X-linked Charcot-Marie-Tooth disease, Arts syndrome, and prelingual non-syndromic deafness form a disease continuum: evidence from a family with a novel PRPS1 mutation.

Abstract:
X-linked Charcot-Marie-Tooth disease type 5 (CMTX5), Arts syndrome, and non-syndromic sensorineural deafness (DFN2) are allelic syndromes, caused by reduced activity of phosphoribosylpyrophosphate synthetase 1 (PRS-1) due to loss-of-function mutations in PRPS1. As only few families have been described, knowledge about the relation between these syndromes, the phenotypic spectrum in patients and female carriers, and the relation to underlying PRS-1 activity is limited. We investigated a family with a novel PRPS1 mutation (c.830A>C, p.Gln277Pro) by extensive phenotyping, MRI, and genetic and enzymatic tests. The male index subject presented with an overlap of CMTX5 and Arts syndrome features, whereas his sister presented with prelingual DFN2. Both showed mild parietal and cerebellar atrophy on MRI. Enzymatically, PRS-1 activity was undetectable in the index subject, reduced in his less affected sister, and normal in his unaffected mother. Our findings demonstrate that CMTX5, Arts syndrome and DFN2 are phenotypic clusters on an intrafamilial continuum, including overlapping phenotypes even within individuals. The respective phenotypic
presentation seems to be determined by the exact PRPS1 mutation and the residual enzyme activity, the latter being largely influenced by the degree of skewed X-inactivation. Finally, our findings show that brain atrophy might be more common in PRPS1-disorders than previously thought.

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