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Novel compound heterozygous mutations in *PRKRA* cause pure dystonia

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We read with interest the paper by Zech *et al.* where they report a new European dystonia family with a homozygous *PRKRA* mutation. Our group recently identified a new Brazilian family with compound heterozygous variants in *PRKRA* and a pure dystonia phenotype of variable severity. The proband is a 37- year-old Brazilian woman of Portuguese ancestry, the fifth child of non-consanguineous parents, who was first assessed at age 8 reporting a history of dystonia since age 4. Birth history was uneventful and, except for speech delay, development milestones were normal until age 4. Dystonia onset was in the right upper limb and generalized in four years, with severe involvement of cervical region, trunk and limbs, but mild dysarthria and dysphonia. No parkinsonian or pyramidal signs were observed. Laboratory screening for Wilson's disease was negative and brain image at ages 8 and 16 were normal. She was not responsive to levodopa and response to anticholinergic drugs was poor. At first, family history of dystonia was negative. Among her five siblings, three were healthy and two were deceased (one from Pertussis at eight months, and another from unknown causes at one month). At age 23 she was enrolled in a genetic study of dystonia, and screening for *TOR1A* and *THAP1* was negative.² At that time, both parents and three siblings were examined by movement disorders specialists. Her younger sister, aged 19, had a very subtle dystonic posture in the third and fourth fingers of the left hand and was rated as

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VB: 1C; 2B

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LJO: 1A; 1B; 1C; 2A; 2B

possible dystonia. She was not aware of the age of onset. At age 28 she developed cervical dystonia and marked dysphonia. When the sibling became affected, the family history was consistent with possible recessive inheritance, which in turn, led us to screen *PRKRA* using Sanger sequencing. In both affected patients, we identified novel variants in exon 2, c.G230C (p.Cys77Ser), and in exon 7, c.G638T (p.Cys213Phe). The first is in the DRBM1 functional domain. A variant affecting the same amino acid c.T637C (p.Cys213Arg), together with c.C665T (p.Pro222Leu) has been previously described in a patient with dystonia, whose symptoms developed after a febrile illness and who had volume loss in the basal ganglia.³ All unaffected family members carry a single variant. The father and two siblings carry the c.G230C variant, the mother carries c.G638T. None of these variants were found in 240 Brazilian control chromosomes and only p.Cys213Phe was reported at an extremely low frequency (7.916e-06) in the Exome Aggregation Consortium (ExAC) (<http://exac.broadinstitute.org>). Three out of four *in silico* predictions support these variants as disease causing (Table 1). Both variants are highly conserved. Since *PRKRA* was first identified as a dystonia cause,⁴ only three other families/individuals have been found with mutations.^{1,3,5} The Brazilian and Polish families with the p.Pro222Leu variant share a dystonia-parkinsonism phenotype and the disease haplotype that could represent a founder mutation¹. Herein we report two novel mutations in siblings with isolated dystonia confirming *PRKRA* as a causative disease gene. Moreover, we suggest that *PRKRA* mutations may be a more widespread cause of generalized dystonia and screening should be considered in familial cases with putative autosomal recessive inheritance.

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Table 1

In silico analysis and frequency of *PRKRA* variants

Variant	Algorithm (score/prediction)				Frequency*	
	PolyPhen2	Mutationtaster	SIFT	CADD ⁶	Overall	European
c.G230C/p.C77S	0.619/possiblydamaging	112/diseasecausing	0.46/tolerated	23.1/Deleterious	0	0
c.G638T/p.C213F	0.902/possiblydamaging	112/diseasecausing	0.12/tolerated	22.3/Deleterious	7.916e-06	1.454e-05
c.T637C/p.C213R ³	0.009/benign	180/diseasecausing	0.12/tolerated	20.2/Deleterious	0	0
c. C665T/p.P222L ^{1,3,4}	0.001/benign	98/diseasecausing	0.07/tolerated	21.3/Deleterious	1.453e-04	1.453e-04

* Frequency data from 63000exomes at Exome Aggregation Consortium (ExAC), Cambridge, MA (<http://exac.broadinstitute.org>) [accessed 10, 2014].