22533433	845	4857	9635	14109	18823	23094875
22533434	847	4859	9637	14111	18825	23094876
22533435	849	4861,4863,5225	9639	14113,14115,14117,14159,14161	18827,18867,18869	23094877
22533436	851	5227	9641	14119,14163	18829,18871	23094878
22533438	853	5229	9643	14121	18831	23094879
22533439	855	5231	9645	14123	18833	23094880
22533440	857	5233	9647	14125	18835	23094881
22533441	859	5235	9649	14127	18837	23094882
22533442	861	5237	9651	14129	18839	23094883
22533443	863	5239	9653	14135	18841	23094884
22533444	865	5241	9655,9657	14137	18843,18845	23094885
22533445	867	5243	9659	14139	18847	23094886
22533446	869	5245	9661,9663	14141	18849	23094887
22533447	871	5247	9665	14143	18851	23094888
22533448	873	5249,5251	9667,9669	14145,14147	18853,18855	23094889
22533449	875	5253,5255	9671	14149	18857	23094890
22533450	877	5257,5641	9673	14151	18859	23094891
22533451	885	5259	9675	14153	18861	23094892
22533452	887,3709	5261,5265,8417	9677,12617	14155,17403,17419	18863,22043	23094893
22533453	889,1187	5263,5267,8691,8693,8701,8711,8723,8731,8735,8745,8753,8755,8761	#########	14157,14165,14475,17699,17701,17751,17777,17795,17799,17837,17861,17863,17865,17867,17869,17901,17917,17937	18865,18875,22479,22483,22511,22513,22517,22539,22645,22655,22657,22669,22681,22735	23094894,23095037
22533454,22535028	891	8345	9683,12557	14167,17301	22473	23094895,24413563
22535029,22535036	897,3583,4039	5269,5271,5273,8257	9691,9895	14173,17215	18877,18879,20369	23094663,23095697,24413550
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22533460,22533461	907,909	5283	9699,9701	14181,14183	18929	23094912,23094913
22533463	913	5287	9705	14187,17695	18933	23094915
22533464	915	5297	9709	17689	18935	23094917
22533465	917	5299	9711	17687	18937,18939	23094918
22533467	921	5301	9713	17807	18943	23094919
22533468	923	5303	9715,9717	14189	18945,18947	23094920
22533469	925	5305	9719	14191	18949	23094921
22533470	927	5307	9721	14193	18951	23094922
22533471	929	5309	9723	14195	18953	23094923,230

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22533472	931	5311	9725	14197	18955	23094924
22533473	933	5313	9727	14199,14267	18957	23094925
22533474	939	5317	9731	14203	18963	23094927
22533475	941	5319,5367	9733	14205	18965	23094928
22533476	943	5321	9735	14207	18967	23094929
22533478	945	5323	9737	14209,14269, 14271	18969	23094930
22533479	947	5325	9739	14211	18971	23094931
22533480	949	5327	9741	14213,14273	18973	23094932
22533481	951	5329	9743	14215	18975	23094933
22533482	953	5331	9745	14217	18977	23094934
22533483	955	5333	9747	14219	18979	23094935
22533484	958	5336	9750	14222	18982	
22533485	959	5337	9751	14223	18983,19025	23094936
22533486	961	5339	9753	14225	18985	23094937
22533487	963	5341	9755,10049	14227	18987	23094938
22533488	965	5343	9757	14229	18989	23094939
22533489	967	5345	9759	14231	18991,19027	23094940
22533490	969,971	5347	9761	14233	18993	23094941
22533491	973	5349	9763	14235	18995	23094942
22533492	975	5351	9765	14237	18997	23094943
22533493	977	5353	9767	14239,14275, 14277	18999	23094944
22533494	979	5355	9769	14241	19001	23094945
22533495	981	5357	9771	14243	19003	23094946
22533496	983	5359	9773	14245	19005	23094947
22533497	985	5361	9775	14247	19007	23094948
22533498	987	5363	9777	14249	19009	23094949
22533499	989	5365,5371	9779	14251	19011	23094950
22533501	993,995	5373	9781	14253	19013,19029	23094952
22533502	997	5375,8763	9783	14255	19015	23094953
22533504	999,1001	5377	9785	14257,14279, 14281,14283, 14285	19017	23094954
22533505	1003	5379	9787	14259	19019	23094955
22533506	1005	5381	9789	14261	19021	23094956
22533507	1007	5383	9791	14263	19023	23094957
22533509	1009	8635	9793	14265	19031	23094958
22533511,22534495	1011,2721	5385,7323	9797,11587	14289,16195, 17739	19035,21023	23094960,24413115
22533512	1013	5387	9799,9801	14291	19037	23094962
22533513	1015	5389	9803	14293	19039	23094963
22533514	1017,4075	5391	9805	14295	19041	23094964
22533515	1019,3925,4073	5393	9807	14297	19043	23094965
22533516	1021,3923	5395	9809	14299	19045	23094966
22533517	1023	5397	9811	14301	19047	23094967
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22533520	1029	5403	9817	14307	19053	23094970
22533521	1031	5405	9819,9821	14309,17779	19055	23094971
22533522	1033	5407	9823	14311	19057	23094972
22533523	1035	5409	9825	14313	19059	23094973
22533526	1039	5413	9827	14315	19173	23094975
22533527	1041	5415	9829	14317	19175	23094976
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22533529	1045	5419	9833	14321	19179	23094978
22533530	1047	5421	9835	14323	19181	23094979
22533531	1049	5423	9837	14325	19183	23094980
22533532	1051	5425,8717	9839	14327	19185	23094981
22533533	1053	5427	9841	14329	19187	23094982
22533534	1055	5429,5431	9843	14331	19189	23094983
22533535	1057	5433	9845	14333,14335	19191	23094984
22533536	1059	5435	9847	14337	19193	23094985
22533537	1061	5437	9849	14339	19195	23094986
22533538	1065	5441	9853	14343	19199,19241	23094988
22533539	1067	5443	9855	14345	19201	23094989
22533540	1069	5445	9857	14351	19203	23094990
22533541	1071	5447	9859	14353	19205	23094991
22533542	1073	5449	9861	14355,14357,14359	19207	23094992
22533544	1075,1077	5451,5481	9863	14361	19209,19243	23094993
22533545	1079	5453	9865	14363	19211	23094994
22533546	1081	5455	9867	14365	19213	23094995
22533547	1083,4257	5457	9869	14367,14443	19215	23094996
22533548	1085,1087,4259	5459	9871	14369,14445	19217	23094997
22533550	1089,1093	5461	9873	14371	19219	23094998
22533551	1091,1095	5463	9875	14373	19221	23094999
22533552	1097	5465	9877	14375	19223	23095000
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22533554	1101	5469	9881	14379	19227,19229	23095002
22533555	1103,1105	5471	9883,12785	14381	19231	23095003
22533556	1107	5473	9885	14383	19233	23095004
22533557	1109,1111	5475	9887	14385	19235	23095005
22533558	1113	5477	9889	14387	19237	23095006
22533559	1115	5479	9891	14389	19239,19245	23095007
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22533561	1119	5485,8669	9907	14393	19249,19251	23095009
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22533629	1125	5623	9913	14399	19257	23095011
22533631	1131	5631	9921	14407	19265	23095012
22533632	1133	5633	9923	14409	19267	23095013
22533633	1135,1141	5635	9925	14411,14447	19269	23095014
22533626,22533637,22534163	1137,4079	5615,5651,6749	9935,11035	14423	19159,19299,20331	23095018,23095676

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22533636	1147	5647	9931	14417,14419	19277,19295	23095017
22533639	1151	5655	9939	14427	19303	23095019
22533640	1153	5657	9941	14429,14453	19305	23095020
22533641	1155,1157	5659,5661	9943	14431	19307	23095021
22533642	1159	5663	9945	14433,14435	19309	23095022
22533643	1161	5665	9947	14437	19311	23095023
22533644	1163	5667	9949	14439	19313	23095024
22533645	1165	5669	9951	14441	19315	23095025
22533646	1167	5671	9953	14455	19317	23095026
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22533648	1171	5675	9957,10007	14459	19323	23095028
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22533650	1175	5679,5681	9961	14463	19327	23095030
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22533673	1235	5697	10107	14517,14519	19343	23095051
22533674	1237	5699	10109	14521	19347	23095052
22533675	1239	5701	10111	14523	19349,19409	23095053
22533677	1241	5703	10113	14525	19351	23095055
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22533679	1245	5707	10117	14529	19355	23095057
22533680	1247	5709	10119	14531	19357	23095058
22533681	1249	5711	10121	14533	19359	23095059
22533682	1251	5713,5737	10123	14535,17815	19361	23095060
22533683	1253	5715	10125	14537,14587	19363	23095061
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22533687	1263	5723	10133	14545,14593	19371	23095065
22534930	1277,3389	8071	10147,12347	14561,16997	19387,21787, 22625	24413460
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22533698	1297	5733,5735	10167,10169, 10171	14583,14603	19407	23095069
22533699	1299	5739	10173	14605	19413	23095070
22533700	1301	5741,5743	10175	14607	19415	23095071
22533701	1303	5745	10177	14609	19417,19419	23095072
22533702	1305	5747,5803	10179	14611,14613	19421	23095073
22533703	1307	5749	10181	14615	19423	23095074
22533704	1309	5751	10183	14617	19425,19427	23095075
22533705	1311	5755	10187	14621	19431	23095076
22533708	1313	5757	10189	14623	19433	23095077
22533709	1315	5759,5761	10191	14625,14683, 17733	19435	23095078
22533710	1317,1319	5763	10193	14627,14685, 14689,14695	19437	23095079
22533711	1321	5765	10195	14629,14687, 14691,14693, 14697,14699	19439	23095080
22533712	1323	5767	10197	14631	19441	23095081
22533713	1325	5769	10199	14633	19443	23095082
22533714	1327	5771	10201	14635	19445	23095083
22533715	1329	5773	10203	14637	19447	23095084
22533716	1331	5775	10205	14639,17879	19449	23095085
22533717	1333	5777	10207	14641	19451	23095086
22533718	1335	5779	10209	14643,17909	19453,19477	23095087
22533719	1337	5781	10211	14645	19455	23095088
22533720	1339	5783	10213	14647	19457	23095089
22533721	1341	5785	10215	14649	19459	23095090
22533722	1343	5787	10217	14651	19461	23095091
22533723	1345,1347	5789	10219	14653	19463,19479	23095092
22533725	1349	5791	10221	14655	19465	23095093
22533726	1351	5793	10223	14657	19467	23095094
22533728	1353	5797,8773	10227	14661	19471	23095096
22533729	1355	5799	10229	14663	19473	23095097
22533730	1357	5801	10231	14665	19475,19481	23095098
22533731	1359	5805	10233	14667	19483,19485	23095099
22533732	1361	5807	10235	14669	19487	23095100
22533733	1363	5809	10237	14671	19489	23095150
22533734	1365	5811	10239	14673	19491,19493	23095151
22533735	1367	5813	10241	14675	19495	23095152
22533736	1369	5815	10243	14677	19497	23095153
22533737	1371	5817	10245	14679	19499	23095154
22533738	1373,1375	5819	10247	14681,14707	19501,22659	23095155
22533739	1377	5821	10249	14709	19503	23095156
22533740	1379	5823	10251	14701,14711	19505	23095157
22533741	1381	5825	10253	14703,14713	19507	23095158
22533742	1383	5827	10255	14705,14717	19509	23095159
22533743	1385	5829,8779	10257	14719	19511	23095160
22533744	1387	5831	10259	14721	19513	23095161
22533746	1389	5833	10261	14723	19515,19521	23095162
22533747	1391	5835	10263	14725	19517,19519,	23095163

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22533751	1395	5843	10271	14733	19533	23095166
22533752	1397	5845	10273	14735	19535	23095167
22533753	1399	5847	10275	14737	19537	23095168
22533754	1401	5849	10277	14739	19539	23095169
22533756	1403	5853	10281	14743	19543	23095171
22533757	1405,1407	5855	10283	14745,14749	19545	23095172
22533758	1409	5857	10285	14747,14751	19547	23095173
22533759	1411	5859	10287	14753	19549	23095174
22533760,22535069	1413,3647,3649	5861,8355,8391	10289	14755,17311	19551	23095175
22533761	1415	5863	10291	14757	19553	23095201
22533762	1417	5865	10293	14759	19555	23095202
22533763	1419	5867	10295	14761	19557	23095203
22533764	1421	5869	10297	14763	19559	23095204
22533765	1423	5871	10299	14765	19561	23095205
22533766	1425	5873	10301	14767	19563	23095206
22533767	1427	5875	10303	14769	19565	23095207
22533768	1429	5877	10305	14771	19567	23095208
22533770	1431	5879	10307	14773	19569,22591	23095209
22533772	1433	5883	10311	14781	19573	23095211
22533773	1435	5885	10313	14783	19575	23095212
22533774	1437	5887	10315	14785	19577	23095213
22533775	1439	5889	10317	14787	19579	23095214
22533777	1441	5891	10319,10321	14789,14809	19581	23095215
22533778	1443	5893	10323	14791	19583	23095216
22533779	1445	5895	10325	14793	19585	23095217
22533780	1447	5897	10327	14795	19587	23095218
22533781	1449	5899	10329	14797	19589	23095219
22533782	1451	5901	10331	14799	19591	23095220
22533783	1453	5903	10333	14801	19593	23095221
22533784	1455	5905	10335	14803	19595	23095222
22533787	1457	5909	10339	14807	19599	23095224
22533789,22534806	1459,1461,3235	5913,7927	10345,12199,12201	14817,16835,16837	19605,21643	23095226,24413392
22533791	1463	5917	10349	14821	19609	23095228
22533792	1465	5919	10351	14823,14825	19611	23095229
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22533794	1469	5923	10355	14829	19615,19625	23095231
22533795	1471	5925	10357	14831	19617	23095232
22533796	1473	5927	10359	14833	19619	23095233
22533797	1475	5929	10361	14835	19621	23095234
22533798	1477,1479	5931	10363	14837	19623,19627	23095235
22533799	1481	5933	10365	14839	19629	23095236
22533803	1483	5941	10373	14847	19637	23095240
22533804	1485	5943	10375	14849	19639	23095241
22533805	1487	5945	10377	14851	19641	23095242
22533806	1489	5947	10379	14853	19643	23095243
22533807	1491,1493	5949	10381	14855,14881	19645	23095244

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22533808	1495	5951	10383	14857,14885	19647	23095245
22533809	1497	5953	10385	14859	19649,19651	23095246
22533811	1499	5955	10387	14861	19653	23095247
22533812	1501	5957	10389	14863,14887	19655,19657	23095248
22533813	1503	5959	10391	14865,14889	19659	23095249
22533814	1505	5961	10393	14867	19661	23095250
22533815	1507	5963	10395	14869	19663	23095251
22533816	1509	5965	10397	14871	19665	23095252
22533817	1511	5967	10399	14873	19667	23095253
22533818	1513	5969	10401	14875	19669	23095254
22533819	1515	8653	10403	14877	19671	23095255
22533826	1517	5987	10415,10417	14901	19683	23095261
22533827	1519	5989	10419	14903	19685	23095262
22533828	1521	5991	10421	14905,14951	19687,19689	23095263
22533829	1523	5993	10423	14907	19691	23095264
22533830	1525	5995	10425	14909	19693	23095265
22533833	1527	5997,5999	10427	14911	19695	23095266
22533834	1529	4783,6001	10429	13657,14913	19697	23094634,23095267
22533835	1531	6003	10431	14915	19699	23095268
22533837	1533	6009	10435	14919	19703	23095270
22533838	1535	6011	10437	14921	19705	23095271
22533839	1537	6013	10439	14923	19707	23095272
22533840	1539	6015,6017	10441	14925	19709	23095273
22533841	1541,1543	6019	10443	14927	19711,22693	23095274
22533842	1545	6021	10445	14929	19713	23095275
22533843	1547,1549,3971	6023	10447	14931	19715	23095276
22533844	1551	6025	10449,10795	14933,15361	19717,20093	23095277
22533845	1553,1555	6027	10451	14935	19719	23095278
22533846	1557	6029	10453	14937	19721	23095279
22533847	1559,4217	6031	10455	14939	19723	23095280
22533849	1561,4011	6035	10459	14943	19727	23095282
22533848	1563	6033	10457	14941	19725	23095281
22533850	1565	6037	10461	14945	19729	23095283
22533851	1567	6039	10463	14947	19731,19773	23095284
22533852	1569	6041	10465	14949,14953	19733	23095285
22533855	1571	6045,8699	10467	14955	19735	23095287
22533856	1573	6047,8697	10469	14957	19737,19775	23095288
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22533860	1585,1593	6055	10477	14965	19745	23095292
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22533862	1589,1597,4283	6059	10481	14969	19749	23095294
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22533867	1607,4025	6069,6071	10491	14979	19761	23095299
22533868	1609,4027	6073	10493	14981	19763	23095300
22533869	1611	6075	10495	14983	19765	23095301
22533870	1613	6077	10497	14985	19767,19779	23095302
22533871	1615	6079	10499	14987	19769	23095303
22533872	1617	6081	10501	14989,15001, 17905	19771	23095304
22533873	1619	6083	10503	14991	19781	23095305
22533874	1625	6085	10505	14993	19783,19785	23095306
22533875	1629	6089	10509	14999	19789	23095308
22533878	1633,1637,41 05	6093	10513	15003	19793	23095310
22533879	1635,1639,41 07	6095	10515	15005	19795	23095311
22533880	1641	6097	10517	15007	19797	23095312
22533881	1643	6099	10519	15009	19799	23095313
22533882	1645	6101	10521	15011	19801,19813, 19815	23095314
22533883	1647	6103	10523	15013,15083	19803	23095315
22533884	1649	6105	10525	15015	19805	23095316
22533886	1651,1653,16 55	6107,6109	10527	15017	19807,19817	23095317
22533887	1657	6111	10529	15019	19809	23095318
22533888	1659	6113	10531	15021	19811	23095319
22533889	1661	6115,6119	10533	15023	19821	23095320
22533890	1663	6117,6121	10535	15025,15027	19823	23095321
22533891	1665,1667,41 61	6123,6125	10537	15029,15081	19825	23095322
22533893	1671,1673,16 75,1677,4129	6129	10541,10543	15033	19829	23095323
22533894	1679,1681	6131	10545	15035	19831	23095324
22533895	1683	6133	10547	15037	19833	23095325
22533896	1685	6135	10549	15039	19835	23095326
22533898	1687	6137	10551	15041,15085	19837	23095327
22533899	1689	6139	10553	15043	19839	23095328
22533900	1691	6141	10555	15045	19841	23095329
22533901	1693,1695	6143	10557	15047	19843,19899	23095330
22533902	1697	6145	10559	15049	19845	23095331
22533903	1699	6147	10561	15051	19847	23095332
22533906	1703	6153	10567	15059	19853	23095335
22533907	1705	6155	10569,10573	15061	19855	23095336
22533908	1707,1709	6157	10575	15063	19857	23095337
22533909	1711	6159	10577	15065	19859	23095338
22533911	1713	6163	10581	15069	19863	23095340
22533912	1715	6165,8677	10583	15071,15087	19865	23095341
22533913	1717	6167	10585	15073	19867	23095342
22533914	1719	6169	10587	15075	19869	23095343
22533915	1721,1723	6171	10589	15077	19871	23095344

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22533917	1727	6175	10593	15091	19875	23095346
22533918	1729	6177	10595	15093	19877	23095347
22533927	1733	6185	10599	15097	19881	23095370
22533928	1735	6187	10601	15099	19883	23095371
22533929	1737	6189,6225	10603,10605	15101,15103	19885	23095372
22533931	1739	6229	10609	15107	19889	23095374
22533932	1741	6231	10611	15109	19891	23095375
22533933	1743	6233	10613,10615	15111,15139	19893	23095376
22533934	1745	6235	10617	15113	19895	23095377
22533935	1747	6237	10619	15115	19897	23095378
22533959	1755	6245	10627	15123	19907	23095382
22533960	1757	6247	10629	15125	19909	23095383
22533961	1759	6249,6325	10631	15127	19911	23095384
22533962	1761	6251	10633	15129	19913	23095385
22533963	1763	6253	10635	15131	19915	23095386
22533966	1767	6257	10639	15135	19919	23095387
22533968	1769	6259	10641	15137	19921	23095388
22533969	1771	6261	10643	15141	19923	23095389
22533970	1773	6263	10645	15143	19925	23095390
22533971	1775	6265	10647	15145	19927	23095391
22533972	1777	6267	10649	15147	19929	23095392
22533973	1779	6269	10651	15149	19931	23095393
22533974	1781	6271	10653	15151	19933	23095394
22533424,22533976	1783	5213,6275	9595,10657	14015,15155	18803,19937	23094866,23095396
22533977	1785,3955	6277	10659	15157	19939	23095397
22533978	1787,3957	6279	10661	15159	19941	23095398
22533979	1789	6281	10663	15161	19943	23095399
22533980	1791	6283	10665	15163,15167	19945	23095400
22533981	1793	6285	10667	15165	19947	23095401
22533982	1795,4007,4009	6287	10669	15169	19949,19951	23095402
22533983	1797	6289	10671	15171	19953	23095403
22533984	1799	6291	10673	15173	19955	23095404
22533986	1801	6293	10675,10677	15175,15177	19957	23095405
22533987	1803,1805	6295	10679	15179,15181	19959	23095406
22533990	1811	6329	10683	15231	19965	23095407
22533991	1813	6331	10685	15233	19967	23095408
22533992	1815	6333	10687	15235	19969,20041	23095409
22533993	1817	6335	10689	15237	19971	23095410
22533994	1819	6337	10691	15239	19973	23095411
22533995	1823	6341	10695,10697	15245	19977	23095413
22533996	1825	6343	10699	15247,15259	19979	23095414
22533997	1827	6345	10701	15249,15261,15263	19981	23095415
22533998	1829	6347	10703	15251	19983	23095416
22533999	1831	6349	10705	15253	19989	23095417
22534000	1833	6351	10707	15255	19991	23095418
22533157,225	1835	4631,6353,63	9071,10709	13491,15257,	19993	23094571,230

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22534003	1839	6359	10713	15269	19997	23095421
22534004	1841	6361,6383	10715	15271,15301	19999	23095470
22534005	1843	6363	10717	15273	20001	23095471
22534007	1845	6365	10719	15275	20003	23095472
22534008	1847	6367	10721	15277	20005	23095473
22534009	1849	6369	10723	15279,15303	20007	23095474
22534010	1851	6371	10725	15281	20009,20043	23095475
22534011	1853	6373	10727	15283	20011	23095476
22534012	1855	6375	10729	15285	20013	23095477
22534013	1857	6377	10731	15287	20015	23095478
22534014	1859	6379	10733	15289	20017,20045	23095479
22534015,22535008	1861,3547	6381,6385,8233	10735,12503	15291,17187, 17229	20019,20021, 20023,21927	23095480,24413534
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22534016	1863	6387,6389,6391,6393	10737	15305,17697	20025	23095481
22534017,22534018	1865,1867	6395	10739,10741	15307,15309	20027,20029	23095482,23095483
22534022	1869	6403	10749	15317	20037	23095487
22534023	1871,1873	6405	10751	15319	20039	23095488
22534025	1875	6409	10755	15323	20049	23095490
22534026	1877	6411	10757,10759, 10763	15325,15327, 15329,17801	20051,20053	23095491
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22534029	1881	6415,6451,6453	10767	15333,15407	20057,20059	23095493
22534030	1883	6455	10769	15335	20061	23095494
22534031	1885	4743,6457	10771	15337	20063	23095495
22534032	1887	6459	10773	15339	20065	23095496
22534033	1889	6461,6465	10775	15341	20067	23095497
22534034	1891	6463,6467,6471	10777	15343	20069	23095498
22534035	1893	6469,6473	10779	15345	20071,20079	23095499
22534036	1895	6475	10781	15347	20073	23095500
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22534038	1899	6479	10785	15351	20077,20081	23095502
22534039	1901	6481	10787	15353	20083	23095503
22534040	1903	6483	10789	15355	20085	23095504
22534041	1905	6485,8719	10761,10791	15357	20087,20089	23095505
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22534060	1951	6529	10839	15381	20119	23095521
22534062	1953	6533,6535	10843	14883,15385	20123	23095523
22534064	1957	6545	10849	15387	20129	23095525
22534065	1959	6547	10851	15389	20131	23095526
22534066	1961	6549	10853	15391,15409	20133,20149	23095527
22534067	1963	6551	10855	15393	20135	23095528
22534068	1965	6553	10857	15395	20137	23095529
22534069	1967	6555	10859	15397	20139	23095530
22534070	1969	6557	10861	15399	20141	23095531
22534071	1971	6559	10863	15401	20143	23095532
22534073	1973	6561	10865	15403	20145	23095533
22534074	1975	6563	10867	15405,17745	20147	23095534
22534076	1979	6569	10873	15417	20151,22491	23095537
22534078	1981	6571	10875	15419	20153	23095538
22534079	1983	6573	10877	15421	20155	23095539
22534080	1985	6575	10879	15423	20157	23095540
22534081	1987	6577	10881	15425	20159,20243	23095541
22534082	1989	6579	10883	15427	20161	23095542
22534083	1991	6581	10885	15429	20163	23095543
22534084	1993	6583	10887	15431	20165	23095544
22534085	1995	6585	10889	15433,17835	20167	23095545
22534086	1997	6587	10891	15435	20169	23095546
22534087	1999	6589	10893	15437	20171	23095547
22534088	2001	6591	10895	15439	20173	23095548
22534089	2003	6593	10897	15441	20175	23095549
22534090	2005,4063	6595	10899	15443	20177	23095550
22534095	2007	6597	10901	15445	20179,22633	23095552
22534096	2009,2011	6599	10903	15447	20181	23095553
22534097	2013	6601	10905	15449	20183,20245	23095554
22534098	2015	6603	10907	15451	20185,20247	23095555
22534099	2017	6605	10909	15453	20187	23095556
22534100	2019	6607	10911	15455	20189	23095557
22534101	2021	6609	10913	15457	20191	23095558
22534102	2023	6611,8775	10915	15459	20193	23095559
22534103	2025	6613	10917	15461	20195	23095560
22534104	2027	6615	10919	15463	20197	23095561
22534106	2029	6617	10921	15465	20199	23095562
22534107	2031	6619	10923	15467	20201	23095563
22534108	2033	6621	10925	15469	20203	23095564
22534109	2035	6623,6641	10927	15471	20205	23095565
22534110	2037	6625,6643,8729	10929	15473,15481	20207	23095566
22534111	2039	6627	10931	15475	20209	23095567
22534112	2041	6629	10933	15477	20211	23095629
22534113	2043,2045	6631	10935	15479,15483	20213	23095630
22534114	2047,4137,42	6633	10937,12801	15485,17613	20215,22273	23095631

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22534115	2049,2051,3837	6635	10939,10941	15487,17639	20217,20219,22297	23095632
22534117	2053,2055	6637	10943	15489,17765,17767	20221	23095633
22534118	2057	6647	10945	15491	20223	23095634
22534119	2059	6649	10947	15493	20225	23095635
22534120	2061	6651	10949,10951	15495	20227	23095636
22534121	2063	6653	10953	15497	20229	23095637
22534122	2065	6655	10955	15499	20231	23095638
22534123	2067	6657	10957	15501	20233	23095639
22534124	2069	6659	10959	15503	20235	23095640
22534125	2071	6661	10961	15505	20237	23095641
22534126	2073	6663	10963	15507	20239	23095642
22534127	2075	6665	10965	15509	20241	23095643
22534128	2077	6667	10967	15511	20249	23095644
22534129	2079	6669	10969,11025	15513,15563	20251	23095645
22534130	2081	6671	10971	15515	20253	23095646
22534131	2083	6673	10973	15517	20255	23095647
22534132	2085	6675,6677	10975	15519	20257	23095648
22534133	2087	6679	10977,13075	15521	20259	23095649
22534330	2089,2437,2439	6997	11253	15843	20687	24412958
22534134	2091	6639,6681	10979	15523,15565,15571	20261	23095650
22534135	2093	6683	10981	15525,15567	20263	23095651
22534136	2095	6685	10983	15527	20265	23095652
22534137	2097	6687	10985	15529,15573	20267	23095653
22534138	2099	6689,6767	10987	15531	20269	23095654
22534140	2101	6691	10989	15533	20271	23095655
22534141	2103	6693,6769	10991	15535	20273	23095656
22534142	2105	6695	10993	15537	20275	23095657
22534143	2107	6697	10995	15539	20277	23095658
22534144	2109	6699	10997	15541	20279	23095659
22534145	2111	6701	10999	15543	20281	23095660
22534146	2113	6703	11001	15545	20283	23095661
22534147	2115	6705	11003	15547	20285	23095662
22534148	2117	6707	11005	15549,15551	20287	23095663
22534149	2119,2121	6709,6715,6717,6719	11007	15553,15555	20289,20291,20297,20299,20301	23095664
22534151	2123	6721	11009	15557,15569	20303	23095665
22534152	2125	6723	11011	15559	20305	23095666
		6774	11030	17716	20326	
22534170	2127	6761	11047	15591	20343	23095682
22534171	2129	6763	11049	15593	20345,20347	23095683
22534172	2131	6765,6771,8705	11051	15595	20349	23095684
22534173	2133	6773	11053	15597,15599,15601	20351	23095685

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22534174	2135	6775,6777	11055	15603	20353	23095686
22534175	2137	6779	11057	15605	20355	23095687
22534176	2139	6781	11059	15607	20357	23095688
22534177	2141,4145	6783	11061,11063	15609	20359	23095689
	2142	6784	11064	15610	20360	
22534181	2153	6795	11071	15617	20379	23095701
22534182	2155	6797	11073	15619	20381	23095702
22534183	2157	6799	11075	15621	20383	23095703
22534184	2159	6787,6801	11077	15623	20385	23095704
22534185	2161	6803	11079	15625	20387	23095705
22534186	2163,2165	6805	11081	15627	20389	23095706
22534187	2167	6807	11083	15629	20391	23095707
22534188	2169	6809	11085	15631,15633	20393	23095708
22534190	2171	6811	11087	15635	20395	23095709
22534200	2173,4191	6827,6943	11103	15651	20411	23095717
22534201	2175	6829	11105	15653,15655	20413	23095718
22534202	2177	6831,6945	11107	15657	20415	23095719
22534203	2179	6833	11109	15659	20417	23095720
22534204	2181	6835	11111	15661	20419	23095721
22534205	2183	6837	11113	15663	20421	23095722
22534206	2185	6839	11115	15671	20423	23095723
22534207	2187	6841,6947	11117	15673	20425	23095724
22534208	2189	6843	11119	15675	20427	23095725
22534209	2191	6845	11121	15677	20429,20441	23095726
22534210	2193	6847	11123	15679	20431,20443	23095727
22534211,22535115	2195,2197,3735,3737,3739	5103,6849,8443	11125,12643	15681,17443	20433,22067	23095728,24413604
22534212	2199	6851	11127	15683	20435	23095729
22534214	2201	6855	11129	15685	20437	23095730
22534215	2203	6857	11131,11133	15687	20445	23095731
22534216	2205,2207	6859	11135	15689	20447,20449	23095732
22534217	2209	6861,6863	11137	15691	20451	23095733
22534218	2211	6865	11139	15693	20453,20525,20527	23095734
22534219	2213	6867	11141	15695,17919	20455,20529	23095735
22534220	2215	6869	11143	15697	20457	23095736
22534221	2217	6871	11145	15699,15773	20459	23095737
22534222	2219	6873	11147	15701,17755	20461	23095738
22534223	2221	6875	11149	15703	20463	23095739
22534224	2223	6877	11151	15705,15775	20465	23095740
22534225	2225	6879	11153	15707	20467	23095741
22534226	2227	6881	11155	15709	20469	23095742
22534227	2229	6883	11157	15711	20471	23095743
22534228	2231	6885	11159	15713	20473	23095744
22534229	2233	6889	11161	15715	20475	24412859
22534230	2235	6891	11163	15717	20477	24412860
22534231	2237	6893	11165	15719	20479	24412861
22534232	2239	6895	11167	15721	20481	24412862
22534233	2241	6897	11169	15723	20483	24412863
22534235	2243	6899	11171	15725	20485	24412864

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22534236	2245	6901	11173	15727	20487	24412865
22534237	2247,2249	6903	11175	15729	20489	24412866
22534239	2253,2255	6905	11179	15733	20491	24412867
22534240	2257,2259	6907	11181	15735	20493	24412868
22534241	2261	6909	11183	15737	20495	24412869
22534242	2263	6911	11185	15739	20497	24412870
22534243	2265	6913	11187	15741	20499	24412871
22534244	2267	6915	11189	15743	20501,22713	24412872
22534245	2269	6917	11191	15745	20503	24412873
22534246	2271	6919,6921	11193,11195	15747,15749	20505	24412874
22534247	2273,2275,2277,2279,2281	6923	11197,11199	15751,17741	20507	24412875
22534248	2287	6927	11203	15755	20511	24412877
22534249	2289	6929	11205	15757	20513	24412878
22534250	2291	6931	11207	15759	20515	24412879
22534257	2295	6949	11219	15777	20531	24412886
22534258,22534268	2297,2327	6951,6973	11221,11241	15779	20551	24412887,24412893
22534259,22534269	2299,2301,2329	6953,6965,6975	11223,11243	15781,15807	20533	24412888
22534260	2303	6955	11225	15783	20535	24412889
22534261	2305	6961	11231	15789	20541	24412890
22534262	2307	6963	11233	15791	20543	24412891
	2313	6967	11235	15795	20545	
22534264	2315,3961	6969,6971	11239	15797	20549	23094836,23095149,23095422,23095568
22534272	2335	6979	11247	15809	22489,22497	24412895
22534325	2427,4031	6981	13003	15831	20679	24412954
22534326	2429,2431,4029	6983	13001	15835	20681	24412955
22534327	2433	6985,6991,6993	11249	15837,15839,15845	20683	24412956
22534329	2435	6995	11251	15841	20685	24412957
22534332	2441	6999	11255	15847	20689	24412959
22534333	2443	7001,7003	11257,11259	15849,15851,15857	20691,20693	24412960
22534335	2445	7005	11263	15855,15859	20697	24412961
22534336	2447	7007	11265	15861	20699	24412962
22534337	2449	7009	11267	15863	20701	24412963
22534339	2451	7013	11271	15867	20705	24412964
22533322,22534340	2453	4981,7015	9411,11273	13801,15869	18555,20707	24412965
22534341	2455	7017	11275	15871,15899	20709	24412966
22534342	2457	7019	11277	15873	20711,20713	24412967
22534343	2459	7021	11279	15875	20715	24412968
22534344	2461	7023	11281	15877	20717	24412969
22534345	2463	7025	11283	15879	20719	24412970
22534346	2465	7027	11285	15881	20721	24412971
22534347	2467	7029	11287	15883	20723	24412972

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22534348	2469	7031	11289	15885	20725	24412973
22534349	2471	7033	11291	15887	20727	24412974
22534350	2473	7035	11293	15889	20729	24412975
22534351	2475	7037	11295	15891	20731	24412976
22534352	2477	7039	11297	15893	20733	24412977
22534353	2479	8663	11299	15895	20735	24412978
22534354	2481	8661	11301	15897,15901	20737	24412979
22534359	2483,2485	7041,8739	11309	15909	20745	24412983
22534360	2487	7043	11311	15911,15913	20747	24412984
22534361	2489	7045	11313	15915	20749	24412985
22534362	2491	7047	11315	15917	20751	24412986
22534363	2493,2495	7049	11317	15919	20753,20767	24412987
22534364	2497	7051	11319	15921	20755	24412988
22534365	2499	7053	11321	15923,15925	20757	24412989
22534366	2501	7055,7057	11323,11351	15927	20759	24412990
22534367	2503	7059	11325	15929	20761	24412991
22534368	2505	7061	11327	15931,15935	20763	24412992
22534369	2507	7063	11329	15933,15937	20765	24412993
22534370	2509	7065	11331	15939	20769	24412994
22534371	2511	7071	11333	15941	20771	24412995
22534372	2513	7073,7075	11335	15943,15945	20773,20775	24412996
22534373,22534971	2515,3467,3469,3471,3959	4363,7077,8149	11337,12427	15947,17083	20777,21847	24412914,24412997,24413497
22534377	2517	7083	11343	15953	20783	24413000
22534378	2519	7085	11345	15955	20785	24413001
22534379	2521	7087	11347	15957	20787	24413002
22534380	2523	7089	11349,11353,13065	15959,15965	20789	24413003
22534381	2525	7091	11355	15961	20791,20793	24413004
22534382	2527	7093	11357,11359	15963	20795	24413005
22534383	2529	7101,7103	11361	15967	20797,20799	24413006
22534386	2535	7107	11367	15969,15971	20803	24413009
22534387	2537	7109	11369	15973	20805	24413010
22534388	2539	7111,7113	11371,11373	15975	20807	24413011
22534389	2541	7115	11375	15977	20809,20811	24413012
22534390	2543	7117	11377	15979	20813	24413013
22534391	2545	7119	11379	15981	20815,20817	24413014
22534392	2547	7121	11381	15983	20819	24413015
22534393	2549	7123	11383	15985	20821	24413016
22534394	2551	7125	11385	15987	20823	24413017
22534395	2553	7127	11387	15989	20825	24413018
22534396	2555	7129	11389	15991	20827	24413019
22534397	2557	7131	11391	15993	20829	24413020
22534398	2559	7133	11393	15995	20831	24413021
22534400	2561	7135	11395	15997	20837	24413022
22534401	2563	7137	11397	15999	20839	24413023
22534403	2569	7139	11401	16003	20843,20845	24413025
22534404	2571	5973,7141	11403	16027	20847	24413026
22534405	2573	5971,7143,71	11405	16029	20849,20851	24413027

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22534406	2575	7149	11407	16031	20853	24413028
22534407	2577	7151	11409	16033	20855	24413029
22534408	2579	7153	11411	16035	20857	24413030
22534409	2581	7155,7163	11413	16037	20859,20861	24413031
22534410	2583	7157	11415	16039	22523	24413032
22534412	2587	7161	13069	16043	22519	24413034
22534416	2589	7167	11421,11423	16047	20865	24413038
22534417	2591	7169,7171	11425	16049	20867	24413039
22534418	2593	7173	11427	16051	20869	24413040
22534419	2595	7175	11429	16053	20871	24413041
22534420	2597,3977	7177	11431	16055	20873	24413043
22534421	2599,3979	7179	11433	16057,16059	20875	24413044
22534422	2601	7181	11435	16061	20877	24413045
22534423	2603	7183	11437	16063	20879	24413046
22534424	2605	7185	11439	16065	20881	24413047
22534425	2607	7187	11441,11491	16067	20883	24413048
22534427	2609	7189	11443,11493	16069,16071	20885	24413049
22534428	2611	7191	11445	16073	20887	24413050
22534429	2613	7193	11447	16077	20889	24413051
22534156,22534430	2615	6733,7195	11017,11449	16079	20315,20891	24413052
22534431	2617	7197	11451	16081	20893	24413053
22534432	2619	7199	11453	16083	20895	24413054
22534438	2633	7213	11467	16099,17731	20909	24413061
22534439	2635	7215	11469	16101	20911	24413062
22534440	2637	7217	11471	16103,16111	20913	24413063
22534441	2639	7219	11473	16105	20915	24413064
22534442	2641	7221	11475	16107	20917	24413065
22534443	2643	7223	11477	16109,16113	20919	24413066
22534444	2645	7225,7237	11479	16115	20921	24413067
22534445	2647	7227	11481	16117	20923	24413068
22534446	2649	7229,7235	11483	16119,16127,16129	20925	24413069
22534447	2651,2653	7231	11485	16121	20927,20929	24413070
22534448	2655	7233,8759	11487	16123	20931	24413071
22534449	2657	8757	11489	16125	20933	24413072
22534455	2659	7247	11503	16139	20943	24413077
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22534457	2665	8749	11507	16143,17791	20947	24413079
22534461	2669	7251	11511,11513	16145,16147	20953,20955,22653	24413083
22534462	2671,2673	7253	11515	16149	20957	24413084
22534463	2675	7255	11517	16151	20959	24413085
22534465	2677	7259	11521	16157	20963	24413087
22534474	2679	7273	11539,11541	16179	20979	24413094
22534477	2687	7281	11549	16011	20987	24413098
22534478	2689	7283	11551	16013	20989	24413099
22534483	2699	7293	11561	16005	21001	24413104
22534491	2711	7305,7313,73	11573	16025	21013,22661	24413110

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22534493	2717	7319	11583	16187	21019	24413113
22534494	2719	7321,7349,7351	11585	16189,16193	21021	24413114
22534496	2723	7325	11589	16197	21025	24413116
22534497	2725	7327	11591	16199	21027	24413117
22534498	2727	7329,8747	11593	16201,16217	21029	24413118
22534153,22534499	2729	6725,7331	11013,11595	15561,16203,17845	20307,21031	23095667
22534500	2731	7333	11597	16205	21035	24413119
22534501	2733	7335	11599	16207	21037	24413120
22534502	2735	7337,7355,8737	11601	16209	21039,22515	24413121
22534503	2737	7339	11603	16213	21041	24413122
22534504	2739	7341,8767	11605	16215,16219	21043	24413123
22534505	2741	7343	11607	16221,16299	21045	24413124
22534507	2743	7345	11609	16223	21047	24413125
22534508	2745	7357	11611	16225	21049	24413126
22534509	2747	7359	11613	16227	21051	24413127
22534510	2749	7361	11615	16229	21053	24413128
22534511	2751	7363	11617	16231	21055,21125	24413129
22534512	2753	7365	11619	16233	21057,21127	24413130
22534514	2755	7367	11621	16235	21059	24413131
22534528	2761	7395	11641	16257,16301	21079	24413141
22534529	2763	7397	11643	16259,16303	21081	24413142
22534530	2765,2767	7399	11645	16261	21083	24413143
22534537	2769	7409	11653	16271	21091	24413147
22534538	2771	7411	11655	16273	21093	24413148
22534540	2773	7415	11659	16277,16305,17793	21097	24413150
22534541	2775,2777	7417	11661	16279	21099,21133	24413151
22534542	2779	7419	11663	16281	21101	24413152
22534543	2781	7421	11665	16283	21103	24413153
22534544	2783	7423	11667	16285,16287	21105	24413154
22534545	2785	7425	11669	16289	21107	24413155
22534546	2787	7427	11671	16291	21109	24413156
22534547	2789	7429	11673	16293	21111	24413157
22534548	2791	7431	11675	16295	21113	24413158
22534549	2793	7433	11677	16297	21115	24413159
22534552	2801	7437,7439	11681	16307	21135	24413161
22534553	2803	7441,8765	11683	16309	21139	24413162
22534554	2805	7443	11685	16311	21141	24413163
22534558	2811	7445	11687	16317	21143	24413165
22534560	2813,2815	7447	11689,11691	16319	21145	24413166
22534561	2817	7449	11693	16321	21147	24413167
22534562	2819	7451	11695	16323	21149	24413168
22534563	2821,2823	7453	11697	16325	21151,21153	24413169
22534565	2825	7457	11701	16331	21157	24413171
22534566	2827	7459	11703	16333	21159	24413172

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22534567	2829	7461	11705	16335	21161	24413173
22534568	2831	7463	11707	16337	21163	24413174
22534569	2833	7465	11709	16339	21165	24413175
22534571	2835	7467	11711	16341,16421	21167	24413176
22534572	2837	7469	11713	16343,16345, 16423	21169	24413177
22534573	2839	7471	11715	16347	21171	24413178
22534574	2845	7477	11719	16351	21175	24413181
22534575	2847	7479	11721	16353	21177	24413182
22534576	2849	7481	11723	16355	21179	24413183
22534577	2851	7483	11725	16357	21181	24413184
22534578,22534581	2853	7485,7487	11727	16359,16361	21183	24413185
22534582	2855,2857	7489,7533	11729	16363,17775	21185	24413186
22534583	2859	7491	11731	16365	21187	24413187
22534584	2861	7493	11733	16367	21189	24413188
22534585	2863	7495	11735	16369	21191	24413189
	2864	7496	11736	16370	21192	
22534587	2865	7497	11737	16371,17787	21193	24413190
22534588	2867,2869	7499,8689	11739	16373	21195	24413191
22534589	2871	7501	11741	16375	21197	24413192
22534590	2873	7503	11743	16377	21199	24413193
22534592	2875	7505	11745	16379	21203	24413194
22534593	2877	7507	11747	16381	21205	24413195
22534594	2879	7509	11749	16383,16425	21207	24413196
22534595	2881	7511	11751	16385,16427	21209,21211	24413197
22534597	2883	7515	11755	16389,16391	21215	24413199
22534598	2885	7517	11757	16393	21217	24413200
	2887	7520	11760	16395	21220	
22534599	2889	7521	11761	16397	21221	24413202
22534602	2891	7525	11765	16401	21225	24413203
22534603	2893	7527	11767	16403	21227	24413204
22534604	2895,2897	7529	11769	16405	21229	24413205
22534605	2899	7531,7537	11771	16407	21231,21243	24413206
22534606	2905	7539	11773	16411	21233	24413207
22534607,22534608	2907,2909	7541,7543	11775,11777	16413	21235,21237	24413208,24413209
22534609	2911	7545	11779	16415	21239	24413210
22534610	2913	7547	11781	16417	21241	24413211
22534612	2915	7549	11783	16419	21245,21247	24413212
22534613	2917	7551	11785	16429	21249	24413213
22534615	2919	7553,7555	11787	16431,16433	21251	24413214
22534616	2921	7557	11789,11791	16435	21253	24413215
22534617	2923	7559	11793	16437	21255	24413216
22534618	2925,2927	7561	11795	16439	21257	24413217
22534619	2929	7563,7565	11797	16441	21259,21261	24413218
22534620	2931	7567	11799	16443	21263	24413219
22534621	2933	7569	11801,13037	16445	21265	24413220
22534622	2935	7571	11803	16447	21267	24413221
22534623	2937	7573	11805	16449	21269	24413222

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22534625	2941	7577	11809	16455	21273	24413224
22534626	2943	7579	11811	16457	21275	24413225
22534627	2945	7581	11813	16459	21277	24413226
22534628	2947	7583	11815	16461	21279	24413227
22534629	2949,4123,4125	7585,7587	11817	16463	21281,21283	24413228
22534630	2951,4127	7589	11819,11821	16465	21285	24413229
22534632	2955	7593	11825	16469	21287	24413231
22534633	2957	7595	11827	16471	21289	24413232
22534634	2959	7597	11829	16473	21291	24413233
22534635	2961	7599,8713	11831	16475	21293	24413234
22534636	2963	7601	11833	16477	21295	24413235
22534637	2965	7603	11835	16479	21297	24413236
22534639	2967	7605	11837,11841	16481	21299	24413237
22534640	2969	7607,7609	11839,11843	16483	21301	24413238
22534641	2971	7611	11845	15205,16485	21303	24413239
22534642	2973	7613	11847	16487,16535	21305	24413240
22534643	2975	7615	11849	16489	21307	24413241
22534644	2977	7617	11851	16491,16537	21309	24413242
22534645	2979	7619	11853	16493	21311	24413243
22534646	2981	7621	11855	16495	21313	24413244
22534647	2983	7623	11857	16497	21315	24413245
22534649	2987	7627	11861	16501	21321	24413246
22534651	2989	7629	11863	16503	21323,21359	24413247
22534652	2991	7631	11865	16505	21325	24413248
22534653	2993	7633	11867	16507	21327	24413249
22534654	2995	7635	11869	16509	21329	24413250
22534655	2997	7637	11871	16511	21331	24413251
22534656	2999	7639	11873	16513	21333	24413252
22534658	3001	7641	11875	16515	21335	24413253
22534659	3003	7643,7645	11877	16517	21337	24413254
22534660	3005	7647	11879,13111	16519	21339	24413255
22534661	3007	7649	11881	16521	21341	24413256
22534662	3009	7651	11883	16523	21343	24413257
22534668	3011	7663	11895	16541	21361	24413263
22534669	3013	7665	11897	16543	21363	24413264
22534670	3015	7667	11899	16545	21365	24413265
22534671	3017	7669	11901	16547	21367	24413266
22534672	3019	7671	11903	16549,17843	21369	24413267
22534673	3021	7673	11905	16551	21371	24413268
22534674	3023	7675	11907	16553	21373	24413269
22534675	3025	7677	11909	16555	21375	24413270
22534677	3027	7681	11913	16559	21377	24413271
22534679	3029	7683	11915	16573	21379	24413272
22534680	3031	7685	11917	16575	21381	24413273
22534682	3035	7689	11921	16579,16581	21385	24413274
22534683	3037	7691	11923	16583	21387	24413275
22534684	3039	7693	11925	16585	21389	24413276
22534685	3041	7695	11927	16587	21391	24413277

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22534688,22535015	3045,3563,3565,4071	7699,8243	11931,12513	16591,16593,17199,17231	21395,21937	24413279,24413539
22534689	3047	7701	11933	16595	21397	24413280
22534690	3049	7703	11935	16597	21399	24413281
22534691	3051	7705,7707	11937	16599	21401	24413282
22534692	3053	7709	11939	16601	21403	24413283
22534699	3055	7725	11953	16615	21421	24413290
22534700	3057,4169	7727	11955	16617	21423,21439	24413291
22534701	3059,4171	7729	11957	16619	21425	24413292
22534702	3061	7731	11959	16621	21427	24413293
22534703	3063	7733	11961,11963	16623	21429,21441	24413294
22534704	3065	7735	11965	16625	21431	24413295
22534705	3067	7737	11967	16627	21433	24413296
22534708	3069	7743	11973	16633,16639,16641	21445	24413299
22534709	3071	7745	11975	16635	21447,22613	24413300
22534711,22534768	3073,3163	7747,7873	11977,12089	16637,16643,16753	21449,21557	24413301,24413358
22534712	3075	7749,7751	11979	16645	21451	24413302
22534719	3077	7765	11999	16659	21465	24413309
22534720	3079	7767,7771	12001	16661	21467	24413310
22534721	3081	7769,7773,7775	12003	16663	21469,21477	24413311
22534722	3083	7777	12005	16665	21471	24413312
22534723	3085	7779	12007	16667	21473	24413313
22534724	3087	7781	12009	16669	21475,21481	24413314
22534725	3089	7785	12011	16671	21483	24413315
22534726	3091	7783,7787	12013	16673	21485	24413316
22534728	3093	7789	12015	16675	21487	24413317
22534729	3095	7791	12017	16677	21489	24413318
22534730	3097	7793	12019	16679	21491	24413319
22534739	3103	7817	12031	16691	21505	24413330
22534740	3109	7821	12035	16695,16707	21511,22627	24413332
22534741	3111	7823	12037,12039	16697,16699	21513,21517	24413333
22534743	3113	7825	12041	16701,16709	19293,21519	24413334
22534744	3115	7827	12043	16703,16711	19291	24413335
22534745	3117	7829	12045	16705,16713	19289	24413336
22534746	3119	7831	12047	17903	19287	24413337
22534749	3125	7837	12053	16715	19279,21521	24413340
22534750	3127	7839	12055	16717	21523	24413341
22534751	3129	7841	12057	16719	21525	24413342
22534752	3131	7843,7887	12059	16721	21527	24413343
22534753	3133	7845,7889	12061	16723,16735	21529,21573	24413344
22534755	3135	7847	12063	16725	21531	24413345
22534756	3137	7849	12065	16727	21533	24413346
22534757	3139	7851	12067	16729	21535	24413347
22534758	3141	7853,7891	12069	16731	21537	24413348
22534759	3143	7855	12071	16733	21539	24413349
22534760	3145	7857	12073	16737	21541	24413350

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22534762	3149	7861	12077	16741	21545	24413352
22534763	3151	7863	12079	16743	21547	24413353
22534764	3153	7865	12081	16745	21549	24413354
22534765	3155	7867	12083	16747	21551	24413355
22534766	3157	7869	12085	16749	21553	24413356
22534767	3159,3161	7871	12087	16751	21555	24413357
22534769	3165,3167	7875	12091,12093	16755	21559	24413359
22534770	3169	7877	12095	16757	21561	24413360
22534771	3171	7879	12097	16759	21563	24413361
22534772	3173	7881	12099	16761	21565	24413362
22534773	3175,4065	7883	12101	16763	21567	24413363
22534774	3177,3179,3683,4067	7885,7893	12103	16765	21569	24413364
22534775	3181	7895	12105,12159	16767	21571,21575	24413365
22534776	3183	7897	12107	16769,16795	21577	24413366
22534777	3185,3187	7899	12109	16771,17829	21579,21595,21597	24413367
22534779	3189	7901	12111	16773	21581	24413368
22534781	3191	7145,7905	12115	16777	21585	24413370
22534783	3195	7907	12151	16781	21601	24413371
22534784	3197	7909	12153	16783	21603	24413372
22534785	3199	7911	12155	16785,16787	21605	24413373
22534786	3201	7913	12157	16789	21607	24413374
22534787	3203	7915	12161	16791	21609	24413375
22534792	3207	6301	12169	16803	21617	24413379
22534793	3209,3211	6303,8769	12171	16805,16827	21619	24413380
22534794	3213	6305	12173	16807	21621	24413381
22534795	3215	6307	12175	16809,16811	21623	24413382
22534796	3217	6309	12177	16813	21625	24413383
22534797	3219	6311	12179	16815	21627	24413384
22534798	3221	6313	12181	16817	21629	24413385
22534799	3223	6315	12183	16819	21631	24413386
22534800	3225	6317	12185	16821	21633	24413387
22534801	3227	6319	12187	16823	21635	24413388
22534802	3229	6321	12189	16825,16829	21637	24413389
22534804	3231	6323,7921	12191,12193,12195	16831	21639	24413390
22534805	3233	7923,7925	12197	16833	21641	24413391
22534807	3237	7929,7931	12203	16839,16841	21645	24413393
22534808	3239	7933	12205	16843	21647	24413394
22534809	3241	7935	12207	16845	21649	24413395
22534810	3243	7937	12209	16847	21651	24413396
22534811	3245	7939	12211	16849	21653	24413397
22534812	3247	7941	12213	16851	21655	24413398
22534813	3249	7943	12215	16853	21657	24413399
22534814	3251	7945	12217	16855	21659	24413400
22534815	3253	7947	12219	16857	21661	24413401
22534816	3255,3257	7949	12221	16859	21663	24413402
22534819	3265	7955	12227	16865,16895	21669	24413405

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22534821	3269	7959	12231	16869	21673	24413407
22534822	3271	7961	12233,12249	16871,16873	21675	24413408
22534823	3273	7963	12235,12251	16875	21677	24413409
22534824	3275	7965	12237	16877	21679	24413410
22534825	3277	7967	12239	16879	21681	24413411
22534826	3279	7969	12241	16881	21683	24413412
22534827	3281	7971	12243	16883	21685	24413413
22534829	3283	7973	12245	16885	21687	24413414
22534830	3285	7975	12247	16887	21689	24413415
22534832	3289,3291	7979	12255,12257	16897,17773	21691	24413417
22534834	3295	7981	12259	16903	21693	24413418
22534835	3297	7983,7985	12261	16905	21695	24413419
22534837	3301,3969,3973	7987	12263	16907,16909,17749	21697	24413420
22534838	3303	7989	12265	16911	21699	24413421
22534839	3305	7991	12267,12301	16913	21701	24413422
22534840	3307	7993	12269	16915	21703,21705	24413423
22534841	3309,3311	7995	12271	16917	21707	24413424
22534842	3313	7997	12273	16919,16947	21709	24413425
22534843	3315,3317	7999	12275	16921	21711	24413426
22534844	3319	8001	12277	16923	21713	24413427
22534845	3321	8003	12279	16925	21715,21717	24413428
22534847	3323	8005	12281	16927	21719	24413429
22534848	3325	8007	12123,12283	16929	21721,22431	24413430
22534849	3327	8009	12285	16931	21723	24413431
22534850	3329	8011	12287	16933	21725	24413432
22534851	3331	8013	12289	16935	21727	24413433
22534852	3333	8015	12291	16937	21729	24413434
22534853	3335	8017,8021	12293	16939	21731	24413435
22534854	3337	8019,8023	12295	16941,16945,16949	21733	24413436
22534855	3339	8025	12297	16951	21735	24413437
22534857	3341	8029	12303	16955	21739,21741	24413440
22534858	3343	8031	12305	16957	21743	24413441
22534859	3345	8033	12311	16959	21745	24413442
22534860	3347,3349,3351	8035	12313	16961	21747,21749	24413443
22534861	3353	8037	12315	16963	21751,21755	24413444
22534862	3355	8039,8059	12317	16965	21753,21757	24413445
22534864	3359	8043	12321	16969,17757	21761	24413447
22534865	3361	8045	12323	16971	21763	24413448
22534866	3363	8047	12325	16973	21765	24413449
22534867	3365	8049	12327	16975	21767	24413450
22534868	3367	8051	12329	16977	21769	24413451
22534870	3369	8053	12331	16979	21771	24413452
22534871	3371	8055	12333	16981,16983	21773	24413453
22534872	3373	8057	12335	16985	21775	24413454
22534873	3375	8061	12337	16987	21777	24413455
22534874	3377	8063	12339	16989	21779	24413456

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22534928	3385	8067	12343	16993	21783	24413458
22534929	3387	8069	12345	16995	21785	24413459
22534932	3391	8073	12349	16999	21789	24413461
22534933	3393	8075	12351	17001	21791	24413462
22534935	3395	8079	12355	17005	21795	24413463
22534936	3397	8081	12357	17007	21797	24413464
22534937	3399	8083	12359	17009	21799	24413465
22534938	3401	8085	12361	17011	21801	24413466
22534950	3425	8107	12381	17035	21805	24413477
22534951	3427	8109	12383	17037	21807	24413478
22534952	3429	8111,8113	12385,12399	17039,17043,17935	21809,21821	24413479
22534954	3431	8115	12387	17041,17045	21811	24413480
22534955	3433	8117	12389	17047,17049	21813	24413481
22534956	3435	8119	12391,12401	17051	21815	24413482
22534957	3437	8121	12393	17053	21817	24413483
22534958	3439	8123	12395	17055,17057	21819	24413484
22534960	3441	8127	12405	17061	21825	24413486
22534961	3443	8129	12407	17063	21827	24413487
22534962	3445	8131	12409	17065	21829	24413488
22534963	3447	8133	12411	17067	21831	24413489
22534964	3449	8135	12413	17069	21833,21969	24413490
22534965	3451,3455	8137	12415	17071	18919,21835	24413491
22534966	3453,3457	8139	12417	17073	21837	24413492
22534967	3459	8141	12419	17075,17157	21839,21971	24413493
22534968	3461	8143	12421	17077	21841	24413494
22534969	3463	8145	12423	17079	21843	24412908,24413495
22534970	3465	8147	12425	17081	21845	24412913,24413496
22534972	3473	8151	12429	17089	21849	24412915,24413498
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22534975	3477	8155	12433	17093	21853	24413500
22534976	3479	8157,8159,8161	12435	17097	21855	24413501
22534977	3481	8163	12437	17099	21857	24413502
22534978	3483	8165	12439	17101	21859	24413503
22534980	3491	8173	12445	17107	21865	24413506
22534981	3493	6191	12447	17109	21867	24413507
22534982	3495,3497	6193	12449	17111	21869,21973	24413508
22534983	3499	8183	12451	17113,17159	21871	24413509
22534984	3501	8185	12453	17115,17161	21873	24413510
22534985	3503	8187	12455	17117,17163	21875	24413511
22534986	3505	8189	12457	17119	21877	24413512
22534987	3507	8191	12459	17121	21879	24413513

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22534989	3511	8195	12463	17125	21883	24413515
22534991	3513	8197	12465	17127,17165	21885	24413516
22534992	3515	8199	12467	17129,17167	21887	24413517
22534993	3517	8201	12469	17131	21889	24413518
22534995	3521	8205	12473	17135,17169	21893	24413520
22534997	3523	8209	12477	17139	21897,21899	24413521
22534998	3525	8211	12479	17141	21901	24413522
22534999	3529	8215	12485	17147	21907,21909	24413524
22535000	3531	8217	12487	17149,17171	21911	24413526
22535001	3533	8219	12489	17151,17173	21913	24413527
22535002	3535	8221	12491	17155,17175	21915	24413528
22535003	3537	8223	12493	17177	21917	24413529
22535004	3539	8225	12495	17179	21919	24413530
22535005	3541	8227	12497	17181	21921	24413531
22535006	3543	8229	12499	17183,17225	21923	24413532
22535007	3545	8231	12501	17185,17227	21925	24413533
22535009	3549,4013	8235	12505	17189,17191	21929	24413535
22535010	3551,3553,4015	8237	12507	17193	21931	24413536
22535011	3555,3559	8239	12509	17195	21933	24413537
22535012	3557,3561	8241	12511	17197	21935	24413538
22535016	3567,4069	8245	12515	17201,17233	21939	24413540
22535017	3569	8247	12517	17203	21941	24413541
22535018	3571	8249	12519	17205	21943	24413542
22535019	3573,3575	8251	12521	17207	21945	24413543
22535020	3577,3579	8253	12529	17209	21947	24413544
22535021	3581	8255	12531	17211	21949	24413545
22535073	3655	8363	12563	17337,17371	21989	24413568
22535076	3659	8367,8675	12567	17343	21995	24413571
22535077	3661	8369	12569,12571	17345	21997	24413572
22535022,22535078	3663	8371	12573	17347	21999,22019,22609	24413573
22535023,22535079	3665	8373	12575	17349	22001,22607	24413574
22535025,22535081	3667	8377	12579	17353	22005	24413575
22535082	3669	8379	12581	17359	22007	24413576
22535026,22535083	3671	8381	12583	17361	22009	24413577
22535027,22535084	3673	8383	12585	17363	22011,22677	24413578
22535085	3675,3677,4173	8385	12587	17365	22013	24413579
22535087	3681	8347,8389	12591	17303,17369	22017	24413581
22535090	3687	8395	12595	17379	22021	24413583
22535092	3689	8397	12597	17381	22023	24413584
22535093	3691,3693	8399	12599,12621	17383,17411,17413	22025	24413585
22535094	3695	8401	12601	17385,17415	22027,22053	24413586

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22535095	3697	8403	12603	17387	22029	24413587
22535096	3699	8405	12607	17391	22033	24413588
22535099	3703	8411	12611	17395,17397	22037	24413590
22535100	3705	8413	12613	17399	22039,22055	24413591
22535101	3707	8415	12615	17401,17417	22041	24413592
22535102	3711	8419	12619	17405,17421	22045	24413593
22535103	3713	8421	12623	17423	22047	24413594
22535104	3715	8423	12625,12627	17425	22049	24413595
22535108	3721	8429	12629	17431	22051	24413598
22535109	3723	8431,8433	12631,12633	17433	22057	24413599
22535110	3725	8435	12635	17435	22059	24413600
22535112	3729	8437,8497	12637	17437	22061	24413601
22535113	3731	8439	12639	17439	22063	24413602
22535114	3733	8441	12641	17441,17871	22065	24413603
22535116	3741	8445	12645	17445	22069	24413605
22535117	3743	8447,8449	12647,12649	17447,17457	22071	24413606
22535118	3745	8451	12651	17449,17459	22073	24413607
22535119	3747	8453	12653	17451	22075	24413608
22535120	3749	8455	12655	17453	22077,22079	24413610
22535121	3751	8457	12657	17455	22081	24413611
22535122	3753	8459	12659	17461	22083	24413612
22535123	3755	8461	12661	17463	22085,22087	24413613
22535124	3757	8463	12663	17465	22089	24413614
22535126	3759	8465,8733	12665	17467	22091	24413616
22533224,22535134	3761	4781,8481	9205,12681,12683	17485	18369,22107	24413624
22535136	3765	8485	12687	17489	22111	24413625
22535137	3767	8487	12689	17491	22113	24413626
22535138	3769	8489	12691	17493	22115	24413627
22535139	3771	8491	12693	17495	22117	24413628
22535140	3773	6449,8493	12695	17497	22119	24413629
	3776	6448	12698	17500	22122	
22535141	3779	6443,7353,8781	12699	17501	22123	24413631
22535142	3781	6441	12701	17503	21975,22181	24413632
22535143	3783	6439	12703	17505	22183	24413633
22535144	3785	6437	12705	17507	22185	24413634
22535146	3787	6433	12709	17511,17781	22189	24413635
22535147	3789	6431	12711	17513	22137,22139,22191	24413636
22535148	3791	6429	12713	17515	22193	24413637
22535150	3793,4109	6427	12715	17517	22195	24413638
22535151	3795	6425	12717	17519	22197	24413639
22535152	3797	6423	12719	17521	22199	24413640
22535153	3799	6421	12721	17523	22201	24413641
22535154	3801	6419	12723	17525	22203	24413642
22535155	3803	6417	12725	17527	22141,22205	24413643
22535156	3805	8645	12727	17529	22143,22207	24413644
22535157	3807	8643	12729	17531	22209	24413645
22535168	3809	8515	12757	17553	22231	24413659

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22535169	3811	8517	12759	17555	22233	24413660
22535170	3813	8519	12761	17557,17575, 17813	22235	24413661
22535171	3815	8521	12763	17559	22237	24413662
22535173	3817	8523	12765	17561	22239	24413663
22535174	3819	8525	12767	17563,17577, 17579,17581, 17883	22241	24413664
22535175	3821	8527	12769	17565,17583	22243	24413665
22535177	3823	8531	12773	17569,17585	22247	24413667
22535178	3825	8533	12775,12777	17571	22249	24413668
22535179	3827	8535	12779	17573,17587	22251,22289, 22291,22665	24413669
22535180	3829	8537	12781	17589,17633	22253	24413670
22535181	3831	8539	12783	17591,17635	22255	24413671
22535182	3833	8541	12787	17593,17899	22257	24413672
22535185	3847	8547	12833	17649	22303	24413675
22535186	3849	8549	12835	17651	22305	24413676
22534913,22535187	3851,3853,3855,3857	8551	12837,12839	17653	22307	24413677
22535188	3859	8553	12841,12843	17655	22309,22313	24413678
22535189	3861,3863	8555	12845	17657	22311,22315	24413679
22535190	3865	6941,8557	12847	17659	22317	24413680
22535192	3867	7535,8559	12849	17661	22319	24413681
22535193	3869	8561	12851,12873	17663	22321	24413682
22535194	3871	8563	12853	17665	22323	24413683
22535195	3873	8565	12855	17667	22325	24413684
22535196	3875	8567	12857	17669	22327	24413685
22535197	3877	8569	12859	17671,17673	22329	24413686
22535198	3879	8571	12861	17675	22331	24413687
22535199	3881	8573	12863	17677	22333	24413688
22535200	3883	8575	12865,12867	17679	22335	24413689
22535201	3885	8577	12869	17681	22337	24413690
22535202	3887	8579	12871,12875	17683	22339	24413691
22535205	3889	8587	12881	14031	22345	24413694
22535206	3891	8589	12883	14033	22347	24413695
22535207	3893	8591	12885	14035	22349	24413696
22535208	3895	8593	12887	14037	22351,22353, 22355	24413697
22535209	3897	8595	12889	14039	22357	24413698
22535210	3899	8597	12891	14041	22359	24413699
22535211	3901	8599	12893	14043	22361,22363	24413700
22535212	3903	8601	12895	14045	22365	24413701
22535213	3905	8603	12897	14047,14049	22367	24413702
22535214	3907	8605	12899	14051	22369	24413703
22535215	3909	8607	12901	14053	22371	24413704
22535216	3911	8609	12903	14055	22373	24413705
22535218	3913	8611	12905	14057	22375	24413706
22535219	3915	8613	12907	14059	22381	24413707
22533936	3953	6239	10621	15117	19901	23095379

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22535183	4019	8543	12789	17595	22259	24413673
22535184	4021	8545	12791	17597	22261	24413674
22534180	4033	6793	11069	15613,15615	20375,20377	23095700
22534179	4035	6791	11067	17761	20373	23095699
22534178	4037	6785,6789	9893,11065	15611,17763, 17943	20371	23095698
22534519	4119	7377,7381	11633	16245	21069,21071	24413136
22534199	4193	6825	11101	15649	20409	23095716
22534198	4195	6823	11099	15647	20407	23095715
22534191	4209	6813	11089	15637	20397	23095710

TABLE VI—Variable coding sequences

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533006	19,3631	4307,8305,8323,8325,8327,8329,8787	-	14079,17271	22401	23094430
22533033	79	-	8827	13207	17987	23094454
22533050	119	-	8861	-	18021	-
22533053	123	4407	8865	13267	-	23094474
22533062	141	-	8883	-	18059	23094483
22533086	187	4489	8933	-	18115	23094506
22533088	189	4491	8935	-	18117	23094508
22533089	191	4493	8937	-	18119	23094509
22533142	277	4597,4599	9041	13457	22175	-
-	283	4601	9043	13459	-	-
-	331	4649	9093	13511	18251	23094580
22533175	353	4677	9117	-	18271	23094592
22533179	361	4685	9125	13539	18279	-
22533180	363	4687	9127	13541	-	23094596
22533196	395	4717	9157	13571	18317,18321	-
-	455	-	-	-	18377	23094639
22533230	457	-	9215	-	18379	23094640
22533234	461	-	9223	-	18385	23094643
22533235	463	-	9225	-	18387	23094644
22533236	465	-	9227	-	18389	23094645
22533238	467	-	9229	-	18391	23094646
22533239	469	-	9231	-	18393	23094647
22533240	471	-	9233	-	18395	23094648
22533242	475	4815	9241,12547	-	18399,21965,22459	23094650
22533243	477	4817	9243	-	18401	23094651
22533244	479	4819	9245,9247	-	18403	23094653
22533246	483	4825	9251	-	18409	23094654
22533247	485	4827	9253	-	18411	23094655
22533248	487	4829	9255	-	18413	-
22533249	489	4831	9257	13163	18415	-
22533261	507	-	9479	13667	18131	-
22533262	509	-	9481	13669,13689	18133	-
22533263	513	-	9483	-	-	-
22533264	515	-	9485	-	18439	-
22533324	629	-	9415	13805	18559	23094723
-	633	4987	9419	13809	18563	23094725
22533275,22533562,22533988,22534486,22534579,22535047	879,1623,1807,2331	6713,7067	12307,12559,12755,13113	-	19961,19985,20295,20835,21979,22125,22177,22379,22649	-
22533274,22533563,22533989,22534485,22534580,22535046	881,883,1621,1809,2333	6327,6711,7069	12309,12561,12753,13041,13115	-	19963,19987,20293,20833,21977,22127,22179,22377	-

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22533455	893	8343	9685	14169,17299	-	23094896
22533457	895	-	9687	14171	-	-
-	899,901	5275,5277	9693	14175,14177	18881,18885, 22563	23094907
22533459	905	5281	9697	-	18927	23094911
22533462	911	-	9703	14185	-	23094914
22533466	919	-	-	-	18941	-
-	935,937	5315	9729	14201	18959,18961	23094926
22533484	957	5335	9749	14221	18981	-
22533500	991	-	-	-	-	23094951
22533525	1037	5411	-	-	19061	23094974
-	1063	5439	9851	14341	19197	23094987
-	1123	5621	9911	14397	19255	-
-	1127	5625	9915	14401	19259	-
-	1129	5627	9917	14403	19261	-
22533627	1139	5617	-	-	-	-
22533628	1149,3951	5619,5653	9937	14425	19171,19301	-
22533653	1179	-	10059	14467	-	23095032
22533654	1181	-	10061	14469	-	23095033
22533655	1183	-	9965,10063	14471	-	23095034
-	1185	-	10065	-	-	23095035
22533656	1189	5649,6959	9933,10069,1 1229	14421,14477, 15787	19297,20539	-
22533657	1191,1193,23 23,2325	-	10071	14479,15805	-	23095038
-	1195	-	10073	14481	-	23095039
22533659	1199	-	10079	14489	-	23095041
22533660	1203,1205	-	10081	14491	-	23095042
22533661	1207,1211	-	10083	14493	-	23095043
22533666	1223	-	10093	14503	19345	23095047
-	1227	5689	10099	14509	19335	23095048
22533667	1229	5691	10101	14511	19337	-
22533688	1265	-	10135	14547	19373	-
22533689	1267	-	10137	14549	19375	-
22533690	1269	-	10139	14551	19377,19411	-
22533692	1271	-	10141	14553,14555, 14595	19379	-
-	1273	-	10143	14557	19381,19383	-
-	1275	-	10145	14559	19385	-
22533693	1279,1281	-	10149,10151	14563,14565, 14567,14569, 14597,14599	19389,19391, 19393	-
22533695	1283	-	10153,10155	14571,14601	19395	-
22533696	1285	5725	10157	14573	19397	-
-	1287,1289,12 91	5727	10159,10161	14575,14577	19399,19401	23095066
-	1293	5729	10163	14579	19403	23095067
-	1627	6087	10507	14995,14997	19787	23095307
22533877	1631	6091	10511	-	19791	23095309
22533892	1669	6127	10539	15031	19827	-

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
-	1731	6179	-	-	19879	-
-	1751	6241	10623	15119	19903	23095380
-	1753	6243	10625	15121	19905	23095381
22533964	1765	-	10637	15133	19917	-
-	1821	6339	10693	15241,15243	19975	23095412
22534042	1907	6487	10793	15359	20091	-
22534044	1909	6491	-	15363	-	23095506
22534045	1911	6493	-	15365	-	23095508
22534046	1913	6495	10797	15373	-	23095509
22534048	1915	6499	-	-	-	23095510
-	1923	6507	-	-	-	23095511
22534051	1925	6509	10825	-	-	23095512
22534052	1927	6511	-	-	-	23095513
22534055	1937	6517	-	-	-	23095516
22534056	1939,1943	6519,6521	10833	-	20111	23095517
22534063	1955	6537,6543	10845,10847	-	20125,20127	23095524
-	1977	6565	10869	15411	22495	23095535
-	2143	-	-	-	-	23095690
-	2145	-	-	-	-	23095691
-	2147	-	-	-	-	23095692
-	2151	-	-	-	-	23095693
-	2283	6925	11201	15753	20509	24412876
-	2285	-	-	-	-	24413553
-	2293	6933	11209	15761	20517	24412880
22534263	2311	-	-	14715,15053, 15793	-	-
-	2313	6967	11235,11237	15795	20545,20547	24412892
22534265	2317	-	-	15799	-	-
22534266	2319	-	-	15801	-	-
-	2321	-	-	15803	-	-
22534273	2337	-	13025,13053	15811	20565,22499	24412896
22534274	2339	-	13027,13055	15813	20567,22501	24412897
22534275	2341	-	-	-	20569	24412907
22534276	2343	-	-	-	20571	24412918
22533658	2345	-	-	14483	20573	24412919
22534278	2347	-	-	-	20575	-
22534282	2353,2355	-	-	-	20585,20603	-
22534283	2357	-	-	-	20587	-
22534285	2359	-	-	-	20589,20605	-
22534286	2361	-	-	-	20591	-
22534287	2363,2365	-	-	-	20593	-
-	2367	-	-	-	20595	-
22534288	2371,4151,4177	-	-	-	20599	-
22534290	2373	-	-	15189	20601	-
22534291	2375	-	-	-	20607	-
22534293	2377,4103	-	9899,9901,9903	-	20361,20363, 20365,20611	23095694
22534294	2379	-	-	-	20613	-
22534295	2381	-	-	-	20615	-

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
22534296	2383	-	-	-	20617	-
22534299	2385	-	-	-	20623	24412926
22534300	2387	-	-	-	20625	24412927
22534301	2389	-	-	-	20627	24412928
22534305	2391	-	-	-	20633,20635, 20637,20675, 22543	24412932
22534306	2393	-	-	-	20639	24412934
22534307	2395	-	-	-	20641	24412935
22534308	2397	-	-	-	20643	24412936
22534310	2399	-	-	-	20645	24412937
22534311	2401	-	-	-	20647	24412938
22534313	2405	-	-	-	20651	24412940
22534314	2407	-	-	-	20655	24412942
22534315	2409	-	-	-	20657	24412943
-	2411	-	-	-	20659	24412944
22534316	2413	-	-	-	20661	24412945
22534317	2415	-	-	-	20663	-
22534318	2417	-	-	-	20665	24412947
22534321	2419	-	-	-	20669	24412950
22534322	2421	-	-	-	20671	-
22534323	2423	-	-	-	20673	24412952
22534324	2425	-	-	-	20677	24412953
22534384	2531	7105	11363	-	-	24413007
22534385	2533	-	11365	-	20801	24413008
22534402	2567	-	11399	16001	20841	24413024
22534411	2585	7159	-	16041	22521	24413033
22534433	2621	7201	11455	-	20897	24413055
22534436	2627	7207	11461	-	20903	24413058
-	2631,2713	7211,7315	11465,11575, 11577,11579	-	20907,21015	24413060
22534458	2667	-	11509	-	-	24413080
-	2681	7275	11543	17709	20981	24413095
22534475	2683	7277	11545	-	20983	24413096
22534476	2685	7279	11547	-	20985	24413097
22534479	2691	7285	11553	-	20991	24413100
22534481	2695	7289	11557	-	20997	24413102
22534482	2697	7291	11559	-	20999	24413103
22534484	2701	7295	11563	-	21003	24413105
-	2703	7297	11565	-	21005	24413106
22534487	2705	7299,7309	11567	-	21007	24413107
22534488	2707	7301	11569	-	21009	24413108
22534489	2709	7303,7311	11571	-	21011,21119	24413109
22534523	2757	7387	11639	16251	21077	-
22534524	2759	-	-	-	-	24413139
22534550	2795	7435	11679	-	21117	24413160
22534551	2797,2799,2901,2903,3293,4289	4785	-	13409,13411, 16075,16211, 16409,16899, 16901,17407,	18191	23094635

2603vr	18rs21	515	cjb111	coh1	h36b	NEM316
				17735,17769, 17771,17855		
22534091	2807	-	-	14133,14347, 15669,15765, 16181,16313, 17087,17357	-	-
22534092	2809	-	-	14131,14349, 15665,15667, 15763,16183, 16315,17085, 17355,17711, 17789	20583	-
-	2841,2843	7473,7475	11717	16349	21173	24413179
-	2887	7519	11759	16395	21219	24413201
22534631	2953	7591	11823	16467	-	24413230
22534648	2985	7625	11859	16499	21317	-
22534681	3033	7687	11919	16577	21383	-
-	3105,3107	7819	12033	16693	21507,21509	24413331
22534748	3123	7835	12051	-	19281	24413339
22534782	3193	-	-	16779	22583	-
22534817	3259	-	-	16861,16891	-	-
22534831	3287	7977	12253	16889	-	24413416
22534836	3299	-	-	-	-	-
22534939	3403	8087	12363	17013	-	24413467
22534940	3405	8089	12365	17015	-	24413468
22534941	3407	8091	12367	17017	-	24413469
22534942	3409	8093	12369	17019	-	24413470
22534943	3411	8095	12371	17021	-	24413471
22534945	3413	8097	12373	17023	-	24413472
22534946	3415	8099	12375	17025	-	24413473
22534947	3417	8101	12377	17027	-	24413474
22534948	3419	8103	12379	17029	-	24413475
22534949	3421,3423	8105	-	17031,17033	21803	24413476
-	3485,3489	8169,8171	12443	17105	21863	24413505
-	3527	8213	12483	17145	21905,22551	24413523
22535037	3585	8259	-	17217	-	23094905
22535038	3587	8261	-	17219	-	-
22535039	3589	8265,8271	-	17221	-	23094903
22535040	3591	8273	-	17223,17235	-	23094902
22535041	3593,3595	8275	-	17237	-	23094901
22535044	3597	8277	-	17239	-	-
22535045	3599,3601	8279	-	17241,17243	-	-
22535048	3603	8281	-	17245	-	-
22535049	3605	8283	-	17247	-	-
22535050	3607	8285	-	17249	-	-
22535056	3609	-	-	-	-	-
22535057	3611	-	-	17261,17263	-	-
22535058	3613	8299	-	17265	-	-
22535059	3615	8301	-	17267	-	-
22535060	3617	8303	-	17269	-	-

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22535071	3653	8359	-	17315	21983,21987	24413567
22535075	3657	-	12565	17341	21993	24413570
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22535111	3727	-	-	-	-	-
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-	4277	-	12821	17825	22293	-
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22533115	-	4547	8989	13395	18181	23094533
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22533130	-	4581	9019	13433	18213	23094547
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22533785	-	5907	10337	14805	19597	23095223
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-	-	-	12143	-	22451	-
-	-	-	12481	17143,17947	21903	-
-	-	-	12605	17389	22031	-
-	-	-	12817	17629	22509	-
-	-	-	12929	-	18873	-
-	-	-	13045	15817	-	-
-	-	-	-	17213	21951	-
-	-	-	-	17615	22275	-
-	-	-	-	17617	22277	-
-	-	-	-	17621	22281	-

TABLE VII – Phase-variable coding sequences

Variable gene [1]	Location of repeat	Position of repeat [2]
SEQ ID NO: 1821	5' end	145
SEQ ID NO: 1861	5' end	2
SEQ ID NO: 957	5' end	116
SEQ ID NO: 1941	5' end	13
SEQ ID NO: 2141	5' end	11
SEQ ID NO: 2863	5' end	21
SEQ ID NO: 2887	5' end	295
SEQ ID NO: 3191	5' end	18
SEQ ID NO: 2447	5' end	3
SEQ ID NO: 3775	5' end	301
SEQ ID NO: 6773	5' end	76
SEQ ID NO: 3723	Middle	1120
SEQ ID NO: 2313	3' end	3185
SEQ ID NO: 719	Promoter	40
SEQ ID NO: 4631	Promoter	103
SEQ ID NO: 2373	Promoter	1

[1] Given for one strain only; Table II can be used to find any homologs in other strains.

[2] relative to ATG

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CLAIMS

1. An isolated polypeptide comprising an amino acid sequence which has at least 75% sequence identity to one or more of the even-numbered amino acid sequences selected from the group consisting of SEQ ID NOS:2-22740.

2. The polypeptide of claim 1, comprising one or more of the even-numbered amino acid sequences selected from the group consisting of SEQ ID NOS:2-22740.

3. An isolated polypeptide comprising a fragment of at least 7 consecutive amino acids from one or more of the even-numbered amino acid sequences selected from the group consisting of SEQ ID NOS:2-22740.

4. The polypeptide of claim 3, wherein the fragment comprises a T-cell or a B-cell epitope from an even-numbered amino acid sequence selected from the group consisting of SEQ ID NOS:2-22740.

5. An antibody which binds to the polypeptide of any preceding claim.

6. The antibody of claim 5 which is monoclonal.

7. An isolated nucleic acid comprising a nucleotide sequence which has at least 75% sequence identity to one or more of the odd-numbered nucleotide sequences selected from the group consisting of SEQ ID NOS:1-22739.

8. The nucleic acid of claim 7, comprising a nucleotide sequence which is an odd-numbered nucleotide sequence selected from the group consisting of SEQ ID NOS:1-22739.

9. An isolated nucleic acid which can hybridize to the nucleic acid of claim 8 under high stringency conditions.

10. An isolated nucleic acid comprising a fragment of 10 or more consecutive nucleotides from one or more of the odd-numbered nucleotide sequences selected from the group consisting of SEQ ID NOS:1-22739.

11. An isolated nucleic acid encoding the polypeptide of any one of claims 1 to 4.

12. A composition comprising: (a) polypeptide, antibody, and/or nucleic acid of any preceding claim; and (b) a pharmaceutically acceptable carrier.

13. The composition of claim 12, further comprising a vaccine adjuvant.

14. The nucleic acid, polypeptide, or antibody of any one of claims 1 to 11 for use as a medicament.

15. A method of treating a patient, comprising administering to the patient a therapeutically effective amount of the composition of claim 12.

16. Use of the nucleic acid, polypeptide, or antibody of any one of claims 1 to 11 in the manufacture of a medicament for treating or preventing disease and/or infection caused by GBS.