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Functional Rna Elements As Targets For Amelioration Of Aberrant Pre-Mrna Splicing

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OTHER INFORMATION

KEYWORDS

Exonic Splicing Enhancers, Exonic Splicing Silencers, Single Nucleotide Polymorphisms, Genetic Disorders, Inherited Diseases, Rare Diseases, Antisense, RNA therapeutics, siRNA, Splicing Mutations

CATEGORIZED AS

- **Biotechnology**
  - Health
- **Medical**
  - Disease: Genetic Diseases and Dysmorphic Syndromes
  - Therapeutics

RELATED CASES

2011-892-0

BACKGROUND

Exonic sequences of messenger RNA are well known for encoding the primary sequence determinants of proteins. Sequence and structural elements of exons also contribute to pre-mRNA splicing. Exons frequently contain cis acting elements that can activate (exonic splicing enhancers) or repress (exonic splicing silencers) splicing. Roughly 10% of inherited disorders are known to alter consensus splice sites and thereby result in aberrant pre-mRNA splicing. Such splicing mutations often arise in protein coding regions but do not result in a change in protein function.

Once these mutant sequences are identified, antisense RNA compounds that interact with exonic splicing enhancers or repressors can be generated. These can repress the aberrant splicing and restore the wild type phenotype. Exonic sequences of messenger RNA are well known for encoding the primary sequence determinants of proteins. Sequence and structural elements of exons also contribute to pre-mRNA splicing. Exons frequently contain cis acting elements that can activate (exonic splicing enhancers) or repress (exonic splicing silencers) splicing. Roughly 10% of inherited disorders are known to alter consensus splice sites and thereby result in aberrant pre-mRNA splicing. Such splicing mutations often arise in protein coding regions but do not result in a change in protein function.

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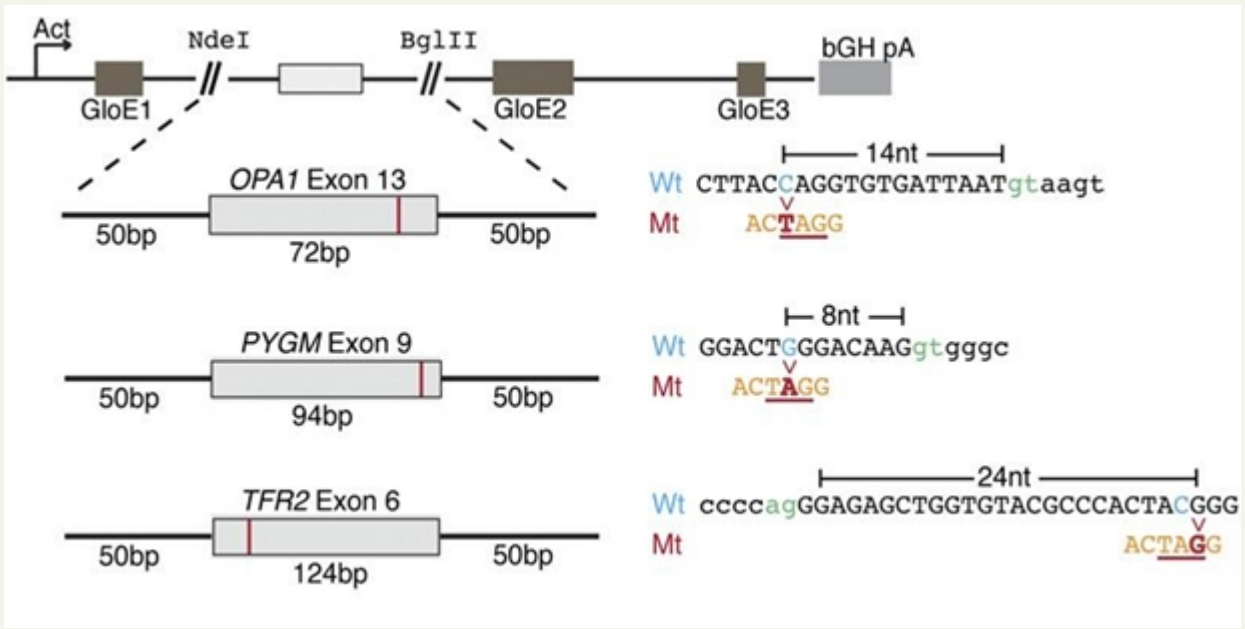
TECHNOLOGY DESCRIPTION

Antisense oligonucleotides that interfere with regulatory sequences that comprise the nucleic acid hexamers ACUAGG, CUUAGG, AUUAGG, UAGGUA, or GUAGUU are described. These sequences regulate a wide variety of disease associated genes including OPA1, PYGM, TFR2, RPS6KA3, AAPC, SLC5A1, and COL4A3.



Splicing reporter constructs created from matched pairs of wild-type (Wt) or mutant (Mt) alleles that give rise to a gain of the ACUAGG silencer in constitutive exons in three different disease genes: OPA1, PYGM, and TFR2. GloE1, GloE2, and GloE3 designate exons 1–3 of beta-globin. The polyadenylation signal from the bovine growth hormone 1 gene is indicated by bGH pA. (Blue) Wild-type allele; (red) the mutant; (orange) the silencer sequence created by the mutation. From Sterne-Weiler T *et al*, *Genome Res* 21, 1563-1571 (2011)

APPLICATIONS

Treatment of rare diseases

Identification of otherwise silent mutations that result in inherited disease

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	10,443,101	10/15/2019	2011-892
United States Of America	Issued Patent	9,765,398	09/19/2017	2011-892

United States Of America	Published Application	20210254163	08/19/2021	2011-892	
United States Of America	Published Application	20190352718	11/21/2019	2011-892	

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