A recurrent *EIF2AK2* missense variant causes autosomal-dominant isolated dystonia

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We read with interest the article by Kuipers and colleagues[1], reporting the identification of an *EIF2AK2* c.388G>A (p.Gly130Arg) missense variant in 9 individuals with dystonia from 3 families. Although bioinformatics algorithms almost universally predicted a benign impact of the variant[2], the authors demonstrated complete co-segregation of c.388G>A (p.Gly130Arg) in 7 affected subjects from the index family and its *de-novo* occurrence in another pedigree. Moreover, the authors were able to elucidate abnormally increased activation of EIF2AK2 in c.388G>A (p.Gly130Arg)-harboring patient cells, consistent with a gain-of-function effect. Notably, a set of *de-novo EIF2AK2* missense variants affecting amino-acid positions other than glycine-130 have been described as causative for a neurodevelopmental syndrome with leukoencephalopathy, developmental delay, and episodic neurologic regression (Fig.1A)[3]. In an attempt to replicate the association between the *EIF2AK2* c.388G>A (p.Gly130Arg) variant

and dystonic presentations, we re-analyzed whole-exome sequencing data from 953 patients with various forms of dystonia[4, 5].

We identified *EIF2AK2* c.388G>A (p.Gly130Arg) in 1 German kindred for which exome-sequences of 3 affected subjects had been generated, but no mutations in previously reported dystonia-related genes were found (Fig.1A-C). The *EIF2AK2* mutation finding in the present family was not reported as part of the original paper by Kuipers et al.[1]. The index patient (III-1), a 10-year-old girl, manifested isolated dystonia, starting in the legs at the age of 2 years and progressing to generalized dystonia with involvement of all 4 extremities, the trunk, and larynx. At the age of 3 years and 9 months, she underwent bilateral DBS electrode implantation in the GPI, leading to sustained symptom relief. The index patient`s mother (II-2) reported onset of lower-limb dystonic movements during adolescence, causing intermittent wheelchair-dependence. Symptoms were progressive after III-1`s birth (40 years old), with spread of dystonia to the trunk, neck, and orofacial region resulting in anarthria. Because brain structural abnormalities excluded GPI as a target for neuromodulation, DBS implantation in the nucleus subthalamicus was performed (49 years). Since then, she was able to perform directed grasps with her upper limbs and pronounce simple words. IIII-1`s grandmother (I-2), last examined at the age of 68 years, displayed a dystonic phenotype consisting of late-adulthood-onset blepharospasm and spasmodic dysphonia with no need for specific treatment. The index patient`s maternal uncle (II-1, genetic testing unavailable) had childhood-onset dystonia mostly affecting the right hemibody, which exhibited excellent response to GPI-DBS performed at the age of 40 years.

Our findings confirm that a recurrent *EIF2AK2* missense variant produces isolated dystonia phenotypes with variable expressivity. Given that DBS seems to be effective in this new

monogenic entity, *EIF2AK2* testing should be considered to stratify patients before surgical intervention.

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Potential Conflicts of Interests

Nothing to report.

References

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Figure legend

Figure 1 Recurrent *EIF2AK2* missense variant in dystonia. (A) Schematic representation of EIF2AK2 protein with indication of functional domains and the locations of disease-related

variants. The c.388G>A (p.Gly130Arg) variant, identified in the present family and in 3 families from Kuipers et al.[1], is shown above the protein; variants linked to a neurodevelopmental disorder with leukoencephalopathy, developmental delay, and episodic neurologic regression[3] are shown below the protein. (B) Pedigree structure of the present family. Individuals subjected to exome sequencing are indicated with asterisks; wt/mut, heterozygous carrier of the c.388G>A (p.Gly130Arg) variant; n.a., genetic testing unavailable. (C) IGV visualization of the c.388G>A (p.Gly130Arg) variant in 3 affected subjects from the present family.