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LETTER TO THE EDITOR

Reply: Complicated hereditary spastic paraplegia due to *ATP13A2* mutations: what's in a name?

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Sir,

We have recently shown biallelic *ATP13A2* mutations to cause hereditary spastic paraplegia (HSP) even in the absence of any extrapyramidal involvement (Estrada-Cuzcano *et al.*, 2017). *ATP13A2* mutations are typically associated with a phenotype dominated by juvenile-onset parkinsonism and accompanied by cognitive impairment, supranuclear gaze palsy and pyramidal tract features. The multi-systemic involvement in *ATP13A2* mutation carriers has led to the confusing situation that *ATP13A2*-associated disease, initially termed Kufor-Rakeb syndrome, has been assigned to several disease classifications, following the perceived 'main disease manifestation' in individual families: PARK9 (parkinsonism) (Ramirez *et al.*, 2006), CLN12 (neuronal ceroid lipofuscinosis) (Bras *et al.*, 2012), NBIA (neurodegeneration with brain iron accumulation) (Schneider *et al.*, 2013), and most recently SPG78 (HSP) (Estrada-Cuzcano *et al.*, 2017).

ATP13A2 thus exemplifies a common dilemma in human genetics and maybe particularly in neurogenetics: phenotypes are multidimensional and variable. Due to the hesitant progress in discovering the genetic aetiology of many disorders, the field has long been dominated clinically. The current classification systems—including the 'traditional' locus classification system by the Human Genome Nomenclature Committee (HUGO; http://www.genenames.org/) that is now continued by the Online Mendelian Inheritance in Man (OMIM; https://www.omim.org/) as well as the recent classification system proposed by the International Parkinson and Movement Disorder Society Task Force (Marras *et al.*, 2016) are phenotype-centric and group diseases by phenotypic presentation, e.g. PARK, DYT, HSP, SCA.

For a long time, this system has worked like a 'self-fulfilling prophecy'. Single-gene testing was performed in cohorts matching the initially described clinical features, thus confirming the expected phenotype. This phenotypic bias in genetic screenings has been drastically decreased by the upturn of unbiased next generation sequencing-based screenings in the past 5 years. One among innumerable examples is the *PNPLA6* gene, which had been associated with spastic paraplegia complicated by motor axonal neuropathy and accordingly assigned the locus designation SPG39 (Rainier *et al.*, 2008). Years later it was discovered that *PNPLA6* mutations cause both Gordon Holmes syndrome as well as Boucher-Neuhäuser syndrome and we have learned since that ataxia is much more persistently present in *PNPLA6*-associated disease than pyramidal involvement (Synofzik *et al.*, 2014), including even pure ataxia presentations (Wiethoff *et al.*, 2017), and that *PNPLA6*-associated disease would therefore much more aptly be classified as a recessive ataxia.

The current static HUGO/OMIM classification system that was designed upon the assumption of 2D relationships between gene and phenotype fails to adapt to evolving phenotypic spectra. The only way variability of phenotypes can be captured in the HUGO/OMIM system is by registering genes in multiple disease classifications in order to define the clinical spectrum by its extremes. In the case of *ATP13A2*-associated disease, classification as SPG78 in addition to the existing classifications as PARK9, NBIA and CLN12 is necessary to clarify that *ATP13A2* mutations can manifest with an HSP phenotype without parkinsonism, brain iron accumulation or stigmata of ceroid lipofuscinosis that would be covered by the existing

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classification assignments. In this respect, the *ATP13A2* cases we describe in Estrada-Cuzcano *et al.* (2017) go beyond the case report initially published in van de Warrenburg *et al.* (2016) and now detailed in the letter to the editor by de Bot *et al.* (2017) that has clear signs of extrapyramidal involvement as well as the case included in the whole exome sequencing series of Kara *et al.* (2016) that featured vertical gaze palsy.

The need to actually register novel phenotypes like the manifestation of *ATP13A2* mutations as SPG78 is further emphasized by the fact that although pyramidal involvement had been known to be a recurring feature of the Kufor-Rakeb phenotype for over a decade, the *ATP13A2* gene was not represented on most of the commercial or academic HSP panels at the time of submission of our paper (Estrada-Cuzcano *et al.*, 2017).

The classification proposed by Marras *et al.* (2016) that de Bot and colleagues favour in their Letter to the Editor is a clear advancement compared to the 'old' HUGO/OMIM classification in that it is restricted to phenotype–gene relationships and removes the additional layer of locus assignment. It's phenotype-centric nature defines its purpose: to allow clinicians and geneticists to keep track of potential genetic causes of a given phenotype. It reduces the multidimensionality of gene-to-phenotype relationships to the 2D space of gene–phenotype lists by multiplying entries and including genes like *ATP13A2* in more than one phenotype list. This pragmatic design, however, also poses several limitations. Phenotypic prefixes are restricted to phenotypes present in the majority of observed cases. Although arguably a comprehensible decision once the 'true phenotypic spectrum' associated with a gene is known, this system is in danger of introducing bias in the collection and reporting of unusual clinical presentations, perceptionally re-enforcing known phenotypes, and preserving overly narrow clinical engrams. Moreover, the classification repeats the concept of fixed diagnostic categories when what we really observe for many genes, including *ATP13A2* (Estrada-Cuzcano *et al.*, 2017), *PNPLA6* (Synofzik *et al.*, 2014), *POLR3A* (Minnerop *et al.*, 2017) and *PLA2G6* (Ozes *et al.*, 2017; Synofzik and Gasser, 2017) are fluid, complex, multisystemic phenotypes affecting various regions and/or systems of the nervous system whereby the predominance of certain system affections can vary not only between family members but also in individuals over time. *ATP13A2*-associated disease with its multisystem affection (extrapyramidal, pyramidal, cerebellar, cortical, visual, and peripheral) that translates phenotypically into a spectrum of variably associated signs and symptoms, including spasticity, parkinsonism, progressive cognitive impairment, ataxia, supranuclear gaze palsy, and peripheral neuropathy beautifully exemplifies the need for a 'dynamic modular phenotyping' approach that is required to complement the complex genomic information we gather on our patients.

Just as the Marras classification reduces complex phenotypes to broad phenotypic engrams, it also limits genetic complexity to the single gene level. It leaves no room to capture the multitude of modifying genetic interactions that ultimately determine the phenotype resulting from a variant driving the disease (Riordan and Nadeau, 2017). Studying genetic modifiers is challenging. Yet the variability of phenotypes within family members sharing identical disease-causing mutations as well as the inconsistancy of expressivity in mouse models with different genetic background document the powerful influence of disease modifiers on the phenotype. The phenotype is thus determined by a patchwork of variants, some with stronger, others with less strong effect. As we are hopefully continuing to deepen our understanding of the intricate interactions between multidimensional genotypes and phenotypes, a classification system would need to be designed to incorporate this growing complexity on both the genotypic as well as the phenotypic level. The classification of the Movement Disorder Society task force thus still represents the 'old order', while the field of human genetics moves towards increasingly complex individualized disease concepts and therapies.

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