Whole exome sequencing revealed biallelic IFT122 mutations in a family with CED1 and recurrent pregnancy loss

To the Editor:

Cranioectodermal dysplasia-1 (CED1), also known as Sensenbrenner syndrome (MIM 218330), is characterized by skeletal, craniofacial, and ectodermal abnormalities (1). Here, we report a family with CED1 and recurrent abortions.

I-2, 39-year-old woman, was referred to our hospital for consultation regarding recurrent abortions. Although she had one healthy boy (II-2), she suffered from two artificial abortions due to fetal hydrops at 13 weeks of gestation (II-1) and skeletal anomalies at 21 weeks of gestation (II-8), one intrauterine fetal death with hydrops at 13 weeks of gestation (II-7), and four recurrent miscarriages (II-3 at 6 weeks, II-4 at 8 weeks, II-5 at 8 weeks, and II-6 at 7 weeks) (Fig. 1a). Postmortem physical findings of II-8 included a skull deformity and blisters beside the nasal bridge due to obstetric intervention, low set ears, nuchal edema, a narrow thorax, and acromelic shortening of the limbs, posterior bowing of the lower legs and bilateral 2–3 toe syndactyly (Fig. 1b). Postmortem radiography and 3-D computed tomography showed generalized skeletal alterations which were thought to fit to CED1, though the sharp angulation of the tibiae was very unusual (Fig. 1b).

Exome sequencing was performed in I-2, II-2, and II-8 as previously described (2). We identified compound heterozygous mutations in IFT122 in the fetal skeletal anomalies (II-8): c.1108delG (p.E370Sfs*51) in exon 11 and c.1636G>A (p.G546R) in exon 14 was inherited from his father, though it was not directly confirmed. Of note, we confirmed the same compound heterozygous mutations (c.1108delG: 2 of 29 clones, c.1636G>A: 13 of 30 clones) by capillary sequence of polymerase chain reaction (PCR) product from cloned DNA from paraffin-embedded chorionic villi (II-6) (Fig. 1c). Accordingly, c.1108delG found in II-6 and II-8 was presumed to be inherited from the father, though it was not directly confirmed.

Walczak-Sztulpa et al. reported homozygous missense mutations of IFT122 in three patients from two consanguineous pedigrees with CED1: p.V553G in family CED-01, p.S373F in family CED-02, and compound heterozygous mutations, c.502+5G>A and p.W7C in one sporadic case, family CED-03 (1) (Fig. 1c). The four patients with IFT122 mutations showed skeletal anomalies. We found compound heterozygous mutations in a fetus with skeletal anomalies (II-8) and the villous tissues (II-6). Clinical skeletal features of the aborted fetus (II-8) are consistent with those of the reported CED patients carrying biallelic IFT122 mutations. Because they were found in the villous tissues (II-6) that was sequenced, biallelic IFT122 mutations may have caused some of the recurrent abortions in this family. All four IFT122 missense mutations (including ours) are predicted to be damaging for IFT122 function (Table 1).

CED1 belongs to a group of short rib dysplasias, including Ellis van Creveld syndrome, Jeune asphyxiating thoracic dysplasia, short rib polydactyly syndrome (SRPS) I (Saladino-Noonan), SRPS II (Majewski), SRPS III (Verma-Naumoff) and SRPS IV (Beemer-Langer) (3). The skeletal manifestation of the present fetus shared some features with other short rib dysplasias. For example, humeral bowing resembles that commonly seen in Ellis van Creveld syndrome. Severe tibial angulation was somewhat reminiscent of tibial hypoplasia in SRPS II (Majewski type). Generally, CED1 is a non-lethal disorder. However, the present family showed recurrent abortions, which can be considered as the severest phenotypes caused by biallelic IFT122 mutations in human. Interestingly, IfT122-null mice show multiple developmental defects with embryonic lethality consistent with recurrent pregnancy loss in our family (4).

On the basis of the assumption that recessive mutations may cause recurrent pregnancy loss, the literatures have been carefully reviewed, but only a homozygous HERG mutation in a family were found to show recurrent intrauterine fetal loss (5).

In conclusion, we were able to find causative IFT122 mutations in a non-consanguineous family with recurrent abortions. This information is useful for future counseling including preimplantatory diagnosis in this family.

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Fig. 1. Clinical finding of fetal skeletal anomalies (II-8) and genetic studies. (a) Familial pedigree. II-1 and II-8 were artificially terminated, II-3, II-4, II-5, II-6 and II-7 were spontaneously aborted. * DNA was available. (b) Clinical photographs and 3D computed tomography of II-8. (i–v) Postmortem physical findings included a skull deformity due to obstetric intervention, blisters beside the nasal bridge, low set ears, nuchal edema, a narrow thorax, and acromelic shortening of the limbs, anterior bowing of the lower legs and bilateral 2–3 toe syndactyly. (vi–vii) Postmortem 3-D computed tomography showed generalized skeletal alterations. The thorax was narrow with short ribs. The lower ribs showed a wavy appearance. The spine and ilia were normal. The long bones were not apparently short. However, the humeri were medially bowed, and the tibiae showed sharp bending at their proximal part. Ossification of the proximal and middle phalanges was defective. (c) The gene structure of IFT122 (upper) and its protein structure (lower) containing seven WD40 domains (blue). Mutations found in this family and in the previous report are depicted above and below the protein, respectively. (d) Sequence electropherogram of family members. Compound heterozygous mutations are indicated in II-8, while healthy members (I-2 and II-2) only carry one of the two mutations. (e) Sequence electropherogram of the villous tissue at 7 weeks of gestation (II-6). Amplified PCR products were cloned into pCR4-TOPO vector and each clone was subjected to sequencing. Compound heterozygous mutations are indicated.
**Letter to the Editor**

Table 1. IFT122 mutation and their pathogenicity prediction

<table>
<thead>
<tr>
<th>Allele 1</th>
<th>Allele 2</th>
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<tbody>
<tr>
<td>Family; Ref.</td>
<td>Nucleotide change</td>
</tr>
<tr>
<td>CED-01: Walczak-Sztulpa et al. (1)</td>
<td>c.1658T&gt;G</td>
</tr>
<tr>
<td>CED-02: Walczak-Sztulpa et al. (1)</td>
<td>c.1118C&gt;T</td>
</tr>
<tr>
<td>CED-03: Walczak-Sztulpa et al. (1)</td>
<td>c.21G&gt;C</td>
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<tr>
<td>CED-01: Walczak-Sztulpa et al. (1)</td>
<td>c.1636G&gt;A</td>
</tr>
<tr>
<td>CED-02: Walczak-Sztulpa et al. (1)</td>
<td>c.502+5G&gt;A</td>
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**References**


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