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Novel LRPPRC Mutation in a Boy With Mild Leigh Syndrome, French–Canadian Type Outside of Québec

Velda Xinying Han, MBBS, MMED, MRCPCH[1], Teresa S. Tan, MBBS, MMED, MRCPCH[1], Furene S. Wang, MBBS, MMED, MRCPCH[1], and Stacey Kiat-Hong Tay, MBBS, MMED, MRCP, FRCPCH[1,2]

Abstract

Background: Leigh syndrome, French–Canadian type is unique to patients from a genetic isolate in the Saguenay–Lac-Saint-Jean region of Québec. It has also been recently described in 10 patients with LRPPRC mutation outside of Québec. It is an autosomal recessive genetic disorder with fatal metabolic crisis and severe neurological morbidity in infancy caused by LRPPRC mutation. **Methods and Results:** The authors report a boy with a novel LRPPRC compound heterozygous missense mutations c.3130C>T, c.3430C>T, and c.4078G>A found on whole-exome sequencing which correlated with isolated cytochrome c-oxidase deficiency found in skeletal muscle. **Conclusion:** LRPPRC mutation is a rare cause of cytochrome c-oxidase–deficient form of Leigh syndrome outside of Québec. Our patient broadens the spectrum of phenotypes of Leigh syndrome, French–Canadian type. LRPPRC mutation should be considered in children with early childhood neurodegenerative disorder, even in the absence of metabolic crisis. Early evaluation with whole-exome sequencing is useful for early diagnosis and for genetic counseling.

Keywords

children, developmental delay, epilepsy, metabolism, mitochondrial disorder, neurodevelopment

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Leigh syndrome, French–Canadian type is unique to patients from a genetic isolate in the Saguenay–Lac-Saint-Jean region of Québec. It is an autosomal recessive genetic disorder caused by LRPPRC mutation and has been found to be phenotypically distinct from other types of Leigh syndrome with fatally severe metabolic crises.[1-3] Leigh syndrome, French–Canadian type has also been described outside of Québec with 4 novel mutations found.[4] The authors report a Chinese boy with a novel LRPPRC missense mutation who has a milder phenotype compared to the previous patients with Leigh syndrome, French–Canadian type described in the literature.

Case Report

This boy was born to nonconsanguineous Chinese parents. He was born at term, weighed 3100 g with good Apgar scores. He had global developmental delay at 7 months of age with severe head lag and generalized hypotonia. He was brachycephalic with hypopigmented hair. He had poor weight gain with swallowing dysfunction and significant reflux disease requiring gastrostomy feeding. He started having orofacial and limb dyskinesias at 1.5 years of age and subsequently developed refractory multifocal epilepsy at 3 years of age requiring multiple antiepileptics and ketogenic diet to control his seizures. Electroencephalogram showed focal and diffuse slowing

[1] Khoo Teck Puat–National University Children's Medical Institute, National University Health System, Singapore, Singapore
[2] Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Corresponding Author:
Stacey Kiat-Hong Tay, MBBS, MMED, MRCP, FRCPCH, Khoo Teck Puat–National University Children's Medical Institute, National University Hospital, National University Health System, Singapore, Singapore; Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, NUHS Tower Block Level 12, 1E Kent Ridge Road, Singapore 119228, Singapore.
Email: paetaykh@nus.edu.sg

Table 1. Respiratory Chain Enzymes in Muscle.[a]

Complex	Activity	Reference Range	% Activity	% CS Ratio	% CII Ratio
Complex I	49 nmol/min/mg	19-72	119	103	88
Complex II	61 nmol/min/mg	26-63	135	116	
Complex II + III	15 nmol/min/mg	30-76	32	28	24
Complex III	19.2 /min/mg	13-51	66	55	48
Complex IV	0.65 /min/mg	3.3-9.1	10	9	7
Citrate synthase	149 nmol/min/mg	85-179	115		

Abbreviations: CI, complex I; CII, complex II; CIII, complex III; CIV, complex IV; CS, citrate synthase.

[a]Enzyme activities are shown as absolute values and as % residual activity relative to protein (% Activity), % CS ratio, and % CII ratio. Results are diagnostic of a CIV respiratory chain defect, with the low CII + CIII activity likely to be secondary.

consistent with background encephalopathic state, with frequent multifocal epileptiform discharges bilaterally. He developed central and obstructive sleep apneas at 3.5 years of age and was initiated on night bilevel positive airway pressure.

He was evaluated with magnetic resonance imaging brain scan and chromosomal microarray at 8 months of age, which was normal. Whole-exome sequencing and direct sequencing confirmed that he harbored compound heterozygous missense mutations c.3130C>T (p.Arg1044Cys), c.3430C>T (p.Arg1144Cys), and c.4078G>A (p.Ala1360Thr) in the LRPPRC gene mapped to chromosome 2p21-p16. Parents were carriers of the mutation.

His muscle biopsy showed normal muscle architecture with no "ragged-red" fibers, necrotic fibers, or regenerating fibers seen. Cytochrome c-oxidase was positive in most of the fibers. There were no light microscopic or ultrastructural features to support mitochondrial myopathy. Respiratory chain enzymes in skeletal muscle were diagnostic for complex IV defect (Table 1).

He is currently 5 years of age, has generalized dystonia, and is mainly chair-bound. He has intermittent eye contact and minimal vocalization. His baseline lactates ranged from 1.5 to 3.6 mmol/L with mild intermittent metabolic acidosis. However, there were no episodes of acute ketosis, glycemic derangements, or any acute stroke-like episodes.

The parents' first child was diagnosed with steroid-resistant nephrotic syndrome at 18 months of age requiring tacrolimus treatment. Their second pregnancy was terminated at 22 weeks' gestation due to antenatal diagnosis of Ebstein's anomaly and multiple valvular abnormalities.

Discussion

Leigh syndrome, French–Canadian type was first described in children from the Saguenay–Lac-Saint-Jean region of Québec with clinical features of developmental delay, hypotonia, failure to thrive, and mild facial dysmorphism.[1-3] They were found to be phenotypically distinct from other types of Leigh syndrome with acute fatal metabolic acidotic crises.[1-3] They also experienced acute neurological crises typical of Leigh syndrome involving stroke-like episodes and seizures. Ninety percent of them had 1 or more episodes of acute metabolic or neurologic decompensation resulting in early death at a median age of 1.6 years.[3] Characteristic changes of Leigh disease were found in the central nervous system, and microvesicular steatosis was found in the liver during perimortem examination.[3] The underlying defect was found to be cytochrome c-oxidase deficiency that was particularly severe in brain and liver that correlated with the metabolic and neurological symptoms of Leigh syndrome, French–Canadian type.[2]

LRPPRC was identified as a candidate gene for Leigh syndrome, French–Canadian type.[5] Two LRPPRC founder mutations identified included homozygous A354 V mutation and 1 patient with compound heterozygous A354V/C1277Xdel8 mutation.[3,4]

LRPPRC belongs to a family of pentatricopeptide repeat proteins that is involved in posttranscriptional mitochondrial gene expression, which regulates the stability and handling of mature messenger RNAs.[6-8] Mutant LRPPRC was found to target normally to the mitochondrial compartment, but the mutant LRPPRC protein content is reduced. This results in decreased steady state levels of most mitochondrial messenger RNAs but affects cytochrome c-oxidase messenger RNAs to a greater extent leading to an isolated cytochrome c-oxidase assembly defect.

Biochemical investigation of cytochrome c-oxidase enzyme activity in patients with native Leigh syndrome, French–Canadian type revealed that the biochemical defect was tissue-specific; there was normal complex IV activity in kidney and heart, 50% activity in fibroblasts and skeletal muscle, and severe cytochrome c-oxidase enzyme defect in liver and brain.[2,9,10] This suggests the differential ability of tissue-specific pathways to adapt to the mutation.[10]

Outside of Québec, 10 patients with clinical symptoms similar to that of patients with native Leigh syndrome, French–Canadian type and isolated cytochrome c-oxidase deficiency were found to have LRPPRC mutations.[4] They identified 3 novel homozygous mutations and 1 novel compound heterozygous mutation. This group of patients was even more severely affected with fatal lactic acidosis in the postnatal period, presumably reflecting the severity of their mutations compared with the founder Leigh syndrome, French–Canadian type mutation.[4] A proportion of them were found to have congenital cerebral, cardiovascular, and genitalia malformations not reported in patients with native Leigh syndrome, French–Canadian type, suggesting possible varying cytochrome c-oxidase enzyme deficiency in different mutations.[4]

Our patient with novel compound heterozygous missense mutations appears to have a milder clinical phenotype compared to the previously described patients with Leigh syndrome, French–Canadian type.[3,4] At 5 years of age, he has not experienced any severe metabolic crisis. It is not known whether his parents' second pregnancy with antenatal diagnosis of complex heart disease was related to this mutation, as no genetic studies were performed for that fetus.

Phenotype–genotype correlation of this fatal disease would entail further research to evaluate the effect of the specific LRPRRPC mutation on LRPPRC protein, absolute cytochrome c-oxidase enzyme activities in different tissues with clinical correlation. However, even among A354 V homozygotes, pronounced differences in survival and severity occur, suggesting that other genetic and environmental factors do influence outcome.[1-3]

Conclusion

LRPPRC mutation is a rare cause of cytochrome c-oxidase–deficient form of Leigh syndrome outside of Québec. Our patient adds to and broadens the spectrum of phenotypes of Leigh syndrome, French–Canadian type. LRPPRC mutation should be considered in children with infantile or early childhood neurodegenerative disorder, even in the absence of any metabolic crisis. Early evaluation with whole-exome sequencing is useful for early diagnosis, for prognostication, and to aid in genetic counseling.

Authors' Note

All the relevant data are included in the case report.

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Author Contributions

VXH collected and interpreted the data and drafted and critically revised the manuscript. FSW and TST collected and interpreted the data and critically revised the manuscript. SKT conceptualized the work, interpreted the data, and provided intellectual content. Additionally, all the authors listed approved the manuscript version submitted and take full responsibility for the manuscript.

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Ethical Approval and Patient Consent

Being case report involving a single case, the DSRB approval was not required as per the hospital policy. Also the patient/parent consent was not obtained. However, the case report does not include any identifiable images or information of the patient.

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