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Abstracts

Papers appearing in the October 2020 issue

Manifesting carriers of X-linked myotubular myopathy: Genetic modifiers modulating the phenotype

Objective To analyze the modulation of the phenotype in manifesting carriers of recessive X-linked myotubular myopathy (XLMTM), searching for possible genetic modifiers.

Methods Twelve Brazilian families with XLMTM were molecularly and clinically evaluated. In 2 families, 4 of 6 and 2 of 5 manifesting female carriers were identified. These women were studied for X chromosome inactivation. In addition, whole-exome sequencing was performed, looking for possible modifier variants. We also determined the penetrance rate among carriers of the mutations responsible for the condition.

Results Mutations in the *MTM1* gene were identified in all index patients from the 12 families, being 4 of them novel. In the heterozygotes, X chromosome inactivation was random in 3 of 4 informative manifesting carriers. The disease penetrance rate was estimated to be 30%, compatible with incomplete penetrance. Exome comparative analyses identified variants within a segment of 4.2 Mb on chromosome 19, containing the killer cell immunoglobulin-like receptor cluster of genes that were present in all nonmanifesting carriers and absent in all manifesting carriers. We hypothesized that these killer cell immunoglobulin-like receptor variants may modulate the phenotype, acting as a protective factor in the nonmanifesting carriers.

Conclusions Affected XLMTM female carriers have been described with a surprisingly high frequency for a recessive X-linked disease, raising the question about the pattern of inheritance or the role of modifier factors acting on the disease phenotype. We demonstrated the possible existence of genetic mechanisms and variants accountable for the clinical manifestation in these women, which can become future targets for therapies.

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Novel dominant MPAN family with a complex genetic architecture as a basis for phenotypic variability

Objective Our aim was to study a Hungarian family with autosomal dominantly inherited neurodegeneration with brain iron accumulation (NBIA) with markedly different intrafamilial expressivity.

Methods Targeted sequencing and multiplex ligation-dependent probe amplification (MLPA) of known NBIA-associated genes were performed in many affected and unaffected members of the family. In addition, a trio whole-genome sequencing was performed to find a potential explanation of phenotypic variability. Neuropathologic analysis was performed in a single affected family member.

Results The clinical phenotype was characterized by 3 different syndromes—1 with rapidly progressive dystonia-parkinsonism with cognitive deterioration, 1 with mild parkinsonism associated with dementia, and 1 with predominantly psychiatric symptoms along with movement disorder. A heterozygous stop-gain variation in the *C19Orf12* gene segregated with the phenotype. Targeted sequencing of all known NBIA genes and MLPA of *PLA2G6* and *PANK2* genes, as well as whole-genome sequencing in a trio from the family, revealed a unique constellation of oligogenic burden in 3 NBIA-associated genes (*C19Orf12* p.Trp112Ter, *CP* p.Val105PhefsTer5, and *PLA2G6* dup(ex14)). Neuropathologic analysis of a single case (39-year-old man) showed a complex pattern of alpha-synucleinopathy and tauopathy, both involving subcortical and cortical areas and the hippocampus.

Conclusions Our study expands the number of cases reported with autosomal dominant mitochondrial membrane protein-associated neurodegeneration and emphasizes the complexity of the genetic architecture, which might contribute to intrafamilial phenotypic variability.

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