

Poster Abstract: Diagnostic

Symptomatic Heterozygosity due to Definite GAA Mutations in Late-Onset Pompe Disease

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The genotype and phenotype are reported of 14 members of the third generation of a late-onset Pompe disease family which counts 36 individuals. Clinical, laboratory, and GAA enzymatic and genetic studies disclosed widespread myalgias and low back pain as well as mild weakness of the pelvic girdle muscles in 5 individuals (3 females, 2 males; aged 24–30 years), 3 of whom had a slight increase in CPK. Symptom onset was during the second decade of life. GAA enzyme activity ranged from 2 to 4 $\mu\text{mol/h/L}$ in all patients. Direct sequencing of the GAA gene carrying the mutations, previously identified in their parents, disclosed the R40X mutation in the 5 symptomatic individuals, whereas the splicing

mutation c.2647-7G>A was found in the remaining 9 who did not show any symptoms of neuromuscular disease.

Although the Pompe disease phenotype is, by definition, due to two mutations in the GAA gene, rare symptomatic heterozygosity has been reported. The most relevant finding of our study is the identification of several symptomatic heterozygous individuals in the same family who all share the identical GAA mutation, thus suggesting that specific deleterious mutations, even in heterozygous individuals, may address the prognosis. These symptomatic carriers represent a unique model to identify factors modifying the phenotype.

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