LETTER TO THE EDITOR

A novel missense mutation confirms ATL3 as a gene for hereditary sensory neuropathy type 1

Dirk Fischer,1,2 Maria Schabhüttl,3 Thomas Wieland,4 Reinhard Windhager,3 Tim M. Strom4,5 and Michaela Auer-Grumbach3

1 Department of Neurology, University of Basel Hospital, 4031 Basel, Switzerland
2 Division of Neuropaediatrics, University of Basel Childrens Hospital, 4056 Basel, Switzerland
3 Department of Orthopaedics, Medical University Vienna, 1090 Vienna, Austria
4 Institute of Human Genetics, Helmholtz Zentrum München - German Research Center for Environmental Health, 85764 Neuherberg, Germany
5 Institute for Human Genetics, Technical University Munich, 81675 Munich, Germany

Correspondence to: Michaela Auer-Grumbach, MD, Department of Orthopaedics, Medical University Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria
E-mail: michaela.auer-grumbach@meduniwien.ac.at

Sir,

We read with great interest the article by Kornak et al. (2014) reporting a novel gene in a family with autosomal dominant sensory neuropathy complicated by acro-mutilations and bone destruction. Whole exome sequencing identified a heterozygous missense mutation (c.575A>G; p.Tyr192Cys) in atlastin 3 (ATL3) which was confirmed in all affected individuals by conventional Sanger sequencing. Screening a cohort of 115 further patients exhibiting a similar phenotype detected the same variant in an additional hereditary sensory neuropathy type 1 (HSN1) family. This, together with functional data suggesting a dominant negative effect of the mutation, strongly supported the assumption that particular mutations in ATL3 result in an HSN1 phenotype. Although ATL3 is strongly expressed in the CNS and mutations in ATL1, a GTPase of similar function, is known to cause both hereditary spastic paraplegia and HSN1 (Zhao et al., 2001; Guelly et al., 2011), no upper motor neuron signs were detected in any of the affected individuals. We recently examined a father and son from a Bosnian family who presented with juvenile onset of severe sensory disturbances in the distal parts of the lower limbs leading to painful injuries and foot ulcerations (Fig. 1C). Shooting or lancinating pain was not reported. Patellar tendon reflexes in the lower limbs were brisk but muscle tone was normal. Neurological abnormalities were absent in upper limbs. Sural nerve action potentials were not recordable and motor nerve conduction studies revealed considerable axonal nerve damage (Fig. 1D) although distal muscle weakness and wasting were not found in both patients. After exclusion of mutations in several known HSN genes (SPTLC1, SPTLC2, RAB7A, ATL1 and WNK7) we carried out whole exome sequencing in the older patient. Based on the predicted function, the properties and conservation patterns, we selected variants in 22 interesting candidate genes, of which only nine variants were present in both father and son. Among these we highlighted the c.1013C>G; p.Pro338Arg missense change in ATL3 (Fig. 1A) as a possible disease-causing gene. The findings by Kornak et al. (2014) now further strengthen the hypothesis that particular mutations in ATL3 including p.Pro338Arg may lead to HSN1. Moreover, the clinically and electrophysiologically unaffected second son did not carry this mutation. The phenotype of our two patients widely overlaps with the one described in this article. It is highly interesting that in addition our two patients also exhibit brisk deep tendon reflexes in upper and lower extremities indicating mild upper motor neuron involvement thus broadening the phenotypic spectrum of ATL3 mutations. This finding is not unexpected given the fact that ATL3 is also expressed in the CNS. Remarkably, the same phenotypic variation has been reported in patients carrying mutations in ATL1 (Guelly et al., 2011). The p.Pro338Arg is evolutionarily highly conserved throughout species but also among all three human ATL homologues (Fig. 1B).
Moreover, a heterozygous missense change at Pro342 in ATL1 (p.Pro342Gln), the homologous residue in ATL1 has been reported to result in childhood-onset spastic paraplegia (de Bot et al., 2013). This further underlines the impact of residue Pro338 in ATL3 for a proper function of the protein.

Additional phenotype–genotype correlation studies in HSN1 and possibly also whole exome sequencing of families will figure out the phenotypic spectrum of ATL3 mutations and functional studies will elucidate the underlying mechanisms leading to these diseases.

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References


