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The use of next-generation sequencing to unravel new genes: overcoming challenges posed by rare neurological disorders such as myoclonus-dystonia

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The revolution in next-generation sequencing has brought to light detailed catalogues of genetic variation in both patients with disease and the general population [1]. As such, when patients with rare neurological disorders of genetic origin are identified and put through a meticulous examination, genetic testing can yield a molecular diagnosis in about 40% of cases and, in some instances, 94% of cases [2]. The challenge at hand is to maintain high academic standards in our pursuit of new disease-causing variants and effectively distinguish them from rare, potentially functional variants. Adhering to joint consensus recommendations will help to keep false-positive reports of causality to a minimum and enable us to effectively compare international cohorts for a higher diagnostic yield [1,3].

Recently, Balint *et al.* performed segregation analysis of a family pedigree comprising eight individuals with a phenotype resembling myoclonus-dystonia (M-D) over three generations and identified a novel missense variant in *KCNN2* [NM_021614: c.1112G>A: p.(Gly371Glu)] [5]. M-D is a clinical syndrome characterized by myoclonic jerks and dystonia involving the neck, trunk and upper limbs, with accompanying features such as psychiatric symptoms and alcohol responsiveness [4]. The archetype genetic origin of M-D is a pathogenic variant in the epsilon-sarcoglycan (*SGCE*) gene [4]. Over the past decade, a number of familial phenotypes resembling M-D associated with distinct clinical features have been described and are collectively being classified as 'M-D syndromes'. The phenotype of the family with the novel *KCNN2* variant is similar to classical M-D due to *SGCE* mutations, although it is distinct; overlapping features include writer's cramp, torticollis and dystonic posturing of the hands, and distinct features include myoclonus presenting more distally, balance problems, as well as cerebellar eye signs [5]. As such, *KCNN2* has a possible role as a novel M-D syndrome gene.

To investigate causality of a novel variant for diagnosis of a rare disorder, a number of steps need to be undertaken. Firstly, deleterious variants in known genetic causes need to be evaluated. Balint *et al.* aptly

considered *SGCE*, *KCTD17*, *ANO3*, *SCN8A*, *RELN*, *ADCY5* and *TITF1*, established genetic causes of M-D syndromes [5]. Second, the variant ought to be rare; the novel *KCNN2* variant is rare, as it is yet to be described in population databases (minor allele frequency $\leq 0.1\%$). Other favourable arguments include the variant being highly conserved across species and being predicted as deleterious by various *in-silico* prediction models. Moreover, analysis of public RNA-seq databases shows that *KCNN2* is highly expressed in the cerebellum (a region implicated in M-D pathophysiology) and gene co-regulation analysis reveals similarity between *KCNN2* and other genes implicated in M-D pathophysiology such as *ANO3*, *RELN* and *TUBB2B* [4]. In sum, *KCNN2* is a biologically plausible candidate gene for the phenotype in question.

Nonetheless, neurological and movement disorder units worldwide need to come together to translate efforts into maximal clinical impact. In addition to rigorous phenotyping and genotyping, data sharing and analysis of international cohorts are of paramount importance. We need to achieve the above for more timely determination of pathogenicity and to enable a shift in our focus towards development of disease-modifying treatment for our patients.

Disclosure of conflicts of interest

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