Severe pre and postnatal growth retardation in a child harboring a novel homozygous IGF1 gene mutation.

Background

Human IGF1 gene defects are characterized by intrauterine and postnatal growth retardation, sensorineural deafness, microcephaly and intellectual disability. Few cases have been reported so far, and the underlying pathophysiology has been characterized in only three of them.

Aim

To describe a patient with severe short stature presenting a novel homozygous IGF1 gene mutation and its underlying pathogenic mechanism.

Case Report

Patient born from consanguineous parents at 40 weeks of gestational age with IUDEL. Birth weight: 1910 g (-3.06 SD), length: 38 cm (-6.3 SD), and head circumference: 34 cm (-0.4 SD).

At 3.2 years of age, the patient’s height was 74 cm (-6.15 SD), weight 6.1 kg (-5.1 SD), head circumference 41 cm (-6.05 SD). Physical examination revealed proportionate short stature, microcephaly, and facial dysmorphism (frontal bossing, triangular face, bulbous nose, full lips, retrognathia). He also presented bilateral sensorineural deafness, mild global developmental delay, and hyperactivity behavior.

Molecular Techniques:

- SNP-Array (850K, Illumina) identified multiple loss of heterozygosity regions, including 12q23.2, where IGF1, a potential candidate gene for the patient’s phenotype, maps.
- High Resolution Melting (HRM) for IGF1 gene exonic and known regulatory regions was performed.
- Sanger sequencing of IGF1 fragments with altered mobility detected by HRM identified a homozygous c.322T>C variant, predicted to result in p.Tyr108His change in the protein.

NM_001111283.2: c.322T>C (p.Tyr108His)

In silico studies

- p.Tyr108His variant, which has not been previously described, changes a highly conserved Tyr residue (Tyr60 according to the mature IGF-1 amino acid numbering), in the insulin domain.
- Although it is classified as Variant of Unknown Significance (VUS) according to ACMG guidelines, it is consistently predicted as pathogenic by multiple bioinformatic tools.
- Tyr108 (Tyr60) is located in the A domain of IGF-I and has already been described for IGF-I with its receptor (IGF1-receptor).

In vitro studies

IGF-IR phosphorylation

- IGF1-IR phosphorylation
- Cell proliferation

Conclusion

We described a patient with severe short stature harboring a novel IGF1 mutation involving a change of a conserved amino acid. This change may cause a diminished affinity of IGF-I for its receptor, resulting in a decreased activation of IGF-IR and therefore of its biological activity.