Genotype–Phenotype Correlations in MPAN Due to *C19orf12* Variants

The Editor,

With interest, we read the article by Incecik *et al.* about six Turkish patients with mitochondrial membrane protein-associated neurodegeneration (MPAN) due to the variants c.371_372insT (patient 1 and 5) and c. 166_167insG (patients 2, 3, and 4) in *C19orf12*.[1] It was concluded that patients with neurodegeneration with brain iron accumulation (NBIA) manifesting with cognitive decline, optic atrophy, motor axonal neuropathy, and psychiatric abnormalities but without the "eye of the tiger sign" should be screened for mutations in *C19orf12*.[1] We have the following comments and concerns.

The main shortcoming of the study is that patient 6 was diagnosed with MPAN without confirmation of a *C19orf12* mutation. Diagnosing MPAN solely upon the clinical presentation, nerve conduction studies, and the cerebral MRI is inappropriate. Furthermore, there are cases in which the genotype–phenotype correlation is poor due to questionable pathogenicity of a suspicious *C19orf12* variant.[2] Thus, patient 6 should be excluded from the evaluation.

Missing is the therapeutic management of the presented patients. Since patient 1 presented with some features of Parkinsonism [Table 1],[1] we should know if anti-Parkinson medication was applied and if it had a beneficial effect. It should be mentioned which therapy patients 1, 2, 4, 5, and 6 received for spasticity and dystonia and if these measures reduced dystonia and spasticity.

Patient 2, 3, and 4 carried the same mutation. Nonetheless, their phenotype varied considerably [Table 1]. Also patients 1 and 5 carried the same variant but their phenotype was different [Table 1]. The only phenotypic feature present in each patient was gait disturbance. Five patients had spasticity and dystonia, respectively [Table 1]. An explanation for this

Table 1: Clinical manifestations in the 5 patients with genetically confirmed MPAN

Feature	P1	P2	P3	P4	P5
Age (years)	14	12	np	17	17
Sex (m/f)	M	f	m	f	f
Consanguineous parents	+	+	+	np	np
C19orf12 variant	+	+	+	+	+
Homozygosity	yes	yes	yes	yes	yes
Onset age (years)	10	9	np	10	np
Gait disturbance	+	+	+	+	+
Behavioural disturbance	-	-	-	+	+
Cognitive impairment	+	-	-	+	+
Dysarthria	+	+	-	-	+
Dyskinesia	+	-	-	-	-
Hypomimia	+	-	-	-	-
Bradykinesia	+	-	-	+	-
Intentional tremor	+	+	-	-	+
Spasticity	+	+	-	+	+
Dystonia	+	+	-	+	+
Optic atrophy	-	-	-	+	+
Axonal neuropathy	-	-	-	+	np
HI of GP + SN	+	+	+	+	np

M=Male, f=Female, np=Not provided, HI=Hypointensity, GP=Globus pallidus, SN=Substantia nigra

phenotypic heterogeneity between patients carrying the same variants should be provided.

There are indications that *C19orf12* variants may manifest clinically even if they occur in the heterozygous form.[3] We thus should know if any relatives of the 6 index patients carried any of the described variants in the heterozygous form and manifested clinically. Did any relative present with the allelic variant of MPANSPG43?[4] A thorough family history of the 6 patients is mandatory.

In a previous study of 15 Turkish patients, mean age at onset of symptoms was 24.5 years (range 10–36), thus much later than in the six index patients [Table 1].[5] It should be discussed if MPAN should be divided into an early-onset and late-onset form and if there is genetic or phenotypic difference between these two categories of MPAN.

In another previous study cerebellar atrophy has been reported.[6] We should know if intentional tremor, dysarthria, and gait disturbance were attributable to cerebellar involvement rather than affection of the globi pallidi or the substantia nigra.

It would be interesting to know if any MR-spectroscopy investigations were carried out to see if there was increased lactate in the cerebrospinal fluid or if there was iron overload in the basal ganglia.

Overall, this study has some shortcomings and limitations which need to be solved before drawing final conclusions. MPAN should be diagnosed only in the presence of a pathogenic *C19orf12* variant. Family history and investigation of first-degree relatives is a prerequisite for determining the trait of inheritance and to find out if heterozygosity manifests clinically.

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Conflicts of interest

There are no conflicts of interest.

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