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Fabry disease: twenty-three mutations including ser antisense CpG alterations and identification of a del hot-spot in the α-galactosidase A gene

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Abstract

Fabry disease, an X-linked inborn error of glycosphingolipid catabolism, results from the α-galactosidase A gene at Xq22.1. To determine the nature and frequency of the n lesions causing the classical and milder variant Fabry phenotypes, and for precise car in Fabry families, the α-galactosidase A coding and flanking intronic sequences from Fabry hemizygotes were analyzed. In patients with the classic phenotype, 16 new mis nonsense mutations and four small exonic gene rearrangements were identified: C52 E59K, L89R, R100K, R112H, L131P, A143P, G144V, C172Y, D244N, N272K, A28 Q99X, Q157X, R301X, 25del1, 333del18, 358del6, and 1020del1. The R112H mutat dinucleotide resulted in residual activity and a mild variant phenotype while the R11 caused the classic disease manifestations, defining a genotype/phenotype correlation antisense mutations at the same CpG dinucleotide. In addition, two complex rearrang involving two mutational events, occurred in classic hemizygotes. Both rearrangemer in missense mutations that did not change the reading frame. Notably, three of the de occurred within 11 codons in exon 2, thereby defining a 'hot-spot' for deletions. Thes revealed that most mutations in the α-galactosidase A gene causing Fabry disease we that codons 111–122 defined a deletion hot-spot, and that different substitutions of th resulted in markedly different disease phenotypes.