Premature Ovarian Failure in French Canadian Leigh Syndrome

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In all surviving girls with Leigh syndrome, French Canadian variety, a mitochondrial disease, we detected premature ovarian failure, manifested as absent or arrested breast development, lack of menarche, high follicle-stimulating hormone, a prepubertal uterus, and small ovaries. Pubertal onset and progression should be evaluated in girls with mitochondrial diseases. *(J Pediatr 2017;184:227-9).*

Leigh Syndrome, French-Canadian variety (LSFC, OMIM #220111), is an autosomal recessive mitochondrial disease caused by mutations in the gene encoding leucine-rich pentatricopeptide repeat domain containing protein (*LRPPRC*) on chromosome 2p21. Patients typically manifest mild hyperlactatemia and low serum bicarbonate levels with normal or alkalotic pH because of chronic hyperventilation.[1] In addition, these patients manifest developmental delay, hypotonia, and are at high risk for often fatal acute neurologic and/or acidotic crises.[2] These crises, which can be triggered by infection, illness, stress, intense exercise, and dietary loading, are characterized by dyspnea, coma, shock, marked hyperlactatemia, hyperglycemia, liver dysfunction, multiorgan failure, and sometimes seizures, ataxia, and stroke-like episodes.[1,2] Facial features include large anterior fontanelle, prominent forehead, hypertelorism, wide nasal bridge, anteverted nares, midface hypoplasia, arch-shaped eyebrows, and mild hirsutism.[1,2]

LRPPRC encodes a protein involved in mitochondrial messenger RNA transport and stability.[2] Patients with LSFC have deficient cytochrome C oxidase activity in brain, liver, fibroblasts, and skeletal muscle.[2] The incidence of LSFC is about 1/2000 live births in the Lac Saint-Jean area of Québec because of a high carrier rate for the French Canadian founder mutation p.A354V.[1,2]

Three clinical forms of LFSC are recognized: neonatal, characterized by fulminant acidotic crises; classic, presenting as hypotonia and developmental delay between ages 14 and 24 months; and late, presenting with hypotonia, fatigue, developmental delay, and ataxia. Life expectancy in LSFC is < 5 years of age because of acidotic or neurologic crises, but some patients survive to adulthood.[1]

The purpose of this report is to add premature ovarian failure (POF), defined as cessation of ovarian activity before the age of 40 years,[3] as a feature of LSFC.

Case Reports

The clinical, biochemical, and imaging characteristics of the 3 adolescent girls with LSFC who were evaluated for primary amenorrhea or delayed secondary sex characteristics are depicted in **Table I**. Patient 1 was mentioned in our previous report[1] as having hypergonadotropic hypogonadism, but no details were given. Of note, 2 patients had spontaneous breast development, but all had a prepubertal uterus and small ovaries. All 3 were treated with gradually increasing doses of estradiol, resulting in adult breast development and menarche, after which cyclical estrogen and progesterone treatment was given. In addition, we have recently observed a serum follicle-stimulating hormone concentration of 24.1 mIU/L in a 4-year-old girl with LSFC, suggesting that ovarian damage is already present at that age.

LSFC	Leigh syndrome French-Canadian variety
POF	Premature ovarian failure

Discussion

Female patients with LSFC who survived beyond pubertal age had lack of sexual development or progression, and all 3 patients studied in detail before estrogen replacement had biochemically documented POF. Patients with *LRPPRC* mutations are known worldwide, including some with the p.A354V mutation. We speculate that patients with LRPPRC-related POF will probably be found outside of Québec. It is important to specifically consider POF in survivors of LSFC because it may be overshadowed by other severe complications. In contrast to female patients, all 3 male patients with LSFC who are of pubertal age have reached age-appropriate Tanner stages; this may suggest that mitochondrial function is more critical for the ovaries than for the testes, especially after the onset of pubertal development.[4] On the other hand, there is no evidence that sex steroid replacement affects the natural age-related loss of follicles. Although serum follicle-stimulating hormone was not measured before pubertal age in these patients, their clinical phenotype was POF and not gonadal dysgenesis because the onset of puberty occurred spontaneously in 2 out of 3 patients and because the ovaries, albeit small and devoid of follicles, were visible on imaging.

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The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2017.02.008

Table I. Characteristics of 3 adolescent girls with LSFC and POF

	Patient 1	Patient 2	Patient 3
Age at presentation (y)	16	13	14
Reason for consultation	Primary amenorrhea	Delayed puberty	Delayed puberty
LRPPRC mutation	p.A354V	p.A354V	p.A354V
Age at diagnosis of LSFC (y)	5½ y	2½ y	3 y
Sibling history of LSFC	Sister† at 2 y	Brother† at 2 d	None
Puberty in parents	M: menarche 12 y F: puberty N	M: menarche 13½ y F: puberty N	M: menarche 13 y
Personal history	Intellectual disability (IQ 78)	Intellectual disability, hearing loss, ADD, scoliosis	Intellectual disability
Physical examination	Facial dysmorphisms BMI 85th percentile Tanner B2P4	Facial dysmorphisms BMI 49th percentile Tanner B1P2	BMI 89th percentile Tanner B2P3
Pelvic ultrasound	Prepubertal uterus and small ovaries (right: 8 mm)	Prepubertal uterus and small ovaries	Prepubertal uterus and small ovaries (right 13 × 4 mm)
Bone age (y)	13.5	10	Not done
TSH (mU/L) Normal range 0.1-6.2	2.6	0.9	0.9
FSH (UI/L) Normal range 4-20 (follicular phase)	50	156	77
LH (UI/L) Normal range 6-30 (follicular phase)	26	29	28
Estradiol (pmol/L) Normal range 110-183 (follicular phase)	135	<73	38 (different assay)
Anti-ovarian antibodies	Negative	Negative	Negative

ADD, attention deficit disorder; *BMI*, body mass index; *F*, father; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; *M*, mother; *TSH*, thyroid stimulating hormone.
†Deceased.

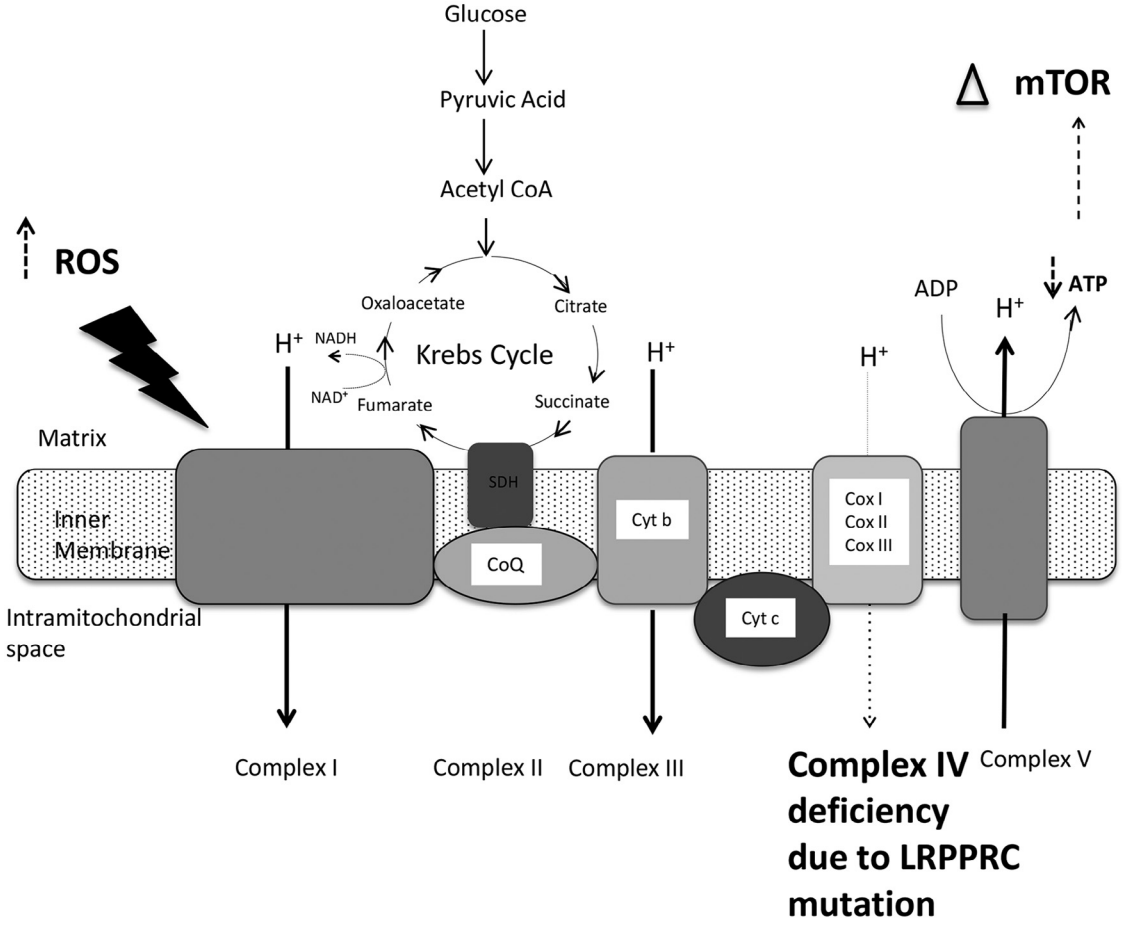

Figure. Depiction of the respiratory chain illustrating the consequences of inactivating mutations in *LRPPRC* which, by decreasing the activity of complex IV, result in the accumulation of ROS upstream and abnormal mammalian target of rapamycin (mTOR) signaling, both contributing to POF. *ADP*, adenosine diphosphate; *ATP*, adenosine triphosphate; *CoQ*, Coenzyme Q; *H*, hydrogen; *NADH*, nicotinamide adenine dinucleotide - hydrogen or reduced; *ROS*, reactive oxygen species.