the general idea of phasing SNPs from long-read sequencing data, using heterozygous SNPs as reference for aligning the sequences from one type of nucleic acid (i.e., DNA or RNA). This method relies on having several heterozygous SNPs in a locus if long distances need to be covered by the sequencing run. However, depending on the target sequence to be analyzed and the positions of the SNPs used for phasing, this may not always be possible.

Therefore, a need exists for a novel method, which overcomes such technical issues related to the necessity for high-input of genomic DNA, short-reads, custom oligonucleotide development or high-error profile.

SUMMARY

In order to tackle the shortcomings of current methods, the present disclosure provides a hybrid analysis of long amplicons generated from genomic DNA and cDNA (mRNA) for pairing of distant information via spatial linkage, i.e., phasing of two or more required loci. Such methods may provide for significant advancements in applied diagnostics and are a prerequisite for allele-specific treatment for genetic diseases such as Huntington's disease. Applying a hybrid approach as disclosed herein using both DNA and cDNA (reverse transcribed from mature mRNA) as a starting material, it is possible to phase a short tandem repeat or an exonic single nucleotide polymorphism of interest and a distant target SNP (intronic or exonic) via an exonic reference SNP using only a very small number of amplicons (e.g., at least one DNA and at least one cDNA amplicon). Herein, the method allows for the analysis of a heterozygous and a homozygous exonic or intronic target SNP. In particular, in order to best resolve the phasing information, the exonic reference SNP should be heterozygous if the target SNP is heterozygous.

The methods and kits are particularly applicable in the field of companion diagnostics, which involves the identification of loci to provide critical information on a patient’s genomic status that can be used to safely and effectively match a patient with a specific treatment or drug therapy thereby identifying and stratifying patients who are most likely to benefit from a particular drug treatment or therapy. Such applications have become increasingly important in recent years as more targeted therapies are being developed. Furthermore, the methods and kits of the disclosure may also be used in basic research, where it can aid in the identification of genetic variations associated with various diseases and conditions. This can lead to a better understanding of the underlying mechanisms of diseases, which can ultimately lead to the development of new therapies and treatments.

In one example, a method of phasing at least one distant single nucleotide polymorphism of interest and short tandem repeats within the same target gene locus of nucleic acids isolated from a

biological sample is provided, the method comprising: (a) performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; (b) performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the short tandem repeats and said at least one exonic reference single nucleotide polymorphism; (c) determining the nucleic acid sequence of the first and the second amplification product; (d) aligning the nucleic acid sequences of the first and the second amplification product determined in step (c) based on the position of the at least one exonic reference single nucleotide polymorphism; and (e) determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats in the sample. In one aspect, the present disclosure refers to a method of phasing at least one distant single nucleotide polymorphism of interest and short tandem repeats within the same target gene locus of nucleic acids isolated from a biological sample, the method comprising: a. performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; b. performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the short tandem repeats and said at least one exonic reference single nucleotide polymorphism; c. determining the nucleic acid sequence of the first and the second amplification product; d. aligning the nucleic acid sequences of the first and the second amplification product determined in step (c) based on the position of the at least one exonic reference single nucleotide polymorphism; e. determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats in the sample. In one example, the at least one distant single nucleotide polymorphism of interest is an intronic single nucleotide polymorphism. In a particular example, the intron carrying the at least one distant single nucleotide polymorphism of interest is located adjacent to the exon carrying the at least one exonic reference single nucleotide polymorphism within the same gene locus of the isolated genomic DNA. In one example, the amplification step (a) and the reverse transcription and amplification step (b) are performed in separate reaction vessels. In another example, the nucleic acid sequence of the first and the second amplification product in step (c) is determined using long-read sequencing, such as PacBio sequencing, also referred to as SMRT (Single Molecule Real Time) sequencing, or nanopore-based DNA long-read sequencing as commercialized by Oxford Nanopore Technologies. In another example, the biological sample is selected from the group consisting of tissue, tumor tissue, blood, saliva and cell lines derived from an individual. In one example, when aligning the nucleic acid sequences of the first and the second amplification product in step (d) the at least one exonic reference single nucleotide polymorphism is heterozygous if the at least one distant single nucleotide polymorphism of interest is heterozygous. In another example, prior to aligning the nucleic acid sequences of the first and the second amplification product in step (d) the method further comprises the step of aligning the nucleic acid sequence of the first and the second amplification product to the nucleic acid sequence of a reference gene of the target gene locus or to the nucleic acid sequence of the complete human genome or to parts thereof comprising a reference gene of target gene locus. In another example, the target gene locus is the huntingtin gene. In a particular example, the short tandem repeats are CAG repeats. In some examples, the at

least one single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099. Herein, the exonic reference single nucleotide polymorphism (such as, e.g., rs362331, rs362273, rs34315806, and rs363099) must not be the same as (i.e., does not correspond to) the at least one single nucleotide polymorphism of interest. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099 if the at least one single nucleotide polymorphism of interest is an intronic SNP. In certain examples, the at least one exonic reference single nucleotide polymorphism is rs362331. In certain examples, determining the haplotype of the short tandem repeats comprises determining the number of the short tandem repeats units. In certain examples, the mRNA is a spliced mRNA (mature mRNA).

In another example, an *in vitro* method for diagnosing if an individual has a risk of developing Huntington's disease is provided, the method comprising: (a) determining the haplotype of at least one distant single nucleotide polymorphism of interest and short tandem repeats in an *in vitro* sample obtained from said individual by performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the short tandem repeats and said at least one exonic reference single nucleotide polymorphism; determining the nucleic acid sequence of the first and the second amplification product; aligning the nucleic acid sequences of the first and the second amplification product determined in the previous step based on the position of the at least one

exonic reference single nucleotide polymorphism; and determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats in the sample; (b) determining the individual's risk of developing Huntington's disease based on the haplotype of the at least one distant single nucleotide polymorphism of interest and the CAG short tandem repeats determined in step (a). In one example, the at least one distant single nucleotide polymorphism of interest is an intronic single nucleotide polymorphism. In a particular example, the intron carrying the at least one distant single nucleotide polymorphism of interest is located adjacent to the exon carrying the at least one exonic reference single nucleotide polymorphism within the same gene locus of the isolated genomic DNA. In one aspect, the present disclosure refers to an *in vitro* method for diagnosing if an individual has a risk of developing Huntington's disease, the method comprising: a. determining the haplotype of at least one distant single nucleotide polymorphism of interest and short tandem repeats in an *in vitro* sample obtained from said individual using the method disclosed herein; b. determining the individual's risk of developing Huntington's disease based on the haplotype of the at least one distant single nucleotide polymorphism of interest and the CAG short tandem repeats determined in step (a). In one aspect, the present disclosure refers to an *in vitro* method of identifying a patient having Huntington's disease as likely to respond to a therapy targeting at least one single nucleotide polymorphism of interest, the method comprising: a. determining the haplotype of the at least one distant single nucleotide polymorphism of interest and short tandem repeats in an *in vitro* sample obtained from said individual using the method disclosed herein; b. identifying the patient as likely to respond to the therapy based on the haplotype determined in step (a) and the determination of the presence of a specific allele of the at least one single nucleotide polymorphism of interest. In one example, the amplification step and the reverse transcription and amplification step are performed in separate reaction vessels. In another example, the nucleic acid sequence of the first and the second amplification product is determined using long-read sequencing, such as PacBio sequencing, also referred to as SMRT (Single Molecule Real Time) sequencing, or nanopore-based DNA long-read sequencing as commercialized by Oxford Nanopore Technologies. In another example, the biological sample is selected from the group consisting of tissue, tumor tissue, blood, saliva and cell lines derived from an individual. In one example, when aligning the nucleic acid sequences of the first and the second amplification product the at least one exonic reference single nucleotide polymorphism is heterozygous if the at least one distant single nucleotide polymorphism of interest is heterozygous. In another example, prior to aligning the nucleic acid sequences of the first and the second amplification product the method further comprises the step of aligning the nucleic acid sequence of the first and the second amplification product to the nucleic acid sequence of a reference gene of the target gene locus or to the nucleic acid sequence of the complete human genome or to parts thereof comprising a reference gene of target gene locus. In another example, the target gene locus is the huntingtin gene. In a particular example, the short tandem repeats are CAG repeats. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099. Herein, the exonic reference single nucleotide polymorphism (such as, e.g., rs362331,

rs362273, rs34315806, and rs363099) must not be the same as (i.e., does not correspond to) the at least one single nucleotide polymorphism of interest. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099 if the at least one single nucleotide polymorphism of interest is an intronic SNP. In certain examples, the at least one exonic reference single nucleotide polymorphism is rs362331. In certain examples, determining the haplotype of the short tandem repeats comprises determining the number of the short tandem repeats units. In certain examples, the mRNA is a spliced mRNA (mature mRNA).

In another example, an *in vitro* method of identifying a patient having Huntington's disease as likely to respond to a therapy targeting at least one single nucleotide polymorphism of interest, the method comprising: (a) determining the haplotype of the at least one distant single nucleotide polymorphism of interest and short tandem repeats in an *in vitro* sample obtained from said individual by performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the short tandem repeats and said at least one exonic reference single nucleotide polymorphism; determining the nucleic acid sequence of the first and the second amplification product; aligning the nucleic acid sequences of the first and the second amplification product determined in the previous step based on the position of the at least one exonic reference single nucleotide polymorphism; and determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats in the sample; (b) identifying the patient as likely to respond to the therapy based on the haplotype determined in step (a) and the determination of the presence of a specific allele of the at least one single nucleotide polymorphism of interest. In some examples, the therapy targeting at least one single nucleotide polymorphism of interest is an antisense oligonucleotide treatment directed to suppress an RNA molecule comprising the specific allele of the at least one single nucleotide polymorphism of interest. In one example, the at least one distant single nucleotide polymorphism of interest is an intronic single nucleotide polymorphism. In a particular example, the intron carrying the at least one distant single nucleotide polymorphism of interest is located adjacent to the exon carrying the at least one exonic reference single nucleotide

polymorphism within the same gene locus of the isolated genomic DNA. In one example, the amplification step (a) and the reverse transcription and amplification step (b) are performed in separate reaction vessels. In another example, the nucleic acid sequence of the first and the second amplification product in step (c) is determined using long-read sequencing, such as PacBio sequencing, also referred to as SMRT (Single Molecule Real Time) sequencing, or nanopore-based DNA long-read sequencing as commercialized by Oxford Nanopore Technologies. In another example, the biological sample is selected from the group consisting of tissue, tumor tissue, blood, saliva and cell lines derived from an individual. In one example, when aligning the nucleic acid sequences of the first and the second amplification product the at least one exonic reference single nucleotide polymorphism is heterozygous if the at least one distant single nucleotide polymorphism of interest is heterozygous. In another example, prior to aligning the nucleic acid sequences of the first and the second amplification product the method further comprises the step of aligning the nucleic acid sequence of the first and the second amplification product to the nucleic acid sequence of a reference gene of the target gene locus or to the nucleic acid sequence of the complete human genome or to parts thereof comprising a reference gene of target gene locus. In another example, the target gene locus is the huntingtin gene. In a particular example, the short tandem repeats are CAG repeats. In some examples, the at least one single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099. Herein, the exonic reference single nucleotide polymorphism (such as, e.g., rs362331, rs362273, rs34315806, and rs363099) must not be the same as (i.e., does not correspond to) the at least one single nucleotide polymorphism of interest. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099 if the at least one single nucleotide polymorphism of interest is an intronic SNP. In certain examples,

the at least one exonic reference single nucleotide polymorphism is rs362331. In certain examples, determining the haplotype of the short tandem repeats comprises determining the number of the short tandem repeats units. In certain examples, the mRNA is a spliced mRNA (mature mRNA).

In another example, a kit for determining the nucleic acid sequence of at least one distant single nucleotide polymorphism of interest and short tandem repeats within the same target gene locus of nucleic acids isolated from a biological sample is provided, the kit comprising a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; and a second set of oligonucleotide primers to produce a second amplification product comprising the at least one exonic single nucleotide polymorphism of interest and said at least one exonic reference single nucleotide polymorphism. In one aspect, the resent disclosure refers to a kit for determining the nucleic acid sequence of at least one distant single nucleotide polymorphism of interest and short tandem repeats within the same target gene locus of nucleic acids isolated from a biological sample, the kit comprising: - a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; - a second set of oligonucleotide primers to produce a second amplification product comprising the at least one exonic single nucleotide polymorphism of interest and said at least one exonic reference single nucleotide polymorphism. Herein, the kit is adapted for performing any of the methods disclosed herein. In a particular example, the first set of oligonucleotide primers comprises an oligonucleotide primer comprising the nucleic acid sequence of SEQ ID NO:1 and an oligonucleotide primer comprising the nucleic acid sequence of SEQ ID NO:2. In another particular example, the second set of oligonucleotide primers comprises an oligonucleotide primer comprising the nucleic acid sequence of SEQ ID NO:3, an oligonucleotide primer comprising the nucleic acid sequence of SEQ ID NO:4 and an oligonucleotide primer comprising the nucleic acid sequence of SEQ ID NO:5. In some examples, the kit further includes at least one of nucleoside triphosphates, nucleic acid polymerase, and buffers necessary for the function of the nucleic acid polymerase and/or a reverse transcriptase. In some examples, the kit further includes any one of reagents for amplification, such as a reverse transcriptase, a DNA polymerase, dNTPs, buffers, and/or other elements (*e.g.*, cofactors or aptamers) appropriate for reverse transcription and/or amplification. Typically, the reagent mixture(s) is concentrated, so that an aliquot is added to the final reaction volume, along with sample (*e.g.*, RNA or DNA), enzymes, and/ or water. In some examples, the kit further comprises reverse transcriptase (or an enzyme with reverse transcriptase activity), and/or DNA polymerase (*e.g.*, thermostable DNA polymerase such as Taq, ZO5, and derivatives thereof).

In another example, a method of phasing at least one distant single nucleotide polymorphism of interest and at least one exonic single nucleotide polymorphism of interest within the same target gene locus of nucleic acids isolated from a biological sample, the method comprising: (a) performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to

produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; (b) performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the at least one exonic single nucleotide polymorphism of interest and said at least one exonic reference single nucleotide polymorphism; (c) determining the nucleic acid sequence of the first and the second amplification product; (d) aligning the nucleic acid sequences of the first and the second amplification product determined in step (c) based on the position of the at least one exonic reference single nucleotide polymorphism; and (e) determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the at least one exonic single nucleotide polymorphism of interest in the sample. In one aspect, the present disclosure refers to a method of phasing at least one distant single nucleotide polymorphism of interest and at least one exonic single nucleotide polymorphism of interest within the same target gene locus of nucleic acids isolated from a biological sample, the method comprising: a. performing an amplification step comprising contacting genomic DNA isolated from said biological sample comprising the target gene locus with a first set of oligonucleotide primers to produce a first amplification product comprising the at least one single nucleotide polymorphism of interest and at least one exonic reference single nucleotide polymorphism in the same gene locus; b. performing a reverse transcription and amplification step comprising contacting mRNA isolated from said biological sample comprising the target gene locus with a second set of oligonucleotide primers to produce a second amplification product comprising the at least one exonic single nucleotide polymorphism of interest and said at least one exonic reference single nucleotide polymorphism; c. determining the nucleic acid sequence of the first and the second amplification product; d. aligning the nucleic acid sequences of the first and the second amplification product determined in step (c) based on the position of the at least one exonic reference single nucleotide polymorphism; e. determining the haplotype of the at least one distant single nucleotide polymorphism of interest and the at least one exonic single nucleotide polymorphism of interest in the sample. In one example, the at least one distant single nucleotide polymorphism of interest is an intronic single nucleotide polymorphism. In a particular example, the intron carrying the at least one distant single nucleotide polymorphism of interest is located adjacent to the exon carrying the at least one exonic reference single nucleotide polymorphism within the same gene locus of the isolated genomic DNA. In one example, the amplification step (a) and the reverse transcription and amplification step (b) are performed in separate reaction vessels. In another example, the nucleic acid sequence of the first and the second amplification product in step (c) is determined using long-read sequencing, such as PacBio sequencing, also referred to as SMRT (Single Molecule Real Time) sequencing, or nanopore-based DNA long-read sequencing as commercialized by Oxford Nanopore Technologies. In another example, the biological sample is selected from the group consisting of tissue, tumor tissue, blood, saliva and cell lines derived from an individual. In one example, when aligning the nucleic acid sequences of the first and the second amplification product in step (d) the at least one exonic reference single nucleotide polymorphism is heterozygous if the at least one distant single nucleotide polymorphism of interest is heterozygous. In another example, prior to aligning the nucleic acid sequences of the first and the second amplification product in step (d) the method further comprises the step of aligning the nucleic acid sequence of the first and the second amplification product to the nucleic acid sequence of a reference gene of the target gene locus or to the nucleic acid sequence of the complete human genome or to parts thereof comprising a reference gene of target gene locus. In another example, the target gene locus is the huntingtin gene. In some examples, the at least one single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086,

rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099. Herein, the exonic reference single nucleotide polymorphism (such as, e.g., rs362331, rs362273, rs34315806, and rs363099) must not be the same as (i.e., does not correspond to) the at least one single nucleotide polymorphism of interest. In some examples, the at least one exonic reference single nucleotide polymorphism is selected from the group consisting of rs362331, rs362273, rs34315806, and rs363099 if the at least one single nucleotide polymorphism of interest is an intronic SNP. In certain examples, the at least one exonic reference single nucleotide polymorphism is rs362331. In certain examples, the mRNA is a spliced mRNA (mature mRNA).

In another example, an antisense oligonucleotide specifically hybridizing to at least one distant single nucleotide polymorphism of interest in an huntingtin (HTT) gene for use for treating a patient having Huntington's disease is provided, wherein the patient is selected for treatment when determining a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the CAG short tandem repeats detected in a biological sample of the patient. In one aspect, the present disclosure refers to an antisense oligonucleotide specifically hybridizing to at least one distant single nucleotide polymorphism of interest in an huntingtin (HTT) gene for use for treating a patient having Huntington's disease, wherein the patient is selected for treatment when determining a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in a biological sample of the patient, and wherein the specific haplotype is determined using the method disclosed herein. In some examples, the at least one distant single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one distant single nucleotide polymorphism of interest is rs7685686. In some examples, the specific haplotype comprises the presence of the A allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In other examples, the specific haplotype comprises the presence of the

G allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In some examples, the antisense oligonucleotide specifically hybridizes to a region in the huntingtin (HTT) gene comprising the A allele for the rs7685686. In some examples, the antisense oligonucleotide is selected to specifically hybridize to the distant single nucleotide polymorphism of interest in an allele specific fashion. In some examples, the specific haplotype is determined using the methods disclosed herein.

In another example, an *in vitro* use of haplotype determination of at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in the huntingtin (HTT) gene determined in a biological sample of an individual for diagnosing Huntington's disease is provided, wherein the detection of a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in a biological sample of the patient indicates that the individual has disease Huntington's disease. In one aspect, the present disclosure refers to *in vitro* use of haplotype determination of at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in the huntingtin (HTT) gene determined in a biological sample of an individual for diagnosing Huntington's disease, wherein the detection of a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in a biological sample of the patient indicates that the individual has disease Huntington's disease, and wherein the specific haplotype is determined using the method disclosed herein. In some examples, the at least one single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the specific haplotype comprises the presence of the A allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In other examples, the specific haplotype comprises the presence of the G allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In some examples, the specific haplotype is determined using the methods disclosed herein.

In another example, an *in vitro* use of haplotype determination of at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in the huntingtin (HTT) gene determined in a biological sample of a patient having from Huntington's disease for determining the patient as likely to respond to a therapy comprising an antisense oligonucleotide specifically hybridizing to at least one distant single nucleotide polymorphism of interest in an huntingtin (HTT) gene, wherein the patient is identified as being more likely to respond to the therapy when a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats is detected in a biological sample of the patient. In one aspect, the present disclosure refers to *in vitro* use of haplotype determination of at least one distant single nucleotide polymorphism of interest and the short tandem repeats detected in the huntingtin (HTT) gene determined in a biological sample of a patient having from Huntington's disease for determining the patient as likely to respond to a therapy comprising an antisense oligonucleotide specifically hybridizing to at least one distant single nucleotide polymorphism of interest in an huntingtin (HTT) gene, wherein the patient is identified as being more likely to respond to the therapy when a specific haplotype of the at least one distant single nucleotide polymorphism of interest and the short tandem repeats is detected in a biological sample of the patient, and wherein the specific haplotype is determined using the method disclosed herein. In some

examples, the at least one single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one distant single nucleotide polymorphism of interest is selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. In some examples, the specific haplotype comprises the presence of the A allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In some examples, the antisense oligonucleotide specifically hybridizes to a region in the huntingtin (HTT) gene comprising the A allele for the rs7685686. In other examples, the specific haplotype comprises the presence of the G allele for the rs7685686, and the number of CAG short tandem repeats is above 36. In some examples, the antisense oligonucleotide is selected to specifically hybridize to the distant single nucleotide polymorphism of interest in an allele specific fashion. In some examples, the specific haplotype is determined using the methods disclosed herein.

Further disclosed is a method of treating a patient having Huntington's disease, the method comprising: (a) determining the haplotype of at least one distant single nucleotide polymorphism of interest and the short tandem repeats in the huntingtin (HTT) gene in a biological sample of the patient; and (b) administering an antisense oligonucleotide specifically hybridizing to the at least one distant single nucleotide polymorphism of interest in an huntingtin (HTT) gene. Herein, the at least one distant single nucleotide polymorphism of interest may be selected from the group consisting of rs7685686, rs362331, rs363088, rs362273, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs34315806, rs2298967, rs362271, rs363099, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an intronic SNP selected from the group consisting of rs7685686, rs363088, rs2024115, rs6446723, rs363064, rs2285086, rs6844859, rs363080, rs2298967, rs362271, rs3121419, and rs16843804. In certain examples, the at least one single nucleotide polymorphism of interest is an exonic SNP selected from the group consisting of rs362331, rs362273, rs34315806 and

rs363099. In a particular example, the at least one single nucleotide polymorphism of interest is intronic SNP rs7685686. Also disclosed is that the haplotype as determined comprises the presence of the A allele for the rs7685686, and the number of CAG short tandem repeats is above 36. Also disclosed is that the antisense oligonucleotide specifically hybridizes to a region in the huntingtin (HTT) gene comprising the A allele for the rs7685686. In other examples, the specific haplotype comprises the presence of the G allele for the rs7685686. In some examples, the antisense oligonucleotide is selected to specifically hybridize to the distant single nucleotide polymorphism of interest in an allele specific fashion. Herein, the specific haplotype may be determined using the methods disclosed herein.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

The details of one or more examples of the disclosure are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the disclosure will be apparent from the drawings and detailed description, and from the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 indicates the distant separation between tandem-repeat region (i.e. CAG) and intronic or exonic SNP of interest. Distance is being represented on genomic DNA level and may span up to 200 kb nucleotides. The intronic and exonic SNP are separated from each other by only around 10 kb and can be amplified with a PCR assay (i.e. F1 and R1 primers). The transcription and mRNA maturation of the gene target involves splicing and thereby reduction of the distance between CAG tandem repeats and exonic reference SNP, which allows for reverse transcription and PCR of a ~10 kb amplicon from a single molecule (i.e. F2 and R2 primers).

FIG. 2 depicts two amplicons i.e. first generated from a genomic DNA and containing the intronic target SNP and exonic reference SNP; second generated from cDNA derived from mature mRNA and containing CAG tandem repeats and exonic reference SNP. The hybrid analysis allows for phasing of distant intronic SNP with a number of CAG tandem repeats by an alignment of exonic SNP between two amplicons.