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**Background**

IGF2 is a paternally expressed gene playing a pivotal role in body growth (Fig.1). Both compromised IGF2 expression caused by H19/IGF2:IG-DMR epimutations (hypo-methylation) and IGF2 mutations on paternal allele lead to Silver-Russell syndrome (SRS) (Fig 3), though a certain degree of phenotypic difference has been implicated.

We report six Japanese patients with IGF2 mutations and compare clinical findings between the two groups including literature cases.

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**Clinical findings of six patients and molecular studies**

All six patients showed growth restriction, and their major clinical findings are shown as below. We performed next generation sequencing-based comprehensive mutation analyses and identified various IGF2 mutations (Fig.2). All the heterozygous mutations resided on the paternally inherited allele, confirmed by SalI/SmaI digestion.

**Phenotypic comparison**

Phenotypic comparison between apparently non-mosaic 14 patients with IGF2 mutations reported to date1-6, including Case 1-5, and patients with H19/IGF2:IG-DMR epimutations are shown in Table 1. IGF2 mutations resulted in 1) SRS with high Nephine-Harbinson score (≥ 5/6), 2) low frequency of hemihypoplasia, 3) high frequency of feeding difficulty, 4) mild degree of relative macrocephaly, 5) occasional development of limb malformations, 6) high frequency of cardiac anomalies, 7) high frequency of developmental delay, 8) high serum IGF-I values, and 9) low serum IGF-II values.

Table. Summary of clinical features in patients with apparently non-mosaic IGF2 mutations and those with H19/IGF2:IG-DMR epimutations.

**Discussion**

The present study indicates that IGF2 mutations are associated with characteristic clinical features. The results are primarily explained by the mosaic condition of epimutations and the non-mosaic condition of IGF2 mutations, and by the H19/IGF2:IG-DMR methylation pattern dependent IGF2 expression in most tissues and the biparental IGF2 expression in the brain and liver (Fig.3, 4).

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**Fig 1. IGF2 expression**

**Fig 2. Identified IGF2 mutations**

**Fig 3. IGF2 expression in most tissues**

**Fig 4. IGF2 expression in Brain and Liver**

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**Table. Summary of clinical features in patients with apparently non-mosaic IGF2 mutations and those with H19/IGF2:IG-DMR epimutations.**