The Novel R211Q POP1 Homozygous Mutation Causes Severe Short Stature But Uniquely Only Subtle Skeletal Dysplasia

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OBJECTIVES & METHODS

A 6 year old boy, born to consanguineous parents, presented with:
• Severe short stature (height 90.5 cm, SDS -5.68).
• Mild legs shortness (US:LS ratio is 1.15:1)
• Mild brachydactyly

• Skeletal survey and whole exome sequencing were performed for the proband. Relative abundance of the RMRP RNA and unprocessed pre5.8s rRNA (a substrate of RNase MRP complex) were measured in the affected siblings, non-affected parents and control.

RESULTS

Processing of Precursor 1 (POP1) is a core protein component of the Ribonuclease-Mitochondrial RNA Processing (RNase-MRP) enzymatic complex, an essential ribonuclease protein in all eukaryotes. Mutations in RMRP, which encodes the RNA moiety of the complex, are known to cause several autosomal recessive skeletal dysplasias: cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders, characterized by severe disproportionate short stature. Recently, five mutations in POP1 have been reported in five patients with anauxetic dysplasia (spondylo-epi-metaphyseal dysplasia with extremely short stature). Despite of the variability in phenotypic severity, involvement of the spine, epiphyses and metaphyses was evident in the five cases.

Skeletal Survey:
• Short forearm & metacarpals.
• Irregularity of metaphyseal borders of long bones (subtle in our report)
• Bone age delay

This report
No Epiphyseal involvement
No Cranium, vertebral bodies or pelvis abnormalities

Previous reports 1, 2
Epiphyseal involvement
Cranium, vertebral bodies & pelvis

Exome Sequencing:
• The proband, his affected brother and cousin were homozygous for the R211Q novel mutation in POP1 gene.
• Parents and healthy siblings were all heterozygous.
• The arginine residue at position 211 is highly evolutionarily conserved.

Expression Studies:
• The RNA moiety of the RNase-MRP complex was dramatically reduced (20 times less) in affected patients compared to non-affected controls.
• Pre5.8s rRNA was not increased in patients’ RNA.

CONCLUSIONS

We describe a novel homozygous POP1 mutation in three patients from a consanguineous family resulting in severe short stature. Unlike the previously reported five cases, skeletal dysplastic changes are subtle and merely metaphyseal. Gene expression assays showed no elevation in levels of pre5.8s rRNA possibly explaining the uniquely mild phenotype. We recommend to consider POP1 mutations in familial cases with severe short stature even when skeletal dysplasia is not strongly evident.

REFERENCES