

WHAT IS CLAIMED IS:

1. A therapeutic polynucleotide construct comprising:
a human endogenous *FMR1* promoter fragment; a human *FMR1* coding sequence, an endogenous human 3' regulatory element, and a polyadenylation signal.
2. The polynucleotide of claim 1, wherein the human *FMR1* coding sequence comprises any of the following sequences: a sequence having at least 80% identity to SEQ ID NO:4, a sequence having at least 90% identity to SEQ ID NO:4, a sequence having at least 95% identity to SEQ ID NO:4, SEQ ID NO:4, or *FMR1* isoform 7 sequence.
3. The polynucleotide of claim 1 or 2, wherein the human endogenous *FMR1* promoter fragment comprises any of the following nucleotide sequences: a nucleotide sequence having at least 80% identity to SEQ ID NO:3 or to SEQ ID NO:12, a nucleotide sequence having at least 90% identity to SEQ ID NO:3 or to SEQ ID NO:12, a nucleotide sequence having at least 95% identity to SEQ ID NO:3 or to SEQ ID NO:12, SEQ ID NO:3 or SEQ ID NO:12.
4. The polynucleotide of any of the previous claims, wherein the 3' regulatory element comprises any of the following nucleotide sequences: a nucleotide sequence having at least 80% identity to SEQ ID NO:5 or to SEQ ID NO:13, a nucleotide sequence having at least 90% identity to SEQ ID NO:5 or to SEQ ID NO:13, a nucleotide sequence having at least 95% identity to SEQ ID NO:5 or to SEQ ID NO:13, SEQ ID NO:5 or SEQ ID NO:13.
5. The polynucleotide of any of the previous claims, wherein the polynucleotide construct comprises any of the following sequences: a polynucleotide sequence having at least 90% identity to SEQ ID NO:2, a polynucleotide sequence having at least 90% identity to SEQ ID NO:9, a polynucleotide sequence having at least 90% identity to SEQ ID NO:11, SEQ ID NO:2, SEQ ID NO:9 or SEQ ID NO:11.
6. The polynucleotide of any of the above claims, further comprising at least one adeno-associated virus (AAV) inverted terminal repeat (ITR).
7. The polynucleotide of claim 6, wherein the polynucleotide comprises two AAV ITRs.
8. A vector comprising the polynucleotide of any of the above claims.
9. The vector of claim 8, wherein the vector is a viral vector.
10. The vector of claim 8 or 9, wherein the vector is an adeno-associated virus (AAV) vector.

- 11.** The vector of claim 10, wherein the AAV vector is an AAV9 vector.
- 12.** A recombinant adeno-associated virus (rAAV), comprising the polynucleotide of any of claims 1 to 7 or the vector of any one of claims 8-11.
- 13.** The rAAV of claim 12, wherein the rAAV is AAV9.
- 14.** A virion comprising the rAAV of claim 12 or 13.
- 15.** A transformed cell comprising the polynucleotide of any of claims 1 to 7, the vector of any of claims 8 to 11, the rAAV of claim 12 or 13, or the virion of claim 14.
- 16.** A pharmaceutical composition comprising the polynucleotide of any of claims 1 to 7, the vector of any of claims 8 to 11, the rAAV of claim 12 or 13, or the virion of claim 14 and a pharmaceutically acceptable carrier.
- 17.** Use of the polynucleotide of any of claims 1 to 7, the vector of any of claims 8 to 11, the rAAV of claim 12 or 13, the virion of claim 14, or the pharmaceutical composition of claim 16 in the manufacture of a medicament for treating Fragile X syndrome and related disorders in a subject.
- 18.** The use of claim 17, wherein administration is by intracerebral ventricular injection or by intracisternal magna administration to the subject.
- 19.** The polynucleotide of any of claims 1 to 7, the vector of any of claims 8 to 11, the rAAV of claim 12 or 13, the virion of claim 14, or the pharmaceutical composition of claim 16 for use as a medicament.