

Novel Homozygous LRP5 Mutations in Patients with Osteoporosis-Pseudoglioma Syndrome

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Introduction

Osteoporosis pseudo glioma syndrome is an autosomal recessive disorder characterized by severe onset Osteoporosis in childhood and congenital or juvenile-onset ocular defects.

These patients are predisposed to recurrent long bone fractures, muscle weakness, and their related deformities including kyphosclerosis, vertebral compression fractures, extremity deformities and short stature in adulthood.

Osteoporosis pseudoglioma syndrome is a rare autosomal recessive disorder due to loss of function mutation in the low-density lipoprotein receptor like protein 5 (LRP5).

The LRP5 is located at 11q13.4. Mutations that inhibit Wnt binding to LRP5 can cause osteoporosis and pseudoglioma through loss of function of the receptor. Various mutations in LRP5 are known for OPPG.

Methods

Two patients (siblings) underwent clinical examination, including a complete ophthalmic evaluation. Diagnosis of Osteoporosis pseudoglioma was based on clinical examination and bone mineral density. The entire coding sequence of LRP5 was examined using target region capture followed by next generation sequencing.

Results

In this study, we report two siblings born to a consanguineous family (the paternal grandparents were sisters) in Iran with no known family history of OPPG. The mother's parents were also cousins. Mother's aunt was blind.

The proband is a 17-year old female born at term by caesarean section and the second child of a consanguineous family of Iranian descent. Birth weight, height, and head circumference was

3.1 kg, 52 cm, and 35 cm, respectively. Soon after birth, the parents noticed her visual impairment. The ophthalmologist identified high intra ocular pressure, bilateral microphthalmia with corneal opacities, congenital phthisis bulbi, and retinal detachments. These findings confirmed the diagnosis of blindness as with her brother.

The other patient is a 24-year old male and the first child of the family with no neurodevelopmental delay. At the time of examination, he was a law student. He was born preterm at 33 weeks by normal vaginal delivery.

Molecular analysis identified a novel homozygous c.351G>A, p.Trp117Ter) variant on chr11:68115574 (hg19) EX2/CDS2 in both sibs. Segregation analysis revealed that the mother showed heterozygosity at the mutation position but the father was not available for testing. The identified mutation in the LARP gene was validated using Sanger sequencing.

Conclusions

One novel homozygous variant was demonstrated in two OPPG cases from Iran. This result expands the spectrum of disease-causing LRP5 mutations. Although this mutation has not been reported, its frequencies in normal population are very low.

References

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