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Is it or is it not a pathogenic mutation? Is it or is it not the podocyte?

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Fabry disease is caused by a deficient activity of alpha-galactosidase A (α -GalA) due to mutations in the X chromosome GLA gene. The enzymatic defect causes intracellular accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (GL-3), as well as increased circulating levels of globotriaosylsphingosine (Lyso-GL-3).

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Fabry disease is caused by a deficient activity of alpha-galactosidase A (α -GalA) due to mutations in the X chromosome GLA gene. The enzymatic defect causes intracellular accumulation of neutral glycosphingolipids, mainly globotriaosylceramide (GL-3), as well as increased circulating levels of globotriaosylsphingosine (Lyso-GL-3) (1). Fabry disease is genetically and phenotypically very heterogeneous. The Human Gene Mutation Database (HGMD) contains 655 GLA mutations (2). Classical Fabry disease is characterized by absent or nearly absent α -GalA activity in male hemizygotes, early onset of acroparesthesias, angiokeratoma, lack of sweating and digestive symptoms and later onset of life-threatening cardiac, central nervous sys-

tem and kidney disease (3). Symptoms in females heterozygous are very variable and are thought to depend on random X chromosome inactivation at the single cell level (Lyonization). Thus, females may be as severely affected as males or oligosymptomatic (4, 5). Given that some females may display severe disease the term recessive is no longer used to refer to Fabry disease. In addition, a number of late-onset variants have been described. In general these variants are caused by less severe mutations, resulting in 1-5% of normal enzymatic activity, and phenotypically may not display many of the multisystem symptoms of classical Fabry disease. Cardiac and renal variants have been recognized based on predominant or only symptoms related to the organs (6,

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7). One key issue when dealing with a suspected late onset variant relates to the pathogenicity of the mutation. Thus, as an example, R118C was described in newborn screening and thought to be a late onset mutation based on cell culture activity data, but, at the time, not a single patient carrying this mutation had been described to have symptoms related to Fabry disease (8).

The current case report by Mukdsi et al. illustrates some key points regarding the genetic and phenotypic variability of Fabry disease (9). The patient described in the report did not have classic symptoms of Fabry disease. Indeed, Fabry disease was suspected based on typical glycolipid inclusion observed by electron microscopy in a renal biopsy. Assessment of α -GalA activity disclosed values 10 to 45% of the lower limit for controls, an unusually high activity for a symptomatic male patient. Genetic analysis disclosed a previously undescribed mutation, C174G. The overall clinical genetic and enzymatic picture is consistent with a renal variant of Fabry disease and indeed the patient was started on enzyme replacement therapy (ERT). While on ERT renal function appeared to remain stable, with serum creatinine around 2 mg/dL despite documented progression in previous years. However, a database search for this particular mutation disclosed that the single nucleotide polymorphism database of functional effects (SNPDBE) still considers C174G a non-pathogenic polymorphism based on predicted functional effects assessed by the SNAP and SIFT scores, although the reliability index of such assessment was low (10). This information should be updated based on the current report. Thus, sometimes is difficult to decide whether a single base pair change is a pathogenic mutation or a SNP. Although R118C has been found in 1% of Portuguese young patients with stroke (11), some genotyping centers in the Ibe-

rian Peninsula inform this variant as of doubtful clinical significance given its high prevalence in the general population. More information is needed on the complete phenotypic spectrum of late onset variants and the role of ERT in these patients. The problem will be compounded by the forthcoming effort at newborn screening, where single base changes of unknown clinical significance are expected to pop up. In this regard, detailed phenotypic descriptions of genetic variants, like the current case report, are necessary additions to the Fabry literature. However, a more detailed description of the genetic analysis would have been welcomed, as certain techniques may miss deletions and other genetic changes that may contribute to the phenotype. In addition, this case report provides information on the pathogenesis of Fabry nephropathy. Since in classical Fabry disease Gb3 deposits are prominent in endothelial cells, and central nervous system symptoms are mainly ischemic in nature (stroke or transient ischemic attacks), it was assumed that glycolipid accumulation in endothelial cells led to physical obstruction of small vessels and ischemic tissue injury in heart and kidneys. This belief is still held by authorities in the field. However, Fabry nephropathy is a progressive proteinuric nephropathy similar to diabetic nephropathy (12). In this regard, podocytes are key targets of injury in proteinuric nephropathies and podocytopenia and increased synthesis of extracellular matrix are early features of diabetic nephropathy. In recent years, evidence is accumulating for a central role of the podocyte in Fabry nephropathy. Thus, podocyte GL-3 inclusion volume density (but not endothelial or mesangial inclusion volume densities) increased progressively with age, and foot process also progressively increased with age and correlated with proteinuria (13). Furthermore, lyso-Gb3, at concentrations found in Fabry patients, elicits in

cultured human podocytes the same pro-fibrotic response observed when podocytes are cultured in high glucose (14). Thus, lyso-Gb3 increased TGFbeta1 and TGFbeta-1 mediated fibronectin and type IV collagen production and also increased the apoptosis related molecule CD74 in cultured podocytes (14, 15). Furthermore, as observed in this case report, the podocyte response to ERT is slow and this may underlie the observation that proteinuria is the main risk factor for loss of renal function both in treatment naïve and ERT-treated Fabry patients (16,17). The definite unraveling of podocyte injury to the pathogenesis of Fabry nephropathy awaits the availability of adequate animal models of Fabry disease.

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