A single-base substitution within an intronic repetitive element causes dominant retinitis pigmentosa with reduced penetrance

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4610333
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Year 2009
Title A single-base substitution within an intronic repetitive element causes dominant retinitis pigmentosa with reduced penetrance
Journal Human mutation
Volume 30
Number 9
Pages / **Article-Number** 1340-1347
Mesh terms Alleles; Base Sequence; Eye Proteins, genetics, metabolism; Genes, Dominant, genetics; Humans; Introns, genetics; Molecular Sequence Data; Mutation; Pedigree; RNA Splice Sites; RNA Splicing; RNA, Messenger, metabolism; Repetitive Sequences, Nucleic Acid, genetics; Retinitis Pigmentosa, genetics; Sequence Analysis, DNA

We report the study of a large American family displaying autosomal dominant retinitis pigmentosa with reduced penetrance, a form of hereditary retinal degeneration. Although the inheritance pattern and previous linkage mapping pointed to the involvement of the PRPF31 gene, extensive screening of all its exons and their boundaries failed in the past to reveal any mutation. In this work, we sequenced the entire PRPF31 genomic region by both the classical Sanger method and ultrahigh throughput (UHT) sequencing. Among the many variants identified, a single-base substitution (c.1374+654C>G) located deep within intron 13 and inside a repetitive DNA element was common to all patients and obligate asymptomatic carriers. This change created a new splice donor site leading to the synthesis of two mutant PRPF31 isoforms, degraded by nonsense-mediated mRNA decay. As a consequence, amounts of PRPF31 mRNA derived from the mutant allele were very reduced, with no evidence of mutant proteins being synthesized. Our results indicate that c.1374+654C>G causes retinitis pigmentosa via haploinsufficiency, similar to the vast majority of PRPF31 mutations described so far. We discuss the potential of UHT sequencing technologies in mutation screening and the continued identification of pathogenic splicing mutations buried deep within intronic regions.

Publisher Wiley
ISSN/ISBN 1098-1004
URL https://onlinelibrary.wiley.com/doi/abs/10.1002/humu.21071
edoc-URL https://edoc.unibas.ch/81795/
Full Text on edoc Available;
Digital Object Identifier DOI 10.1002/humu.21071
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/19618371