Association of Mutations in SCO2, a Cytochrome c Oxidase Assembly Gene, With Early Fetal Lethality

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Background: SCO2 is a cytochrome c oxidase (COX) assembly gene that encodes a mitochondrial inner membrane protein that probably functions as a copper transporter. Mutations in SCO2 have been associated with severe COX deficiency and early-onset fatal infantile hypertrophic cardiomyopathy, encephalopathy, and neurogenic muscle atrophy. Fetal wastage has not been described in association with mutations of SCO2.

Objective: To investigate a case of early spontaneous abortion in a family carrying mutations in SCO2.

Design: Case report.

Patients: Spontaneous abortion in the first trimester occurred in a woman whose first pregnancy had also resulted in a miscarriage in the first trimester and whose only child had died at 53 days of life from cardiomyopathy. This child was a compound heterozygote for mutations in SCO2, and her parents were heterozygous for each mutation.

Main Outcome Measures: Mutations in the abortus by sequencing the SCO2 gene and confirmation of the point mutations as determined by restriction fragment length polymorphism analysis.

Results: As in the previous affected child, we found a missense mutation (E140K) and a nonsense mutation (Q53X) in the abortus.

Conclusions: The typical clinical presentation of SCO2 mutations is severe, rapidly progressive hypertrophic cardiomyopathy that presents in the neonatal period and is often associated with respiratory difficulties, metabolic acidosis, and hypotonia. The experience in this family suggests that mutations in SCO2 may also be associated with early spontaneous abortions and fetal wastage.

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The affected child (II-2) was a full-term, 3460-g product of normal pregnancy and delivery. She was mildly hypotonic at birth and at 15 hours was noted to have a cardiac murmur. She developed respiratory distress and required assisted ventilation. She had lactic acidosis, and a 2-dimensional echocardiogram showed a severely thickened left ventricle with no evidence of outflow tract obstruction. A magnetic resonance image of the brain was normal. By 42 days of life, a subsequent 2-dimensional echocardiogram showed more severe cardiac hypertrophy and obliteration of the left ventricular cavity during systole. After ventilatory support was withdrawn, she died at 33 days of life.

Autopsy showed a grossly enlarged globular heart, a mildly enlarged and congested liver, and cerebral atrophy. The cardiac left ventricle and septum were markedly hypertrophic. The cerebral hemispheres showed an abnormal gyral pattern.

Microscopic examination of the heart showed myocardial fibrous disarray and occasional myocyte hypertrophy. Skeletal muscle showed rounded myocytes with increased variation of fiber size. Brain histologic analysis showed cerebral white matter gliosis with focal white matter necrosis and petechial hemorrhages, focal cortical dysplasia of the left temporal lobe, and mild cortical and hippocampal neuronal dropout. The cerebellum had focal heterotopia and collections of granular cell neurons in the dentate nucleus. The spinal cord showed mild gliosis and white matter spongiosis. COX activity was decreased in postmortem tissues (data published previously), especially in cardiac muscle, where it was 8% of control. The child was a compound heterozygote of the Q53X nonsense mutation (C1280T) and the E140K missense mutation (G1541A). The father (I-1) was heterozygous for the Q53X mutation and the mother (I-2) was heterozygous for the E140K mutation.

For the third pregnancy, prenatal diagnosis was sought, but spontaneous abortion occurred before the prenatal testing could occur. There were no other complications in any of the pregnancies, such as uterine abnormalities, endocrine or immunological dysfunction, or infections that could have led to the previous spontaneous abortions (II-1 and II-3).

SCRENNING FOR MUTATIONS IN SCO2

The DNA was extracted by a standard protocol from blood of the parents, autopsy tissues of II-2, and the product of conception II-3.16 The SCO2 gene was amplified and directly sequenced as described previously.8

RESTRICTION FRAGMENT LENGTH POLYMORPHISM ANALYSIS

Restriction fragment length polymorphism analysis of the E140K and the Q53X mutations was performed as described.8

RESULTS

Sequencing of the SCO2 gene in the DNA extracted from tissue of the abortus revealed the E140K (G1541A) mutation and the Q53X (C1280T) mutation (Figure 2). Restriction fragment length polymorphism analysis similarly confirmed that II-3 was a compound heterozygote with the E140K and Q53X mutations.

COMMENT

The typical clinical presentation of SCO2 mutations is severe, rapidly progressive hypertrophic cardiomyopathy in the neonatal period, often associated with respiratory difficulties, metabolic acidosis, and hypotonia. Homozygosity of the E140K mutation has been associated with later onset, longer survival, and higher COX activity in the tissues tested (Table).13 Jaksch et al described a family in which the 2 affected siblings were compound heterozygotes. Their mother had 2 miscarriages in the 11th and 12th weeks of pregnancy.

It is not surprising that both families in whom recurrent abortions were reported harbored heterozygous mutations, because the phenotype in compound heterozygotes is more severe than that of E140K homozygotes, who
Clinical Features in Patients With SCO2 Mutations

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Onset</th>
<th>Death, mo</th>
<th>COX Residual Activity, %</th>
<th>Reference</th>
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<td>Not performed</td>
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</tbody>
</table>

Compound Heterozygotes

Homozygotes

Abbreviations: COX, cytochrome c oxidase.
*aPatient II-2 in the pedigree described.
†Abortion II-3 in the pedigree described.

present predominantly with demyelination and denervation of the peripheral nervous system. The more severe SCO2 mutations are likely to cause COX deficiency in the developing brain and heart, which are heavily dependent on respiratory chain function. This probably impairs organogenesis in the fetus and may account for the first-trimester spontaneous abortions. It is unlikely that merely being heterozygous for the E140K mutation causes women to have difficulty carrying to term, since we followed up at least 1 family in which the mother was heterozygous for the E140K mutation and sought prenatal diagnosis.17 The fetus was also heterozygous for the E140K mutation and was carried to term normally.

Cardioencephalomyopathy due to SCO2 mutations appears to be relatively rare, since only 11 patients have been described in the literature so far (Table).6,8,15,17,18 However, the frequency of this condition may be underestimated if, as suggested by this family and the one described by Jaksch et al,8 fetal wastage is common in pedigrees harboring SCO2 mutations.

Genetic abnormalities are a frequent cause of spontaneous abortions. In a study by Eiben et al19 of 750 spontaneous abortions that occurred between the 5th and 25th weeks of gestation, the frequency of abnormal karyotypes was 50.1%. However, if other genetic causes are included, the percentage is likely to be much larger. Families with a history of recurrent abortions, intrauterine deaths, hydrops fetalis, and especially neonatal deaths characterized by cardiomyopathy, myopathy, or encephalopathy should be screened for SCO2 mutations.

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REFERENCES