Early-onset parkinsonism in a pedigree with phosphoglycerate kinase deficiency and a heterozygous carrier: do PGK-1 mutations contribute to vulnerability to parkinsonism?

Satoshi Sakaue1, Takashi Kasai2,3, Ikuko Mizuta2, Masaya Suematsu1, Shinya Osone1, Yumiko Azuma2, Toshihiko Imamura1, Takahiko Tokuda2,3,4, Hitoshi Kanno5, Omar M. A. El-Agna6, Masafumi Morimoto1, Masanori Nakagawa2,7, Hajime Hosoi1 and Toshiki Mizuno2

INTRODUCTION
Phosphoglycerate kinase 1 (PGK-1) is a glycolytic enzyme encoded by PGK-1, which maps to the X chromosome. PGK-1 deficiency causes X-linked recessive hereditary chronic hemolytic anemia, myopathy, and neurological disorders due to insufficient ATP regeneration. Early-onset parkinsonism has occasionally been reported as a neurological complication of this condition. However, heterozygous carriers of PGK-1 deficiency were thought to be neurologically asymptomatic. Here, we report a boy with PGK-1 deficiency and his mother, a carrier of a heterozygous mutation in PGK-1, both of whom presented with early-onset parkinsonism. The boy developed parkinsonism at 9 years of age. His parkinsonism partially responded to levodopa treatment.1234 metaiodobenzylguanidine (MIBG) uptake was normal. His mother, who exhibited normal PGK-1 activity in erythrocytes, developed parkinsonism at 36 years of age. Her symptoms were undistinguishable from those of Parkinson’s disease (PD), despite her normal uptake of MIBG. Neither a point mutation in nor multiplication of SNCA was found. Additionally, hotspots of LRRK2 and GBA were not mutated. To our knowledge, this report provides the first description of parkinsonism in a carrier of PGK-1 deficiency. Interestingly, PGK-1 is located within the confirmed susceptibility locus for PD known as PARK12. These observations suggest that PGK-1 mutations confer susceptibility to PD.

npj Parkinson’s Disease (2017) 3:13; doi:10.1038/s41531-017-0014-4

ARTICLE

Case 1
(III1 in Fig. 1). A 16-year-old boy with PGK-1 deficiency developed parkinsonism. We previously reported that this patient was diagnosed with PGK-1 deficiency at 3 years of age based on decreased PGK activity in erythrocytes (16 IU/g Hb, normal: 255–325 IU/g Hb) and the novel PGK-1 missense mutation c.1060G > C; p.A354P.4 (Notably, this mutation was originally described as A353P, which indicates an amino-acid substitution at the 353rd position from the NH2-terminal serine residue). He had been repeatedly hospitalized for recurrent episodes of myoglobinuria with hemolytic anemia every few months. Moderate intellectual disability had been identified prior to 3 years of age. No epileptic seizures were observed. At 9 years of age, the patient presented with action tremor in his extremities. Rigidity developed at 11 years of age. Therapy with carbidopa/levodopa 25/100 mg three times daily produced immediate but partial improvement in the patient’s parkinsonism. However, his symptoms gradually progressed. When the patient was 16 years of age, neurological examination revealed severe action tremor in his extremities, especially his left arm, and a mask-like face. Marked rigidity with a dystonic posture was observed in all limbs and the neck. He could no longer walk without assistance. He exhibited

1Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan; 2Department of Neurology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan; 3AMED-CREST, Japan Agency for Medical Research and Development, Kyoto 602-8566, Japan; 4Department of Molecular Pathobiology of the Brain Diseases, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan; 5Department of Transfusion Medicine and Cell Processing, Tokyo Women’s Medical University, Tokyo 162-8666, Japan; 6Neurological Disorders Center, Qatar Biomedical Research Institute (QBRI), and College of Science and Engineering, Hamad Bin Khalifa University (HBKU), Education City, Qatar Foundation, Doha P.O. Box 5825, Doha, Qatar and 7North Medical Center, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
Correspondence: Takashi Kasai (kasai@koto.kpu-m.ac.jp)
Satoshi Sakaue and Takashi Kasai contributed equally to this work.

Received: 19 April 2016 Revised: 13 July 2016 Accepted: 14 November 2016
Published online: 31 March 2017

Published in partnership with the Parkinson’s Disease Foundation
Early-onset Parkinson’s disease
S Sakaue et al.

To exclude known causes of autosomal dominant parkinsonism, we performed genetic analyses of the coding region and gene dose of SNCA, the hotspot of GBA (exons 5, 6, 8, and 10, including R120W and L44P/RecNciI), and the hotspot of LRRK2 (exons 31, 35, 41, and 48, including R1441G/H/C, Y1699C, G2019S, I2020T and G2385R). No mutation was found in either of the aforementioned cases.

DISCUSSION

Here, we describe a boy with PGK-1 deficiency and his mother, a heterozygous carrier of a PGK-1 mutation, both of whom presented with early-onset parkinsonism. It is unknown whether II3 died from PGK-1 deficiency. Unfortunately, we could not obtain consent for a genetic test from the maternal grandmother of case 1 (I2), who appeared to be neurologically normal. Therefore, we have no information regarding whether the mutation in case 2 was inherited from the patient’s mother or was a de novo mutation. Neurological symptoms of the boy in case 1 included parkinsonism and were accompanied by cerebellar atrophy, autonomic dysfunction, and normal MIBG uptake. These symptoms may be similar to those of multiple system atrophy-parkinsonism rather than PD. Symptoms exhibited by this boy’s mother included levodopa-responsive parkinsonism with resting tremor and were consistent with clinical diagnostic criteria for PD, despite her normal uptake of MIBG. To our knowledge, this report provides the first evidence that parkinsonism can develop not only in a patient with PGK-1 deficiency but also in a heterozygous carrier of a PGK-1 mutation without an enzymatic deficiency. We did not comprehensively exclude all known genetic abnormalities related to susceptibility to parkinsonian syndromes, including PD. However, our cases appear unlikely to be caused by known parkinsonism-related mutations for the following reasons. First, parkinsonism that develops in patients under the age of 10 years is quite unusual for known dominantly inherited forms of PD. Second, in our cases, parkinsonism was more severe and exhibited an earlier age of onset in the child compared with the mother. The appearance of more severe symptoms at earlier ages in successive generations has not been reported in known hereditary parkinsonian syndromes, whereas this phenomenon is easy to understand when we consider differences in gene dosages of PGK-1 between males and females.

According to a current database (OMIM #311800), PGK-1 lies on the X chromosome at 78,065,188–78,129,296, a region within Xq21.1, although PGK-1 was originally reported to map to chromosome Xq13. Interestingly, the region between Xq21 and Xq25 is known as a susceptibility locus for classical PD associated with PARK12 (OMIM #300557), and the causative gene for this disease has not been identified. We therefore speculate that mutations in PGK-1 may contribute to the pathogenesis of PARK12-associated PD.

Parkinsonism in patients with PGK-1 deficiency has been postulated to occur due to insufficient ATP regeneration in the substantia nigra as a result of low levels of PGK activity. In heterozygous carriers, the mutant allele of PGK-1 on the X chromosome is randomly inactivated during early embryonic stages due to lyonization, resulting in a “mosaic” or “patchy” pattern of enzymatic activity. Therefore, selective enzymatic deficiency in the substantia nigra is possible in heterozygous carriers even when erythrocytes exhibit normal enzymatic activity, as observed in the present case. Based on this hypothesis, the penetrance of parkinsonism in PGK-1 deficiency is expected to be incomplete since variability in lyonization would lead to considerable variability in the severity of parkinsonism in female carriers.

Several studies have established an association between heterozygous mutations in GBA, which is responsible for Gaucher disease, and PD. These findings have induced a paradigm shift in the PD field from the “common disease: common variant”...
hypothesis to the “common disease: multiple rare variant” hypothesis. We may have encountered a similar situation in this family. Neurologists and pediatricians should therefore look carefully for parkinsonism in not only PGK-1 deficiency patients but also carriers of this deficiency. Further studies are needed to clarify whether multiple rare variants of PGK-1 confer susceptibility to PD or other parkinsonian syndromes.

ACKNOWLEDGEMENTS

This work was supported by AMED, AMED-CREST (to T.T.), and a Grant-in-Aid (No. 15K09319) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (to T.K.).

AUTHOR CONTRIBUTIONS

S.S. and T.K.: study concept and design; S.S., T.K., M.S., S.O., T.I. and Y.A.: collection of clinical information; I.M., T.I., and M.M.: genetic testing; H.K.: Enzymatic testing; T.T., O.E. and M.N.: critical revision of the manuscript for important intellectual content; H.H. and T.M.: study supervision.

COMPETING INTERESTS

T.K. has received research support from a Grant-in-Aid (No. 15K09319) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and from AMED and AMED-CREST. T.T. has received research support from AMED and AMED-CREST. O.M.A.E-A. has received research support from The Michael J. Fox Foundation for Parkinson’s Research (NY). The remaining authors declare no competing interests.

REFERENCES

1. Beutler, E. PGK deficiency. Br. J. Haematol. 136, 3–11 (2007).
2. Sotiriou, E., Greene, P., Krishna, S., Hirano, M. & DiMauro, S. Myopathy and parkinsonism in phosphoglycerate kinase deficiency. Muscle Nerve 41, 707–710 (2010).
3. Konrad, P. N., McCarty, D. J., Mauer, A. M., Valentine, W. N. & Paglia, D. E. Erythrocyte and leukocyte phosphoglycerate kinase deficiency with neurologic disease. J. Pediatr. 82, 456–460 (1973).
4. Morimoto, A. et al. A novel missense mutation (1060G -->C) in the phosphoglycerate kinase gene in a Japanese boy with chronic haemolytic anaemia, developmental delay and rhabdomyolysis. Br. J. Haematol. 122, 1009–1013 (2003).
5. Mitsui, J. et al. Mutations for Gaucher disease confer high susceptibility to Parkinson disease. Arch. Neurol. 66, 571–576 (2009).
6. Rudenko, I. N. & Cookson, M. R. Heterogeneity of leucine-rich repeat kinase 2 mutations: genetics, mechanisms and therapeutic implications. Neurotherapeutics 11, 738–750 (2014).
7. Willard, H. F., Goss, S. J., Holmes, M. T. & Munroe, D. L. Regional localization of the phosphoglycerate kinase gene and pseudogene on the human X chromosome and assignment of a related DNA sequence to chromosome 19. Hum. Genet. 71, 138–143 (1985).
8. Pankratz, N. et al. Genome-wide linkage analysis and evidence of gene-by-gene interactions in a sample of 362 multiplex Parkinson disease families. Hum. Mol. Genet. 12, 2599–2608 (2003).
9. Hardy, J., Cai, H., Cookson, M. R., Gwinn-Hardy, K. & Singleton, A. Genetics of Parkinson’s disease and parkinsonism. Ann. Neurol. 60, 389–398 (2006).
10. Tossici-Bolt, L., Hoffmann, S. M., Kemp, P. M., Mehta, R. L. & Fleming, J. S. Quantification of [123I]FP-CIT SPECT brain images: an accurate technique for measurement of the specific binding ratio. Eur. J. Nucl. Med. Mol. Imaging 33, 1491–1499 (2006).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/

© The Author(s) 2017

Supplementary Information accompanies the paper on the npj Parkinson’s Disease website (doi:10.1038/s41531-017-0014-4).