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Fabry Disease: Identification of Novel Alpha-Galactosidase A Mutations and Molecular Carrier Detection by Use of Fluorescent Chemical Cleavage of Mismatches ☆

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Abstract

Fabry disease (FD) (angiokeratoma corporis diffusum) is an X-linked inborn error of glycosphingolipid metabolism caused by defects in the lysosomal α-galactosidase A gene (*GLA*). The enzymatic defect leads to the systemic accumulation of neutral glycosphingolipids with terminal α-galactosyl moieties. Clinically, affected hemizygous males have angiokeratoma, severe acroparesthesia, renal failure, and vasculopathy of the heart and brain. While demonstration of α-galactosidase deficiency in leukocytes is diagnostic in affected males, enzymatic detection of female carriers is often inconclusive, due to random X-chromosomal inactivation, underlining the need of molecular investigations for accurate genetic counseling. By use of chemical cleavage of mismatches adapted to fluorescence-based detection systems, we have characterized the mutations underlying α-Gal A deficiency in 16 individuals from six unrelated families with FD. The mutational spectrum included five missense mutations (C202W, C223G, N224D, R301Q, and

Q327K) and one splice-site mutation [IVS3 G(-1) → C]. Studies at the mRNA level showed that the latter led to altered pre-mRNA splicing with consequent alteration of the mRNA translational reading frame and generation of a premature termination codon of translation. By use of this strategy, carrier status was accurately assessed in all seven at-risk females tested, whereas enzymatic dosages failed to diagnose or exclude heterozygosity.

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Standardising clinical outcomes measures for adult clinical trials in Fabry disease: A global Delphi consensus

2021, Molecular Genetics and Metabolism

> *Citation Excerpt :*
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> ...Two clinical phenotypes have been described: “classical” and “later-onset” [3]. These cannot be predicted exclusively by genotype [4,5]. Classical FD is characterised by a multi-system involvement with early acroparaesthesia, sweating abnormalities and gastrointestinal disturbance, whereas most of the later onset phenotypes may be an attenuated form of the disease, commonly involving a single organ system, usually cardiac or sometimes renal [3]....

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> ...The X-chromosome inactivation pattern that is observed in female patients with Fabry disease correlates with the variation in phenotype and disease course (Echevarria et al., 2016). Fabry disease is further characterised by a large number of pathogenic variants in the GLA gene (Germain et al., 1999), including variants associated with the classic presentation of the disease, later onset or atypical disease presentations (Germain, 2001; Germain et al., 1996, 2018) and of uncertain significance. Thus,

pooling results from hemizygous male patients and heterozygous female patients is another source of bias in study data (Dobrovolny et al., 2005; Echevarria et al., 2016; Germain, 2007)....

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Fabry disease: Four case reports of meningioma and a review of the literature on other malignancies

2017, Molecular Genetics and Metabolism Reports

Citation Excerpt :

...However, little has been reported on the occurrence of meningioma in association with metabolic disorders. These are the first reported cases of meningioma occurring in Fabry disease, an X-linked metabolic disorder caused by a deficiency of lysosomal alpha-galactosidase, resulting in cellular accumulation of the lipid globotriaosylceramide (GL-3) and its deacylated product lyso-Gb3 [6,7]. We review the existing reports of cancer occurring in patients with Fabry disease, and discuss the possible association of metabolic lipid disorders with respect to the evolution of malignancy....

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...When intronic variants are involved, one might entertain the possibility that these induce altered splice sites and skipping of whole exons and thereby may be predictive of disease expression. Studies at the mRNA level have shown that intronic variants induce altered splicing with consequent alteration of the mRNA translational reading frame (Germain and Poenaru, 1999); using this strategy, female patients were identified despite the presence of residual enzyme (Germain and Poenaru, 1999). On the other hand, none of the intronic variants studied here appeared to aberrantly affect transcript splicing....

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