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From PARK9 to SPG78: The clinical spectrum of *ATP13A2* mutations

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Sir,

Mutations in *ATP13A2* have initially been described in Kufor-Rakeb syndrome (formerly termed PARK9), a form of juvenile-onset parkinsonism complicated by pyramidal signs, cognitive impairment and supranuclear gaze palsy [1] and additionally in a single family with neuronal ceroid lipofuscinosis (NCL) [2]. In the latter family, the phenotype was characterized by progressive spinocerebellar ataxia, bulbar syndrome, extrapyramidal and pyramidal involvement, intellectual deterioration, peripheral neuropathy (PNP) and abnormal eye movements [2]. More recently, *ATP13A2* mutations have been further associated with a complicated form of hereditary spastic paraplegia (i.e., SPG78) [3].

We here report on the long-term follow-up of two brothers with *ATP13A2* mutations (Fig. 1A), to highlight the clinical variability of the disorder, which might further be observed in single individuals throughout disease progression.

The older, previously published [4], brother had disease onset at the age of 10 years with progressive gait disturbance and muscle stiffness, and received a diagnosis of pallido-pyramidal syndrome by age 18. Thirty years into disease progression, he had severe parkinsonism with a dystonic gait, axial dystonia, pyramidal signs in the lower limbs, cognitive impairment, and dysarthria. Ocular saccades were slow on the vertical plane and there was a limitation of the upward gaze (video). Currently, he is 50-years old and his phenotype has changed. Although some parkinsonism can be detected in terms of hypomimia and appendicular hypokinesia, signs of a peripheral neuropathy have developed with widespread muscle atrophy, hypotonia, reduced strength and absent reflexes. There are no pyramidal signs including Babinski sign and/or clonus. Continuous facial and upper limbs myoclonus has developed and there is complete vertical supranuclear palsy. Dopaminergic and anti-cholinergic medications have not proved useful, whereas clonazepam slightly reduced myoclonus. He is currently anarthric, uses an enteral tube for feeding and cannot stand or walk.

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His younger brother received a diagnosis of mild mental retardation during childhood, but was otherwise asymptomatic until age 31, when upon examination Babinski sign was present bilaterally along with brisk reflexes, slightly increased axial and appendicular tone and questionable bradykinesia. Over the following 3 years he progressively developed gait disturbances and stiffness in his legs and had several falls. Moreover, his speech became slurred. He is currently 41 and has a spastic gait, hyperreflexia with a bilateral adductor response of knee jerk, reduced strength against resistance and pyramidal hypertone, especially in the lower limbs. His phenotype is further complicated by cerebellar signs (slurred speech, dysdiadochokinesia and balance difficulties), ocular disturbances and very mild parkinsonism (see video and supplemental table). Dopaminergic medications have not proved useful, whereas 25 mg baclofen has improved pyramidal hypertone. Brain magnetic resonance imaging has detected generalized atrophy, which is more evident in the cerebellum, but no iron accumulation on dedicated sequences (Fig. 1B–C). Both patients were found to carry the homozygous mutation c.G2629A of the *ATP13A2* gene as well as the heterozygous mutation c.C1441T of the *FBXO7* gene [4].

In summary, we have reported here two brothers carrying the C.G2629A *ATP13A2* mutation with a PARK9 and SPG78 phenotype, respectively. A profound PNP, which has been reported as axonal variant in both NCL [2] and SPG78 [4], has complicated the clinical picture in the older brother with PARK9 and it currently overshadows other features of pyramidal and extrapyramidal involvement, which might suggest a tendency for these different phenotypes to overlap throughout disease progression. This argues against the concept of "allelic disorders" and would suggest the existence of a continuum, of which PARK9 and SPG78 would represent the two ends. It is unclear whether the PNP has been overlooked in previous reports about PARK9 and this, in the context of early–onset parkinsonism with ocular disturbances and/or facial myoclonus, might represent an additional clinical clue to suspect *ATP13A2* mutations.

The clinical heterogeneity and progression variability of *ATP13A2*-related disorders have been attributed, at least partly, to the type of mutation, with missense variants being usually associated to a more benign phenotype with slow progression over years to decades [5]. However, homozygous frameshift mutations do not necessarily correlate with rapid deterioration [5] and identical mutations have been described with both PARK9 and SPG78 [1,3–5], suggesting that mutation type is not the only factor influencing the clinical phenotype. However, the mechanisms underlying such a phenotypic variability

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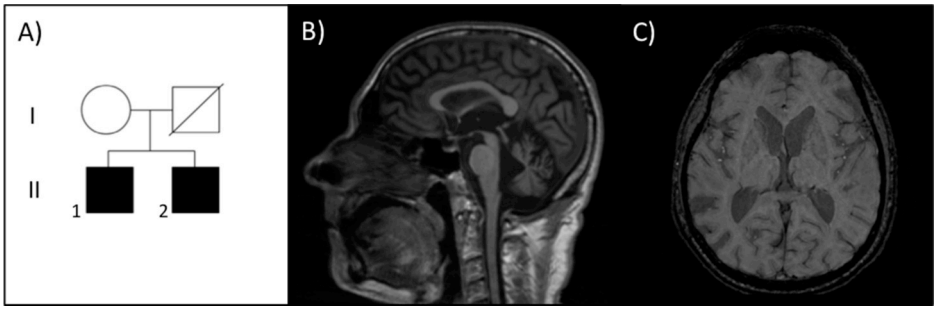

Fig. 1. A) pedigree of the family; B) sagittal T1 sequence showing generalized atrophy, more evident in the cerebellum; and C) axial susceptibility weighted sequence showing no iron accumulation.

remain elusive. Since the *FBXO7* variant was detected in both siblings, this does not seem to have played any role, given the phenotypic differences between our patients, who otherwise fit well with the two disorders classically associated with *ATP13A2* mutations. Therefore, this suggests the existence of strong – genetic or otherwise – unknown modifiers.

Author roles

RE: conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

MP: drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

RM: conception and design of the study, or acquisition of data, or analysis and interpretation of data, final approval of the version to be submitted.

MTP:drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

PB: conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

Conflict of interest related to the current work

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.05.025.

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