seronegative patients) had a higher than the mean control response.

Half of the seronegative patients with NMO had a T-cell response higher than $2 \times$ SD above the mean of the control group. The striking difference in the incidence of anti-AQP4 T cell responses between the NMO and MS groups may provide a more sensitive tool for distinction between these 2 demyelinating diseases.

Discussion. Despite the association of anti-AQP4 antibodies with NMO, there is no convincing evidence that these antibodies are solely responsible for the pathogenesis of the disease. A possible role of T cells in NMO immunopathogenesis has been suggested lately. Warabi et al.³ reported a generalized upregulation of T-cell activity in patients with NMO and Matsuya et al.⁴ described an increase in CD69-activated T cells targeting distinct AQP4 determinants in peripheral blood of patients with NMO during relapses.⁴ Additional support for the role of AQP4-reactive T cells in NMO pathogenesis comes from animal studies, in which it was shown that an NMO-like disease after transfer of AQP4 antibodies is greatly and crucially facilitated by activated T cells.^{5–7}

Two possible scenarios may explain the role of T cells in NMO. 1) In genetically susceptible individuals, anti-AQP4 antibodies may develop and cause astrocyte destruction. Subsequently, AQP4 is released and digested by antigen-presenting cells, and AQP4-specific T cells are produced, which further enhance and maintain the autoreactive inflammatory process. 2) Inflammation induced by T cells could be the initial event, followed by the involvement of humoral autoimmune mechanisms and the production of anti-AQP4 antibodies (representing thus an epiphenomenon) that may target the astrocytes and accelerate tissue loss.

In conclusion, our data provide evidence for a significant involvement of T cells in human NMO. These findings may contribute to a better understanding of the diverse immune mechanisms involved in NMO pathogenesis. Moreover, testing of anti-AQP4 T-cell responses may provide an additional and possibly more sensitive tool for distinguishing between MS and

NMO, especially in patients who are seronegative for AQP4 antibodies.

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MILD PAROXYSMAL KINESIGENIC DYSKINESIA CAUSED BY *PRRT2* MISSENSE MUTATION WITH REDUCED PENETRANCE

Paroxysmal kinesigenic dyskinesia (PKD) is an uncommon disorder characterized by brief episodes of involuntary dystonia or choreoathetosis triggered by sudden voluntary movement.¹ Recently, several groups identified mutations in patients with PKD in the proline-rich transmembrane protein 2 (*PRRT2*) gene.^{2–7} We report a missense c.913G>A (p.Gly305Arg) change in

PRRT2 in 4 siblings with PKD, 2 with infrequent symptoms. The association of a milder phenotype and reduced penetrance with this missense mutation suggests partial loss of function.

Case Reports. Four Caucasian siblings with PKD⁸ as well as an unaffected sibling and both unaffected parents were genotyped (figure). Institutional approval and informed consent were obtained.

Figure Mutation analysis

(A) Family pedigree: filled symbols denote individuals with paroxysmal kinesigenic dyskinesia and unfilled symbols indicate unaffected individuals. DNA from all individuals shown was sequenced. Asterisks indicate individuals with the c.913G>A (p.Gly305Arg) change in the *PRRT2* gene. (B) Sequence conservation (highlighted in red) in the *PRRT2* gene in the region of the changed amino acid across multiple vertebrate species suggests that this region is part of an important functional or structural motif. Adapted from UCSC Genome Browser—Human, February 2009 (GRCh37/hg19 Assembly) (<http://genome.ucsc.edu>).⁹

II-1 is a 24 year-old man with brief episodes of paroxysmal dyskinesia triggered by sudden movement, beginning at age 16. Typically spells were rare, but during stressful times occurred up to 10 times per day and improved dramatically with carbamazepine up to 400 mg. daily. Currently, spells are

nearly resolved with medication taken only at times of increased stress.

II-3, II-4, and II-5 are 19-year-old fraternal triplets. Brief dystonic, tensing, or choreoathetotic movements began between ages 12 and 14. Spells occurred up to 3 times per day (II-4) or, rarely, primarily in association with athletic competitions (II-3 and II-5). Spells were triggered by initiation of movement with greater likelihood of events at times of increased stress or excitement (during athletic competitions or walking to the front of the class to present). Caffeine exacerbated spells in II-3 and II-5. II-3 also noted eye-blinking tics. II-5 had a history of congenital torticollis attributed to intrauterine positioning. His examination showed right-sided shoulder depression and hypertrophy of the paraspinal muscles without scoliosis. Results of examinations of others were normal. In all 3, there was resolution of spells with low-dose carbamazepine (100 mg daily) taken by II-3 and II-5 only rarely before competitions.

Missense change c.913G>A (p.Gly305Arg) in the *PRRT2* gene was identified in II-1 and II-4 by whole exome sequencing. Sanger sequencing of the remainder identified the c.913G>A change in II-3 and II-5 and in the unaffected mother (figure).

Discussion. We report a missense change in the *PRRT2* gene associated with familial PKD with mild phenotype and reduced penetrance. Although the pathogenicity of this alteration cannot be proven, it changes a highly conserved amino acid residue (figure),⁹ was predicted by PolyPhen-2 to be deleterious, and was not identified across 1,000 individuals in our in-house exome database, in 1,092 individuals sequenced in the 1000 Genomes database,¹⁰ or among variants identified by Chen et al.² in 500 Han Chinese control subjects. Recently, this missense change has also been identified by Liu et al.⁵ in a patient with sporadic PKD, consistent with its pathogenicity.

Previous studies reported PKD attack frequency of greater than 20 per day in 31% of patients and at least once per day in 72%.⁸ Comparatively, the phenotype in this family is mild with 2 siblings with infrequent symptoms requiring carbamazepine only rarely. In addition, the mother is a nonsymptomatic carrier. Although the mutation identified in this single family is insufficient to establish a clear genotype-phenotype correlation, it is possible that the missense mutation leads to partial loss of function and a milder phenotype. Nevertheless, additional modifiers are probably at play, because *PRRT2* kindreds can display phenotypic variability that may include infantile convulsions.⁶ Other neurologic symptoms have also been reported in patients and kindreds with

PKD although no definitive association has been established.⁸ These symptoms include dystonia and tics, which were also noted in our patients.

The PRRT2 protein contains 2 extracellular domains, 2 transmembrane domains, and 1 cytoplasmic domain.² The majority of reported mutations to date lead to premature transcription termination and truncated protein products. In vitro, truncated products have been found to mis-localize from membrane to cytoplasm² or, alternatively, to be poorly expressed, resulting in haploinsufficiency.⁷ Reports of patients with possible PKD with deletions encompassing the PRRT2 allele^{11,12} support the idea that haploinsufficiency can result in the PKD phenotype.

The c.913G>A mutation is a missense substitution, located in exon 3, that codes for a change in the cytoplasmic region of the protein. Although we lack functional data, it is likely that this mutation leads to partial loss of function of the affected allele through an as yet undefined mechanism. It has been proposed that PKD is an ionic channelopathy and that PRRT2 may complex with or regulate key properties of ion channels² or that that PKD may result from dysfunction of synaptic regulation due to interaction with SNAP25.⁷ However, the precise role PRRT2 mutations play in PKD remains unknown.

Further study of this and other families will be necessary to establish genotype-phenotype correlations, to confirm the pathogenicity and mechanism of action of the c.913G>A (p.Gly305Arg) change, to identify the spectrum of genetic variations in PRRT2 associated with PKD, and to determine the possible association of PRRT2 mutations with other movement disorders including dystonia and tics.

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