

CLAIMS

1. A rodent, comprising in its genome a deletion in an endogenous rodent Retinoschisin-1 (*Rs1*) gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3.
2. The rodent of claim 1, wherein the *Rs1* locus comprises a reporter gene coding sequence that is fused in-frame to the start (ATG) codon of the *Rs1* gene.
3. A rodent whose genome comprises an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution.
4. The rodent of claim 3, wherein the rodent is a male rodent.
5. The rodent of claim 3, wherein the rodent is a female rodent.
6. The rodent of claim 5, wherein the rodent is homozygous for the engineered *Rs1* gene.
7. The rodent of claim 5, wherein the rodent is heterozygous for the engineered *Rs1* gene.
8. The rodent of claim 3, wherein the rodent develops one or more symptoms of Retinoschisis by 15 days after birth.
9. The rodent of claim 3, wherein the rodent is a rat or a mouse.
10. An isolated rodent cell or tissue whose genome comprises
 - (i) a deletion in an endogenous rodent *Rs1* gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3, or
 - (ii) an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution.
11. An immortalized cell made from the isolated rodent cell of claim 10.

12. A rodent embryonic stem (ES) cell whose genome comprises
- (i) a deletion in an endogenous rodent *Rs1* gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3, or
 - (ii) an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution.
13. A rodent embryo generated from the embryonic stem cell of claim 12.
14. A method of making a genetically modified rodent, comprising:
- modifying a rodent genome so that the modified genome comprises
- (i) a deletion in an endogenous rodent *Rs1* gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3, or
 - (ii) an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution; and
- making a genetically modified rodent comprising the modified genome.
15. The method of claim 14, wherein the rodent genome is modified by a process comprising:
- (a) introducing a nucleic acid sequence into the genome of a rodent ES cell to obtain a genetically modified rodent ES cell whose genome comprises the deletion of (i) or the engineered *Rs1* gene of (ii); and
 - (b) creating a rodent using the genetically modified rodent ES cell of (a).
16. The method of claim 14, wherein the rodent is a male rodent.

17. The method of claim 14, wherein the rodent is a female rodent.
18. The method of claim 17, wherein the rodent is heterozygous for the deletion or the engineered *Rs1* gene.
19. The method of claim 17, wherein the rodent is homozygous for the deletion or the engineered *Rs1* gene.
20. The method of claim 14, wherein the rodent is a mouse or a rat.
21. A method of identifying a therapeutic agent for the treatment of Retinoschisis in a rodent, the method comprising:
 - (a) administering an agent to a rodent whose genome comprises
 - (i) a deletion in an endogenous rodent *Rs1* gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3, or
 - (ii) an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution;
 - (b) performing one or more assays to determine if the agent has an effect on one or more signs, symptoms and/or conditions associated with Retinoschisis; and
 - (c) identifying the agent as a therapeutic agent when the agent has a therapeutic effect on the one or more signs, symptoms and/or conditions associated with Retinoschisis.
22. The method of claim 21, wherein the agent is administered to the rodent at or shortly after birth.
23. The method of claim 22, wherein the one or more assays are performed at 15-24 days after birth.
24. The method of claim 21, wherein the rodent is a rat or a mouse.
25. A nucleic acid construct, comprising:

a nucleic acid sequence to be integrated into a rodent *Rs1* gene at a rodent *Rs1* locus, flanked by a 5' nucleotide sequence and a 3' nucleotide sequence that are homologous to nucleotide sequences at the rodent *Rs1* locus, wherein integration of the nucleic acid sequence into the rodent *Rs1* gene results in

(i) a deletion in an endogenous rodent *Rs1* gene at an endogenous rodent *Rs1* locus, wherein the deletion is of the coding portion of exon 1 from the nucleotide after the ATG start codon to the 3' end of exon 1 and exons 2-3, or

(ii) an engineered *Rs1* gene at an endogenous rodent *Rs1* locus, which engineered *Rs1* gene comprises one or more point mutations in an exon and encodes an RS1 polypeptide comprising at least one amino acid substitution as compared to a wild type RS1 polypeptide, wherein the at least one amino acid substitution is a C59S substitution or a R141C substitution.