**Biallelic SQSTM1 mutations in early-onset, variably progressive neurodegeneration**

Authors

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Abstract

Intracellular clearance of damaged cellular constituents, including protein aggregates and dysfunctional organelles, is necessary for proper neuronal function and long-term survival of neuronal cells. Autophagy contributes significantly to this process, and its defective function has been implicated in a number of neurodegenerative disorders. Here, we describe clinically and molecularly a recently recognized early-onset, variably progressive, neurodegenerative disorder caused by loss of function of SQSTM1, a multidomain protein serving as a selective autophagy receptor. Eleven affected individuals from three consanguineous families shared a homogeneous phenotype characterized by ataxia, hypotonia, dysmetria, dysarthria, ophthalmoplegia, dyskenesia, and cognitive decline as major features. Whole exome sequencing (WES) in two families, and a combined approach based on homozygosity mapping analysis in six affected individuals of the third family coupled to WES performed in a single affected member allowed to identify three homozygous inactivating variants, including a splice site substitution (c.301+2T>A) causing aberrant transcript processing and accelerated degradation of a resulting protein lacking exon 2, and two truncating changes (c.875\_876insT and c.934\_936delinsTGA). *In vitro* studies directed to characterize the consequences of loss of SQSTM1 function on autophagy provided evidence of a decelerated autophagic flux and impaired production of ubiquitin-positive protein aggregates in response to misfolded protein stress. The impact of sqstm1 down-modulation on the structural integrity of the cerebellum was analyzed *in vivo*, using zebrafish as model, documenting a variable but reproducible phenotype characterized by cerebellum anomalies ranging from depletion of axonal connections to complete atrophy. Italian Ministry of Health (R. C. 2017)