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Letter to the Editor

Autosomal recessive axonal neuropathy caused by HINT1 mutation: New association of a psychiatric disorder to the neurologic phenotype

In a recent paper Meng et al. [1] described three Chinese patients with autosomal recessive axonal neuropathy with neuromyotonia (ARAN–NM), caused by mutations in the histidine triad nucleotide binding protein (HINT1) gene.

We report the first 20 years old Italian patient carrying a homozygous mutation in HINT1 gene. He was a second born of consanguineous parents (first degree cousins). He had mild motor delay with independent walking at 20 months of age, with frequent falls. Moreover, bilateral nystagmus was noticed at 4 years of life. At the age of 10, at the first neurological examination, he presented clumsiness, tandem walking difficulties, mild pes cavus, absent deep tendon reflexes and nystagmus. Moreover, he presented a mood disorder and severe conduct disorder treated with risperidone with effectiveness. Laboratory investigations showed high creatine phosphokinase levels (705U/l; normal values: 32-294). Brain and spine MRI were normal. Electroneurography and electromyography revealed chronic motor axonal neuropathy, without neuromyotonia. A first NGS panel for Charcot-Marie-Tooth disease was negative. At 18 years of age the last neurological examination showed distal hypotrophy in the hands and bilateral thighs with severe pes cavus. The last ENG-EMG examination confirmed motor axonal polyneuropathy, with the additional finding of sensory axonal involvement of the sural nerves.

Whole exome sequencing identified the homozygous c.110G>C, (p.Arg37Pro) variant in HINT1 gene, already reported in the literature [2] as pathogenic.

We report our patient's case because in addition to the neurologic phenotype expected in association with pathogenic variants in the HINT1 gene, he also developed psychiatric symptoms, so far undescribed in published reports.

However, evidence for a potential role of HINT1 in psychiatric disorders is starting to gather, as recently outlined by Liu et al. [3] who reviewed data on HINT1 expression in postmortem brains of patients with schizophrenia and mood disorder [4] (demonstrating a decrease in the dorsolateral prefrontal cortex of schizophrenic and bipolar patients and an increase in patients with major depressive disorder without psychotic symptoms) and on the behavior of HINT1 knockout mice, showing manic-like behavior evolving into depression-like behavior under stressful conditions.

Of interest, mice undergoing social isolation show decreased prefrontal cortex and increased hippocampal HINT1 expression. These studies point out that HINT1 is highly related to several psychiatric disorders, acting as a potential neuroplastic mediator.

To our knowledge, the link between HINT1 mutations and psychiatric symptoms has been shown by numerous studies, especially on animal models, but so far no patients with neuropathy and a psychiatric disorder caused by HINT1 gene mutation have been reported in the literature. In our opinion, although we provide description of a single case, literature data seem to support a non-coincidental association for our findings.

The lack of function of HINT1 protein might have an important role in neuropsychiatric diseases, but further studies would be of potential value to better understand specific mechanisms.

References

[1] Meng, Fu J, Lv H, Zhang W, Wang Z, Yuan Y. Novel mutations in HINT1 gene cause autosomal recessive axonal neuropathy with neuromyotonia in two cases of sensorimotor neuropathy and one case of motor neuropathy. Neuromusc. Disord. 2018;28:646–51.

[2] Laššuthová P, Brožková DŠ, Krůtová Marcela. Improving diagnosis of inherited peripheral neuropathies through gene panel analysis. Orph. J. Rare Diseas. 2016;11:118.

[3] Liu, P, Liu, Z, Wang, J, Ma, X, and Dang, Y. HINT1 in neuropsychiatric diseases: a potential neuroplastic mediator neural plasticity volume 2017, Article ID 5181925.

[4] Rodríguez-Muñoz M, Sánchez-Blázquez P, Callado LF, Javier Meana J, Garzón-Niño J. Schizophrenia and depression, two poles of endocannabinoid system deregulation. Transl. Psych. 2017;7:1291.

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