NKX6-2

Hypomyelinating leukodystrophies are a heterogeneous group of genetic disorders with a wide spectrum of phenotypes and a high rate of genetically unsolved cases. Bi-allelic mutations in NKX6-2 were recently linked to spastic-ataxia 8 with hypomyelinating leukodystrophy (SPAX8).

Using a combination of homozygosity mapping, exome sequencing, detailed clinical and neuroimaging assessment we describe a series of new NKX6-2 mutations in a multicentre setting. We then combined all reported NKX6-2 mutations, combining all reported NKX6-2 mutations, analyzing spectrum of NKX6-2-related disease.

We identified 11 new cases from 8 families of different ethnic backgrounds carrying compound heterozygous and homozygous pathogenic variants in NKX6-2, evidencing a high NKX6-2 mutation burden in the hypomyelinating leukodystrophy disease spectrum. Our data reveals a phenotype spectrum with neonatal onset, global psychomotor delay and worse prognosis at the severe end and a childhood onset with mainly motor phenotype at the milder end. We describe the phenotypic and neuroimaging expression in NKX6-2 and show that phenotypes with epilepsy in the absence of overt hypomyelination and diffuse hypomyelination without seizures can occur.

Chelban et al. showed that NKX6-2 mutations should be considered in patients with autosomal recessive, very early onset of nystagmus, cerebellar ataxia with hypotonia that rapidly progresses to spasticity, particularly when associated with neuroimaging signs of hypomyelination. Therefore, we recommend that NXK6-2 should be included in hypomyelinating leukodystrophy and spastic-ataxia diagnostic panels [1)].

Chelban V, Patel N, Vandrovcova J, Zanetti MN, Lynch DS, Ryten M, Botía JA, Bello O, Tribollet E, Efthymiou S, Davagnanam I; SYNAPSE Study Group, Bashiri FA, Wood NW, Rothman JE, Alkuraya FS, Houlden H. Mutations in NKX6-2 Cause Progressive Spastic Ataxia and Hypomyelination. Am J Hum Genet. 2017 Jun 1;100(6):969-977. doi: 10.1016/j.ajhg.2017.05.009. PubMed PMID: 28575651; PubMed Central PMCID: PMC5473715.

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Chelban V, Alsagob M, Kloth K, Chirita-Emandi A, Vandrovcova J, Maroofian R, Davagnanam I, Bakhtiari S, AlSayed MD, Rahbeeni Z, AlZaidan H, Malintan NT, Johannsen J, Efthymiou S, Ghayoor Karimiani E, Mankad K, Al-Shahrani SA, Beiraghi Toosi M, AlShammari M, Groppa S, Haridy NA, AlQuait L, Qari A, Huma R, Salih MA, Almass R, Almutairi FB, Hamad MH, Alorainy IA, Ramzan K, Imtiaz F, Puiu M, Kruer MC, Bierhals T, Wood NW, Colak D, Houlden H, Kaya N. Genetic and phenotypic characterization of NKX6-2-related spastic ataxia and hypomyelination. Eur J Neurol. 2019 Sep 11. doi: 10.1111/ene.14082. [Epub ahead of print] PubMed PMID: 31509304.