DYT16 revisited: exome sequencing identifies PRKRA mutations in a European dystonia family.

Recessive DYT16 dystonia associated with mutations in PRKRA has until now been reported only in seven Brazilian patients. The aim of this study was to elucidate the genetic cause underlying disease in a Polish family with autosomal-recessive, early-onset generalized dystonia and slight parkinsonism, and to explore further the role of PRKRA in a dystonia series of European ancestry.

We employed whole-exome sequencing in two affected siblings of the Polish family and filtered for rare homozygous and compound heterozygous variants shared by both exomes. Validation of the identified variants as well as homozygosity screening and copy number variation analysis was carried out in the two affected individuals and their healthy siblings. PRKRA was analyzed in 339 German patients with various forms of dystonia and 376 population-based controls by direct sequencing or high-resolution melting. The previously described homozygous p.Pro222Leu mutation in PRKRA was found to segregate with the disease in the studied family, contained in a 1.2 Mb homozygous region identical by state with all Brazilian patients in chromosome 2q31.2. The clinical presentation with young-onset, progressive generalized dystonia and
mild parkinsonism resembled the phenotype of the original DYT16 cases. PRKRA mutational screening in additional dystonia samples revealed three novel heterozygous changes (p.Thr34Ser, p.Asn102Ser, c.-14A>G), each in a single subject with focal/segmental dystonia. Our study provides the first independent replication of the DYT16 locus at 2q31.2 and strongly confirms the causal contribution of the PRKRA gene to DYT16. Our data suggest worldwide involvement of PRKRA in dystonia.