# *IGF2* Mutations: Report of Six Japanese Cases and Phenotypic Comparison with *H19/IGF2*:IG-DMR Epimutations Including Literature Cases

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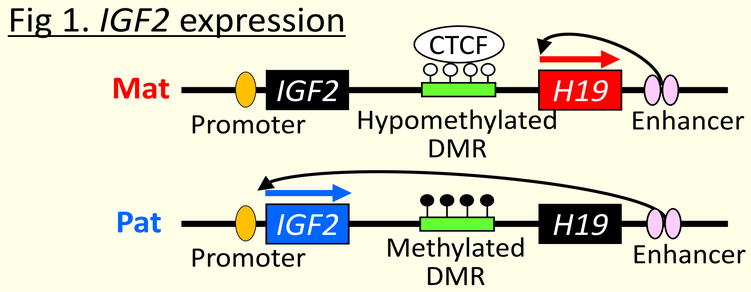
## Background

*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 (hypomethylations) 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.

Fig 1. *IGF2* expression

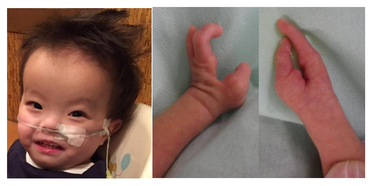


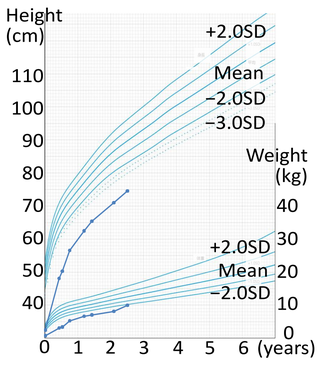

## Clinical findings of six patients and molecular studies

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 *Sal*I/*Sma*I digestion.

**Case 1**: 2y, Male

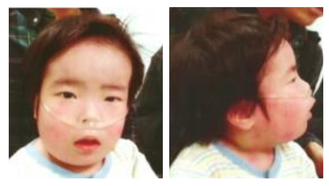
SRS, Fetal growth restriction (FGR), Disorder of sex development (DSD), Ectrodactyly

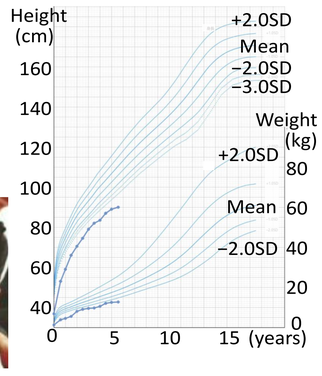





**Case 2**: 6y, Male

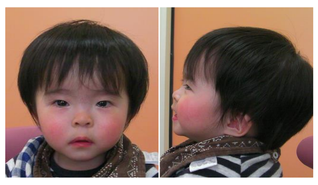
Multiple Congenital anomalies/mental retardation

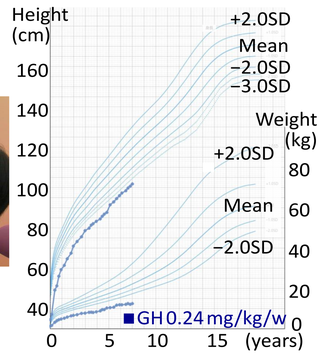





**Case 3**: 7y, Male

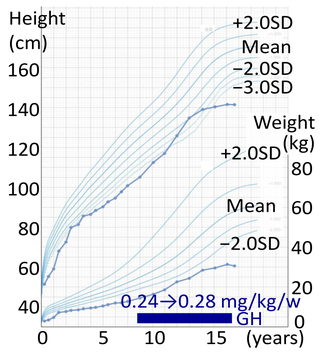
SRS, DSD





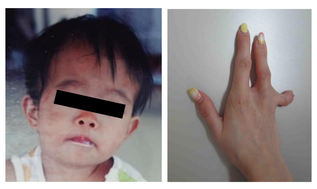

**Case 4**: 15y, Male

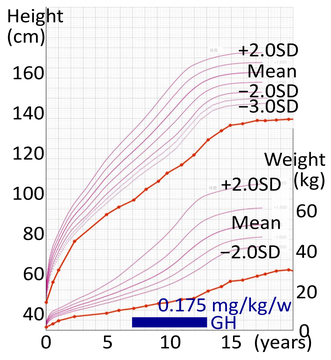
SRS




**Case 5**: 23y, Female

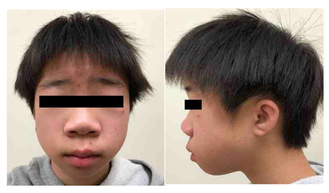
FGR, Ectrodactyly

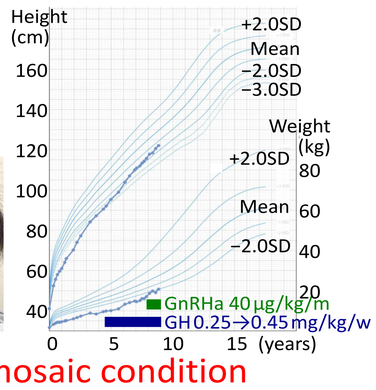





**Case 6**: 9y, Male

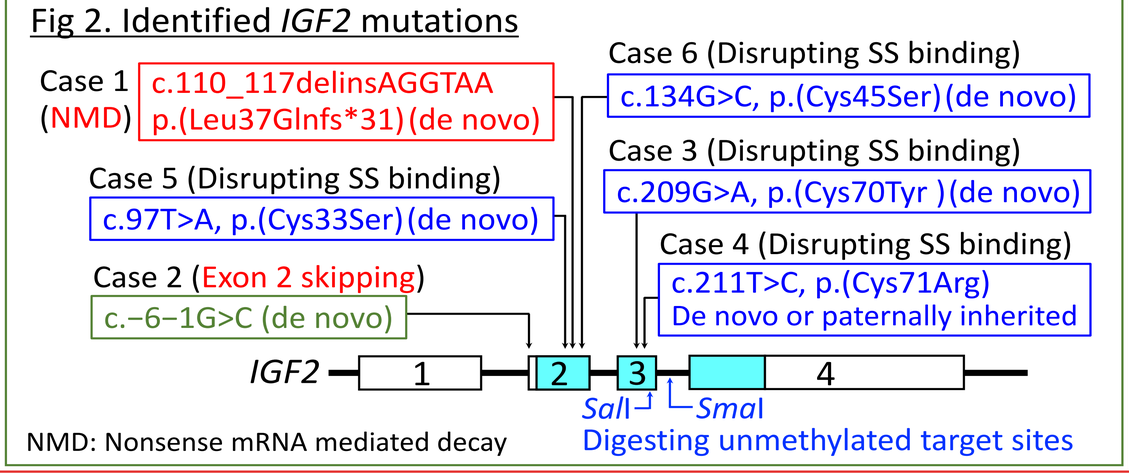
FGR, Extremely high serum IGF-I value






*IGF2* mutation: mosaic condition

Fig 2. Identified *IGF2* mutations




NMD: Nonsense mRNA mediated decay

## Phenotypic comparison

Phenotypic comparison between apparently non-mosaic 14 patients with *IGF2* mutations reported to date[1-6], including Case 1-5, and patients with *H19*/*IGF2*:IG-DMR epimutations are shown in Table.

*IGF2* mutations resulted in 1) SRS with high Netchine-Harbison 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.

| | ***IGF2* mutations** | **Epimutations** | ***P*-value** |
|---|---|---|---|
| **<Netchine-Harbison scoring system features >** | | | |
| Scoring system criteria (6/6) | 3/14 (21.4%) | 10/43 (23.2%)[7] | 1.00 |
| Scoring system criteria (5/6) | 11/14 (78.6%) | 16/43 (37.2%)[7] | **0.012** |
| Scoring system criteria (4/6) | 0/14 (0%) | 17/43 (39.5%)[7] | **0.005** |
| Birth length and/or weight ≤ –2 SDS | 14/14 (100%) | 35/35 (100%)[8] | 1.00 |
| Postnatal height ≤ –2 SDS | 14/14 (100%) | 145/173 (83.8%)[8] | 0.13 |
| Relative macrocephaly | 14/14 (100%) | 111/112 (99.1%)[8] | 1.00 |
| Prominent forehead | 14/14 (100%) | 118/126 (93.7%)[8] | 1.00 |
| Body asymmetry | 3/14 (21.4%) | 175/226 (77.4%)[8] | **<0.001** |
| Feeding difficulties | 14/14 (100%) | 124/173 (71.7%)[8] | **0.023** |
| **<Growth>** | | | |
| Birth length - SDS | –4.2 ± 0.9 (n=14) | –4.1 ± 2.0 (n=31)[7] | 0.86 |
| Birth weight - SDS | –3.9 ± 0.8 (n=14) | –3.5 ± 0.9 (n=42)[7] | 0.15 |
| Birth OFC - SDS | –1.6 ± 0.7 (n=14) | –0.5 ± 1.2 (n=29)[7] | **0.0029** |

| | ***IGF2* mutations** | **Epimutations** | ***P*-value** |
|---|---|---|---|
| **<Other features>** | | | |
| Ectrodactyly | 3/14 (21.4%) | … (0%*)[8] | … |
| Polydactyly | 1/14 (7.1%) | … (0%*)[8] | … |
| Syndactyly | 6/14 (42.8%) | … (0%*)[8] | … |
| Cleft palate | 6/14 (42.8%) | … | … |
| Cardiovascular anomalies | 7/14 (50.0%) | 4/44 (9.1%)[9] | **0.0022** |
| Motor delay | 9/12 (75.0%) | 43/141 (30.5%)[8] | **0.0032** |
| Speech delay | 8/11 (72.7%) | 32/101 (31.7%)[8] | **0.016** |
| **<Endocrine findings>** | | | |
| Serum IGF-I - SDS | +1.5 ± 2.5 (n=12) | –0.0 ± 1.1 (n=17)[10] | **0.033** |
| Serum IGFBP-3 - SDS | +0.5 ± 2.2 (n=9) | +1.4 ± 1.0 (n=17)[10] | 0.17 |
| Serum IGF-II - SDS | –1.6 ± 0.8 (n=10) | +0.2 ± 1.4 (n=17)[11] | **0.010** |

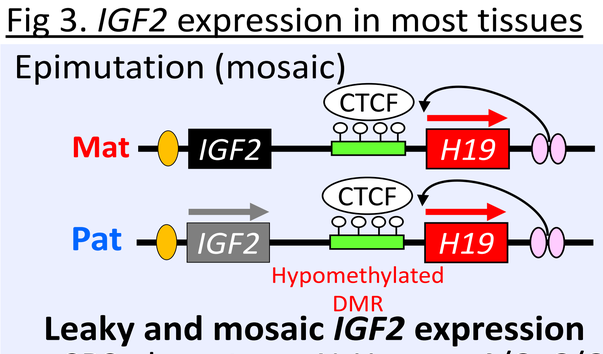
* It is unlikely that these features are present but not reported.

1.*N Engl J Med*. 2015;373:349–356., 2.*Hum Mutat*. 2017;38:953–958., 3.*Front Genet*. 2017;8:105., 4.*Genet Med*. 2018;20:250–258., 5.*Am J Med Genet A*. 2018;176:2561–2563., 6.*Eur J Endocrinol*. 2019;180:K1–13. 7.*PLoS One*. 2013;8:e60105., 8.*Nat Rev Endocrinol*. 2017;13:105–124., 9.*J Med Genet*. 2010;47:760–768., 10.*J Clin Endocrinol Metab*. 2008;93:1402–1407., 11.*J Clin Endocrinol Metab*. 2007;92:3148–3154.

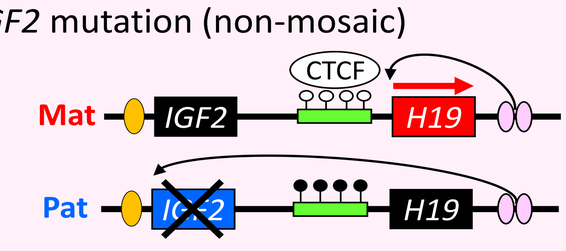
## Discussion

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).

Fig 3. *IGF2* expression in most tissues

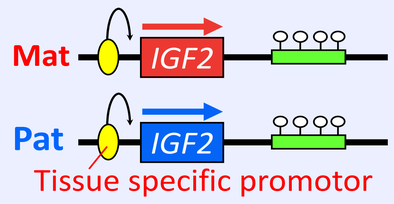



**Leaky and mosaic *IGF2* expression**
- SRS phenotype: N-H score 4/6~6/6
- Asymmetric body

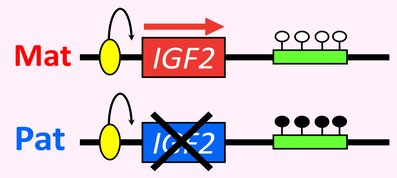



**Null *IGF2* expression**
- SRS phenotype: N-H score 5/6~6/6
- Symmetric body
- Cardiac anomalies, Limb malformations

Fig 4. *IGF2* expression in Brain and Liver




**Normal *IGF2* expression**
- Relative macrocephaly
- Normal serum IGF-II value




**Halved *IGF2* expression**
- Mild relative-macrocephaly
- Developmental delay
- Low serum IGF-II value

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