Early onset of Fazio-Londe syndrome: the first case report from the Arabian Peninsula

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Fazio-Londe syndrome (MIM 211500, ORPHA56965) is a very rare inherited motor neuron disease of childhood and young adulthood. Few cases have been diagnosed worldwide. The disease is characterized by progressive sensorineural deafness, bulbar palsy, and respiratory compromise.1 The age of onset varies from 0.3–17 years, with a mean age of 8.2 years.2 Untreated cases usually die at 0.9–42 years, with a mean of 9.3 years.2 We present here a patient with early onset of Fazio-Londe syndrome who presented at the age of 8 months and died at the age of 24 months.

Our case was a 24-month-old Saudi Arabian boy who was the progeny of healthy consanguineous parents (Figure 1). He was born at term in Riyadh by spontaneous vaginal delivery without any complications. His birth weight, length, and head circumference were at the 50th percentiles. His Apgar score was 9 out of 9 at the first and the fifth minute. He was discharged the following day. He exhibited normal growth and development without any significant medical illness until the age of 8 months, at which time he suffered from cough, feeding and respiratory difficulties, and noisy breathing. Later, he developed cardiopulmonary arrest requiring resuscitation with intubation and prolonged mechanical ventilation. His mother noticed that he was having generalized tonic-clonic seizures. All growth and development gradually declined, and his growth parameters were less than third percentile. He then developed axial hypotonia and peripheral spasticity, bulbar and facial palsy, vertical nystagmus, and ptosis. He completely lost his vision and hearing, and was

![Figure 1.](image-url)
Figure 2. The boy presented decerebrate posture with supportive ventilation at the age of 8 months (a). Facial palsy was obvious at the age of 19 months (b).

Figure 3. MRI of the patient's brain at the age of 11 months. Subtle bilateral diffuse subcortical and deep white matter T2 high-signal intensity was observed, showing evidence of diffusion restriction.
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We investigated him thoroughly. His parents were found to be first-degree cousins (Figure 1). No other family members on either the paternal or maternal side were affected with the same medical illness. A 9-month-old sister of the boy is healthy. The metabolic work-up for the patient, including tandem mass spectrometry for acyl-carnitine profile and plasma amino acids, and urine analysis for organic acids, serum biotinidase, creatinine kinase, lactate acid, ammonia, and oligo- and muco-polysaccharides, was unremarkable. Lysosomal and mitochondrial disorders were excluded by enzyme activity measurement and respiratory chain analysis of skin fibroblasts. Brain magnetic resonance imaging (MRI) showed cortical and subcortical high signal intensity, including basal ganglia (Figure 3). After obtaining written consent, we collected a DNA sample from the patient and his parents and sent it to a commercial lab (Centogene AG, Schillingallee 68, Rostock, Germany) for whole-exome sequencing. On the basis of the Centogene protocol, the sample was processed using the Ion Proton Platform (Life Technologies, Rostock, Germany). Approximately 33 Mb of coding exons (~2% of the entire genome) were covered, as indicated by Consensus Coding Sequences. Highly multiplexed primers pools were used to construct an amplicon library using PCR-based targeted amplification. Following the base calling and primary filtering of low-quality reads, a standard Bioinformatics pipeline was used to annotate detected variants and selected genes of potential impact on the phenotype of interest. A novel homozygous variant, NM_033409(SLC52A3_v001):c.71G>A (NM_033409(SLC52A3_i001):p.(Trp24*)), was detected. The variant was confirmed by Sanger sequencing, including for both parents (Figure 1), and the results were consistent. The mutation is a possible disease-causing nonsense substitution resulting in a reading frame interruption by a premature stop codon.

Fazio-Londe syndrome is an extremely rare disease; indeed, only 74 cases have been reported worldwide. Until now, there have been no cases reported in the Arabian Peninsula. Common presentations involve bulbar palsy (92%), hearing loss (81%), facial weakness (77%), respiratory compromise (64%), and muscle weakness (55%). The mean age of onset is 8.2 years. Our case presented all these common phenotypes starting at the age of 8 months.

In Saudi Arabia, consanguineous marriage occurs in ~60% of the population, and their genetic diseases display a mostly homozygous pattern. Fazio-Londe syndrome is proven to be of autosomal recessive inheritance. The present patient had a homozygous stop codon mutation, c.71G>A [p(Trp24*)], in the SLC52A3 gene.

Mutations detected in the SLC52A3 gene cause a defect in intestinal (hRFT2) riboflavin transport, and supplementation of riboflavin is a lifesaving treatment for a number of young patients. We confirmed the diagnosis of our patient at a terminal stage, and the parents refused the medication.

In conclusion, Fazio-Londe syndrome is a rapidly progressive disorder and can present at a very early age. Prenatal diagnosis can help parents to opt for elective termination of pregnancy or early initiation of medication.

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