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Abstract

Ataxia, dementia, and hypogonadotropism caused by disordered ubiquitination

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The combination of ataxia and hypogonadism was first described more than a century ago, but its genetic basis has remained elusive. We performed whole-exome sequencing in a patient with ataxia and hypogonadotropic hypogonadism, followed by targeted sequencing of candidate genes in similarly affected patients. Neurologic and reproductive endocrine phenotypes were characterized in detail. The effects of sequence variants and the presence of an epistatic interaction were tested in a zebrafish model. Digenic homozygous mutations in RNF216 and OTUD4, which encode a ubiquitin E3 ligase and a deubiquitinase, respectively, were found in three affected siblings in a consanguineous family. All patients had progressive ataxia and dementia. Neuronal loss was observed in cerebellar pathways and the hippocampus; surviving hippocampal neurons contained ubiquitin-immunoreactive intranuclear inclusions. Defects were detected at the hypothalamic and pituitary levels of the reproductive endocrine axis. The syndrome of hypogonadotropic hypogonadism, ataxia, and dementia can be caused by inactivating mutations in RNF216 or by the combination of mutations in RNF216 and OTUD4. These findings link disordered ubiquitination to neurodegeneration and reproductive dysfunction.

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