X-linked Mohr-Tranebjaerg syndrome Syndrome: Variable Phenotype in Females

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Mohr-Tranebjaerg syndrome, also known as Deafness-Dystonia-Optic Neuronopathy syndrome (DDON syndrome), is a rare progressive x-linked syndrome in which males are typically affected with prelingual or postlingual sensorineural hearing impairments, slowly progressive dystonia and/or ataxia, slowly progressive decreased visual acuity from optic atrophy, and dementia. Mohr-Tranebjaerg syndrome is either caused by a contiguous gene deletion syndrome at Xq22 or as a single gene disorder resulting from pathogenic mutations in *TIMM8A*. To date, a total of twenty-one mutations, only two of which are missense, have been reported in the literature. Here, we present a novel *TIMM8A* missense alteration, c.127T>C, which was identified in a female proband with sensorineural hearing loss, multiple ear surgeries, and vision problems. The missense variant was also detected in the proband's affected father who suffered from congenital hearing loss and also had white matter disease on MRI, truncal ataxia and wide based gait, nystagmus, atypical renal cyst, drug and alcohol abuse, hallucinations, and psychologically disturbing behaviors including attempted arsenal. The variant was also detected in the proband's paternal grandmother, who wore hearing aids in old age, but this was not clinically relevant. We identified over twenty heterozygous female carriers of *TIMM8A* mutations in the literature, the majority of whom were not symptomatic. Only four heterozygous female carriers presented with symptoms, and only two of them suffered from hearing impairments and/or deafness. The family presented here not only contributes additional phenotypic information regarding *TIMM8A* alterations to the currently limited literature, but also highlights the potential variability of phenotypic presentations of Mohr-Tranebjaerg syndrome in heterozygous female carriers.