Statement of the MFSH regarding reclassification of *GLA* variants as "benign" or "neutral" (April 2023)

This is a statement by the Morbus Fabry Selbsthilfegruppe MFSH (German Fabry Patient Association) regarding *GLA* variants such as D313Y and A143T.

A number of *GLA* variants, including the above two, have been described by some Fabry specialists as "benign" or "neutral" in scientific publications, and a number of other Fabry-treating physicians adopted this notion and service providers for genetic testing have stopped reporting of these variants.

Our experience with patients shows that these variants appear to be disease-causing at least in a number of individuals. In those patients that are most severely affected, symptoms are neither mild nor late-onset. Descriptions of individual patients reported in peer-reviewed journals confirm that these *GLA* variants cause, at least in a number of patients, Fabry disease.[1,2,3,4,5,6,7] In addition, the demonstrably altered physico-chemical properties of the mutated enzyme, i.e. the reduced enzymatic activity, impaired pH stability and delayed processing of the precursor protein appear to be in support of a pathogenic impact.[8,9,10] Experience shows that chaperone therapy is well suited for the treatment of these patients.

We discourage the use of the narrow diagnostic criteria proposed by Van der Tol et al.[11] Instead, we suggest to consider the broader range of symptoms which were described by Lenders and Brand [12] as "classical manifestations in Fabry disease" and which are in part found in patients with the above mentioned *GLA* variants. Some *GLA* variants might lead to a continuum of clinical presentations, as has been suggested for the D313Y variant. [13] Palaiodimou et al. [14] show that the specific criteria defined by Van der Tol et al. [11] are far less common in these patients than neurological manifestations.

The adoption of the notion of a benign impact of certain variants by service providers for genetic testing leads to a situation where physicians suspecting a genetic cause for a patient's symptoms do not learn that a *GLA* variant was indeed found. In our opinion, diagnosis of these patients should be performed by physicians with patient contact. Therefore, we suggest that service providers for genetic testing adopt a classification of these variants as "likely pathogenic" based on ACMG criteria PS3, PP2 and PP3. Alternatively, a classification as "established risk allele" or "predisposing"[15] for Fabry disease and stroke is possible.

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