

We claim:

1. A rodent comprising in its genome a genetically modified endogenous *Ttr* locus comprising a human *TTR* sequence comprising both *TTR* coding sequence and non-coding sequence,

wherein the genetically modified endogenous *Ttr* locus comprises an endogenous *Ttr* promoter, wherein the human *TTR* sequence is operably linked to the endogenous *Ttr* promoter,

wherein the genetically modified endogenous *Ttr* locus comprises a human *TTR* 3' untranslated region,

wherein the endogenous *Ttr* 5' untranslated region has not been deleted and replaced with the corresponding human *TTR* sequence, and

wherein:

(I) the entire *Ttr*_coding sequence of the endogenous *Ttr* locus has been deleted and replaced with the corresponding human *TTR* sequence, and the region of the endogenous *Ttr* locus from the *Ttr* start codon to the *Ttr* stop codon has been deleted and replaced with the corresponding human *TTR* sequence; or

(II) the genetically modified endogenous *Ttr* locus encodes a transthyretin precursor protein comprising a signal peptide, the region of the endogenous *Ttr* locus encoding the signal peptide has not been deleted and replaced with the corresponding human *TTR* sequence, the first exon of the endogenous *Ttr* locus has not been deleted and replaced with the corresponding human *TTR* sequence, and the region of the endogenous *Ttr* locus from the start of the second *Ttr* exon to the *Ttr* stop codon has been deleted and replaced with the corresponding human *TTR* sequence.

2. The rodent of claim 1, wherein the region of the endogenous *Ttr* locus from the *Ttr* start codon to the *Ttr* stop codon has been deleted and replaced with a human *TTR* sequence comprising the corresponding human *TTR* sequence and a human *TTR* 3' untranslated region, and

wherein the endogenous *Ttr* 5' untranslated region has not been deleted and replaced with the corresponding human *TTR* sequence, and

wherein the endogenous *Ttr* promoter has not been deleted and replaced with the corresponding human *TTR* sequence.

3. The rodent of claim 2, wherein:

(i) the human *TTR* sequence at the genetically modified endogenous *Ttr* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 18;

(ii) the genetically modified endogenous *Ttr* locus encodes a protein comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 1;

(iii) the genetically modified endogenous *Ttr* locus comprises a coding sequence comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 90; or

(iv) the genetically modified endogenous *Ttr* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 14 or 15.

4. The rodent of claim 1, wherein the region of the endogenous *Ttr* locus from the second *Ttr* exon to the *Ttr* stop codon has been deleted and replaced with a human *TTR* sequence comprising the corresponding human *TTR* sequence and a human *TTR* 3' untranslated region, and

wherein the first exon and first intron of the endogenous *Ttr* locus have not been deleted and replaced with the corresponding human *TTR* sequence, and

wherein the endogenous *Ttr* 5' untranslated region has not been deleted and replaced with the corresponding human *TTR* sequence, and

wherein the endogenous *Ttr* promoter has not been deleted and replaced with the corresponding human *TTR* sequence.

5. The rodent of claim 4, wherein:

(i) the human *TTR* sequence at the genetically modified endogenous *Ttr* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 19;

(ii) the genetically modified endogenous *Ttr* locus encodes a protein comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 2;

(iii) the genetically modified endogenous *Ttr* locus comprises a coding sequence comprising a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 91; or

(iv) the genetically modified endogenous *Ttr* locus comprises a sequence at least 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the sequence set forth in SEQ ID NO: 16 or 17.

6. The rodent of any preceding claim, wherein the genetically modified endogenous *Ttr* locus does not comprise a selection cassette or a reporter gene.

7. The rodent of any preceding claim, wherein the rodent is homozygous for the genetically modified endogenous *Ttr* locus.

8. The rodent of any preceding claim, wherein the rodent is a rat or a mouse.

9. The rodent of claim 8, wherein the rodent is the mouse.

10. A rodent cell comprising in its genome a genetically modified endogenous *Ttr* locus comprising a human *TTR* sequence comprising both *TTR* coding sequence and non-coding sequence,

wherein the genetically modified endogenous *Ttr* locus comprises an endogenous *Ttr* promoter, wherein the human *TTR* sequence is operably linked to the endogenous *Ttr* promoter,

wherein the genetically modified endogenous *Ttr* locus comprises a human *TTR* 3' untranslated region,

wherein the endogenous *Ttr* 5' untranslated region has not been deleted and replaced with the corresponding human *TTR* sequence, and

wherein:

(I) the entire *Ttr* coding sequence of the endogenous *Ttr* locus has been deleted and replaced with the corresponding human *TTR* sequence, and the region of the endogenous *Ttr* locus from the *Ttr* start codon to the *Ttr* stop codon has been deleted and replaced with the corresponding human *TTR* sequence; or

(II) the genetically modified endogenous *Ttr* locus encodes a transthyretin precursor protein comprising a signal peptide, the region of the endogenous *Ttr* locus encoding the signal peptide has not been deleted and replaced with the corresponding human *TTR* sequence, the first exon of the endogenous *Ttr* locus has not been deleted and replaced with the corresponding human *TTR* sequence, and the region of the endogenous *Ttr* locus from the start of the second *Ttr* exon to the *Ttr* stop codon has been deleted and replaced with the corresponding human *TTR* sequence.