Back

Analysis of splice-site mutations of the α-galactosidase A gene in Fabry disease

L-W Lai, O Whitehair, M-J Wu, M O'Meara, Y-HH Lien

First published: 03 June 2003
https://doi.org/10.1034/j.1399-0004.2003.00077.x
Citations: 28

Abstract

Fabry disease is an X-linked disease caused by a defective lysosomal enzyme, α-galactosidase A, and characterized by skin lesions and multiorgan involvement, including kidney, heart, and the central nervous system. Currently more than 200 genotypes have been identified, including several aberrant splicing. However, most of the mutation analyses were performed using genomic sequencing only, and therefore some of the splicing mutations were misclassified as missense mutations. In order to predict the splicing event caused by each mutation, we conducted a literature search for all published mutations located near the splice sites, including exonic point mutations, and performed a splice-site score (SSS) analysis. The literature search identified 13 donor-site mutations, including four exonic mutations (S65T, D183S, K213N, and M267I), located at the end of exons 1, 3, 4, and 5, respectively, six acceptor-site mutations, and one new exon creation. All mutated splice sites, except for the one associated with the new exon creation, had a lower SSS than their respective natural sites. Cryptic or newly created sites were identified with SSS from 0.09 to 1.0. The predictions, based on SSS analysis, are in agreement with all six mutations with known cDNA sequence from the literature, including five mutations with exon skipping and one mutation with creation of a new acceptor site. For the S65T genotype, we performed reverse transcription–polymerase chain reaction (RT–PCR) analysis using RNA isolated from the whole-blood sample. We verified that a weak cryptic site (SSS = 0.09) 14 nucleotides downstream was activated and resulted in an insertion of 14 bp and a frameshift stop at codon 106. This change is more consistent with the clinical presentation of the patient, the classical Fabry disease, than the amino acid substitution (S65T), which does not affect the enzyme function. In conclusion, the SSS analysis is very useful for predicting splicing events and genotype/phenotype correlation in Fabry disease. As different mechanisms may be involved in pre-mRNA splicing, it is important to obtain cDNA sequencing for molecular diagnosis.

Back

1 Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease: ceremide trihexosidase deficiency. *N Engl J Med* 1967: **276**: 1163 – 1167.

CAS | PubMed | Web of Science® | Google Scholar

2 Desnick RJ, Ioannou YA, Eng CM. α-Galactosidase A deficiency: Fabry disease. In: CR Scriver, AL Beaudet, WAS Sly, D Valle, eds. *The Metabolic and Molecular Basis of Inherited Diseases.* New York: McGraw-Hill, 2001: 3733 – 3774.

Google Scholar

3 Pastores GM, Lien YH. Biochemical and molecular genetic basis of Fabry disease: diagnostic and counseling issues. *J Am Soc Nephrol* 2002: **13** (Suppl. 2): S130 – S133.

CAS | PubMed | Web of Science® | Google Scholar

4 Nakai K, Sakamoto H. Construction of a novel database containing aberrant splicing mutations of mammalian genes. *Gene* 1994: **141**: 171 – 177.

CAS | PubMed | Web of Science® | Google Scholar

5 Cooper TA, Mattox W. The regulation of splice-site selection and its role in human disease. *Am J Hum Genet* 1997: **61**: 259 – 266.

CAS | PubMed | Web of Science® | Google Scholar

6 Liu H-X, Zhang MQ, Krainer AR. Identification of functional exonic splicing enhancer motifs recognized by individual SR proteins. *Genes Dev* 1998: **12**: 1998 – 2012.

CAS | PubMed | Web of Science® | Google Scholar

7 Liu H-X, Chew SL, Cartegni L, Zhang MQ, Krainer AR. Exonic splicing enhancer motifs recognized by human SC35 under splicing conditions. *Mol Cell Biol* 2000: **20**: 1063 – 1071.

CAS | PubMed | Web of Science® | Google Scholar

Back

missense mutations in BRCA1 and other genes. Nat Genet 1994; 7: 533 – 38.

CAS | PubMed | Web of Science® | Google Scholar

9 Messiaen LM, Callens T, Mortier G *et al.* Exhaustive mutation analysis of the NF1 gene allows identification of 95% of mutations and reveals a high frequency of unusual splicing defects. *Hum Mut* 2000: **15**: 541 – 555.

CAS | PubMed | Web of Science® | Google Scholar

10 Chen C, Shyu P, Wu S, Sheu S, Desnick RJ, Hsiao K. Identification of a novel point mutation (S65T) in α-galactosidase A gene in Chinese patients with Fabry disease. *Hum Mut* 1998: **11**: 328 – 330.

CAS | PubMed | Web of Science® | Google Scholar

11 Yokoi T, Shinoda K, Ohno I, Kato K, Miyawaki T, Taniguchi N. A 3′ splice site consensus sequence mutation in the intron 3 of the alpha-galactosidase A gene in a patient with Fabry disease. *Jpn J Hum Genet* 1991: **36**: 245 – 250.

CAS | PubMed | Web of Science® | Google Scholar

12 Sakuraba H, Eng CM, Desnick RJ, Bishop DF. Invariant exon skipping in the human alpha-galactosidase A pre-mRNA. Ag+1 to t substitution in a 5′-splice site causing Fabry disease. *Genomics* 1992: **12**: 643 – 650.

CAS | PubMed | Web of Science® | Google Scholar

13 Eng CM, Resnick-Silverman LA, Niehaus DJ, Astrin KH, Desnick RJ. Nature and frequency of mutations in the alpha-galactosidase A gene that cause Fabry disease. *Am J Hum Genet* 1993: **53**: 1186 – 1197.

CAS | PubMed | Web of Science® | Google Scholar

14 Davies J, Christomanou H, Winchester B, Malcolm S. Detection of 8 new mutations in the α-galactosidase A gene in Fabry disease. *Hum Mol Genet* 1994: **3**: 667 – 669.

CAS | PubMed | Web of Science® | Google Scholar

Back

561.

CAS | PubMed | Web of Science® | Google Scholar

16 Okumiya T, Takenaka T, Ishii S, Kase R, Kamei S, Sakuraba H. Two novel mutations in the alpha-galactosidase gene in Japanese classical hemizygotes with Fabry disease. *Jpn J Hum Genet* 1996: **41**: 313 – 321.

CAS | PubMed | Web of Science® | Google Scholar

17 Eng CM, Ashley GA, Burgert TS, Enriquez AL, D'Souza M, Desnick RJ. Fabry disease: thirty-five mutations in the alpha-galactosidase A gene in patients with classic and variant phenotypes. *Mol Med* 1997: **3**: 174 – 182.

CAS | PubMed | Web of Science® | Google Scholar

18 Matsumura T, Osaka H, Sugiyama N *et al.* Novel acceptor splice site mutation in the invariant AG of intron 6 of alpha-galactosidase A gene, causing Fabry disease. Mutation in brief #146. Online. *Hum Mut* 1998: **11**: 483.

CAS | PubMed | Google Scholar

19 Germain DP, Poenaru L. Fabry disease: identification of novel alpha-galactosidase A mutations and molecular carrier detection by use of fluorescent chemical cleavage of mismatches. *Biochem Biophys Res Commun* 1999: **257**: 708 – 713.

CAS | PubMed | Web of Science® | Google Scholar

20 Topaloglu AK, Ashley GA, Tong B *et al.* Twenty novel mutations in the alpha-galactosidase A gene causing Fabry disease. *Mol Med* 1999: **5**: 806 – 811.

CAS | PubMed | Web of Science® | Google Scholar

21 Ashton-Prolla P, Tong B, Shabbeer J, Astrin KH, Eng CM, Desnick RJ. Fabry disease: twenty-two novel mutations in the alpha-galactosidase A gene and genotype/phenotype correlations in severely and mildly affected hemizygotes and heterozygotes. *J Invest Med* 2000: **48**: 227 – 235.

CAS | PubMed | Web of Science® | Google Scholar

Back

CAS | PubMed | Google Scholar

23 Shabbeer J, Yasuda M, Luca E, Desnick RJ. Fabry disease: 45 novel mutations in the α-galactosidase A gene causing the classical phenotype. *Mol Genet Metab* 2002: **76**: 23 – 30.

CAS | PubMed | Web of Science® | Google Scholar

24 Ishii S, Nakao S, Minamikawa-Tachino R, Desnick RJ, Fan JQ. Alternative splicing in the alpha-galactosidase A gene: increased exon inclusion results in the Fabry cardiac phenotype. *Am J Hum Genet* 2002: **70**: 994 – 1002.

CAS | PubMed | Web of Science® | Google Scholar

25 Ishii S, Suzuki Y, Fan JQ. Role of Ser-65 in the activity of alpha-galactosidase A. characterization of a point mutation (S65T) detected in a patient with Fabry disease. *Arch Biochem Biophys* 2000: **377**: 228 – 233.

CAS | PubMed | Web of Science® | Google Scholar

26 Shahin H, Walsh T, Sobe T *et al.* Genetics of congenital deafness in the Palestinian population: multiple connexin 26 alleles with shared origins in the Middle East. *Hum Genet* 2002: **110**: 284 – 289.

CAS | PubMed | Web of Science® | Google Scholar

27 Li B, Wachtel C, Miriami E *et al.* Stop codons affect 5′ splice site selection by surveillance of splicing. *Proc Natl Acad Sci USA* 2002: **99**: 5277 – 5282.

CAS | PubMed | Web of Science® | Google Scholar

Citing Literature

Download PDF