LETTER: NEW OBSERVATION

Potassium Channel Subunit Kir4.1 Mutated in Paroxysmal Kinesigenic Dyskinesia: Screening of an Italian Cohort

The missing heritability of paroxysmal kinesigenic dyskinesia (PKD) may be explained by genetic heterogeneity with unexplored contributions of genes other than *PRRT2* or *TMEM151A*. Preliminary data published by Wirth et al[1] suggested a causal link between recessive and dominant variants in *KCNJ10* and PKD in four French pedigrees. More recently, Li et al[2] reported on the identification of dominant *KCNJ10* variants in Chinese patients with PKD. In 168 exome-sequenced families, they discovered eight heterozygous missense *KCNJ10* variants in 11 patients presenting attacks of predominantly dystonic character.[2] *KCNJ10* encodes the inward-rectifying potassium (K+) channel Kir4.1, a master regulator of K^+ concentrations in the brain. Kir4.1 channels are enriched in neuroglia, where they contribute to cell-volume maintenance and neurotransmission.[2] Downregulation of Kir4.1 is believed to result in neural death,[3] whereas *KCNJ10* biallelic loss-of-function mutations produce a monogenic disorder with ataxia, seizures, and deafness (EAST/SeSAME syndrome).[4] Functional studies of the Kir4.1 mutants detected by Li et al[2] showed loss of channel activity consistent with haploinsufficiency. Despite these results, the role of *KCNJ10* variants in different PKD populations is not well understood.

To replicate the newly proposed gene–phenotype relationship, we screened *KCNJ10* for nonsynonymous variants in exome data of 25 simplex PKD cases and one kindred with three patients from Italy. Genetic analyses were performed as detailed elsewhere[5]; *PRRT2*, *TMEM151A*, and other established PKD gene-related mutations had been excluded. All patients were diagnosed according to consensus criteria by movement disorder experts at the Neurological Institute "Besta" (Milan, Italy). Written informed consent for study participation was obtained. We singled out a heterozygous c.511C>T, p.Arg171Trp substitution, carried by a 27-year-old man with a 13-year history of PKD. Strikingly, the exact same *KCNJ10* variant was described in one of the families from Li et al[2] (PKD123). Furthermore, an alternative amino acid change at Arg171 has previously been defined as a cause of EAST/SeSAME syndrome,[6] indicating that this residue might represent a disease mutation hot spot. Electrophysiological characterization of p.Arg171Trp demonstrated an ~90% reduction of K^+ currents compared with wild type, indicative of pathological Kir4.1 dysfunction.[2] We classified c.511C>T, p.Arg171Trp as "likely pathogenic" (PS3 + PM1 + PM2 + PP3 according to American College of Medical Genetics and Genomics standards[7]). Our *KCNJ10* p.Arg171Trp-positive patient displayed brief dystonic episodes (5–10 s) triggered by sudden movements. The paroxysms involved the mouth and upper and lower limbs sequentially but on alternate sides; frequency was variable, from daily to monthly, and aggravated by stress. His neurological examination, interictal electroencephalography, and brain magnetic resonance imaging were normal. The phenotype closely matched with the one reported for "PKD123" in Li et al[2] (Table 1); both cases also had a negative family history, indicating that *KCNJ10* variants are associated with incomplete penetrance, similar to *PRRT2*-related PKD. This conjecture is supported by the fact that p.Arg171Trp is seen (at extremely low frequency) in the gnomAD database.

Taken together, we provide additional evidence for the implication of mutant Kir4.1 in the etiology of PKD

***Correspondence to:** Dr. Michael Zech, Institute of Neurogenomics, Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstraße 1, 85764 Neuherberg, Germany; E-mail: michael.zech@mri.tum.de

Relevant conflicts of interest/financial disclosures: Nothing to report.

Funding agencies: This work was supported by the Italian Ministry of Health (RRC). This work was supported by the EJP RD (EJP RD Joint Transnational Call 2022) and the German Federal Ministry of Education and Research (BMBF, Bonn, Germany) awarded to the project PreDYT (PREdictive biomarkers in DYsTonia, 01GM2302). This research was also supported by a "*Schlüsselprojekt*" grant from the Else Kröner-Fresenius-Stiftung (2022_EKSE.185). In addition, this study has received funding from the BMBF and the Free State of Bavaria under the Excellence Strategy of the Federal Government and the Länder, as well as by the Technical University of Munich–Institute for Advanced Study (to M.Z.). M.Z. receives research support from the German Research Foundation (DFG 458949627; ZE 1213/2–1). H.P. acknowledges grant support from the BMBF (Bonn, Germany) through the European Joint Programme on Rare Diseases (EJP RD Joint Transnational Calls 2022 and 2023) for the GENOMIT project.

Received: 12 August 2024; **Accepted:** 19 August 2024

Published online in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30008

TABLE 1 *Comparison of phenotypic features between the present* KCNJ10*-mutated patient and cases previously reported by Li et al[2] and Wirth et al[1]*

Case	Sex	Geographic Origin	Age, y	Age of Onset, y	Movement Disorder Type (Attack)	Duration of Attacks, s	EEG	Brain MRI	Other Neurological Features	Treatment/ Response
PKD-Milan/ Munich-18 (c.511C>T, p.Arg171Trp)	M	European (Italian)	27	14	Dystonia	5–10	Normal	Normal	No	No treatment
PKD123/123-1 (c.511C>T, p.Arg171Trp) from Li et al[2]	M	Asian (Chinese)	27	17	Dystonia	5–10	Normal	Normal	No	Carbamazepine/ complete
Other PKD patients with *KCNJ10* missense variants from Li et al[2] (N = 10)	F, n = 2; M, n = 8	Asian (Chinese)	14–45	9–19	Dystonia, n = 10	1–30	Normal, n = 7; unavailable, n = 3	Normal, n = 7; unavailable, n = 3	No, n = 10	Carbamazepine or oxcarbazepine/ complete, n = 3; carbamazepine or oxcarbazepine/ incomplete, n = 2; levodopa/no, n = 1; no treatment, n = 4
PKD patients with *KCNJ10* missense variants from Wirth et al[1] (N = 9)	F, n = 2; M, n = 7	European, Middle Eastern, Northern African, Turkish (French)	14–39	8–14	Dystonia, n = 8; chorea, n = 3	<10–60	No information	Normal, n = 6; unavailable, n = 1; abnormal, n = 2	No, n = 4; eye movement abnormalities, n = 4; epilepsy, n = 2	Carbamazepine/ complete, n = 6; carbamazepine/ incomplete, n = 1; no treatment, n = 2

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; F, female; M, male; PKD, paroxysmal kinesigenic dyskinesia.

by establishing variant recurrence in independent populations of affected subjects. The study of Kir4.1 aberrations in PKD may offer unique insights into unanticipated roles of glial cells in the pathogenesis of abnormal movements. ■

Acknowledgments: We thank the patients for participating in this study. Open Access funding enabled and organized by Projekt DEAL.

Giovanna Zorzi, MD,[1] Federica Zibordi, MD,[1] Ugo Sorrentino, MD,[2,3,4] Holger Prokisch, PhD,[2,3] Barbara Garavaglia, PhD,[5] and Michael Zech, MD[2,3,6*]

[1]*Unit of Child Neuropsychiatry–Movement Disorder, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy,* [2]*Institute of Human Genetics, Technical University of Munich, School of Medicine and Health, Munich, Germany,* [3]*Helmholtz Center Munich, Institute of Neurogenomics, Neuherberg, Germany,* [4]*Clinical Genetics Unit, Department of Women's and Children's Health, University of Padova, Padova, Italy,* [5]*Medical Genetics and Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, and* [6]*Institute for Advanced Study, Technical University of Munich, Garching, Germany*

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Wirth T, Roze E, Delvallee C, et al. Rare missense variants in KCNJ10 are associated with paroxysmal Kinesigenic dyskinesia. Mov Disord 2024;39(5):897–905.
2. Li YL, Lin J, Huang X, et al. Heterozygous variants in KCNJ10 cause paroxysmal Kinesigenic dyskinesia via Haploinsufficiency. Ann Neurol 2024;.
3. Srivastava R, Aslam M, Kalluri SR, et al. Potassium channel KIR4.1 as an immune target in multiple sclerosis. N Engl J Med 2012;367(2):115–123.
4. Scholl UI, Choi M, Liu T, et al. Seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) caused by mutations in KCNJ10. Proc Natl Acad Sci U S A 2009;106(14):5842–5847.
5. Zech M, Jech R, Boesch S, et al. Monogenic variants in dystonia: an exome-wide sequencing study. Lancet Neurol 2020;19(11):908–918.
6. Morin M, Forst AL, Perez-Torre P, et al. Novel mutations in the KCNJ10 gene associated to a distinctive ataxia, sensorineural hearing loss and spasticity clinical phenotype. Neurogenetics 2020;21(2):135–143.
7. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405–424.

SGML and CITI Use Only
DO NOT PRINT

Author Roles

Giovanna Zorzi: study design and concept, acquisition of data, clinical examination, analysis and interpretation of data, and revision of manuscript for critical intellectual content. Federica Zibordi: acquisition of data, clinical examination, and revision of manuscript for critical intellectual content. Ugo Sorrentino: acquisition of data and revision of manuscript for critical intellectual content. Holger Prokisch: acquisition of data and revision of manuscript for critical intellectual content. Barbara Garavaglia: study design and concept, study supervision, and analysis and interpretation of data. Michael Zech: study design and concept, study supervision, analysis and interpretation of data, and writing of the manuscript.

Disclosures (for the Preceding 12 Months)

Nothing to report.