GENETIC DIAGNOSIS USING WHOLE EXOME SEQUENCING IN TWO CASES WITH MALIGNANT INFANTILE OSTEOPETROSIS

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Background

In 80% of the cases, osteopetrosis is caused by autosomal mutations occurring in seven genes (*TNFRSF11A, TNFSF11, TCIRG1, CLCN7, OSTM1, SNX10, PLEKHM1*). Individual mutation analysis of all these genes would be expensive and time consuming

Whole exome sequencing is being increasingly used given that the cost and the time needed are similar to that of single gene sequencing analysis. Furthermore, the analysis has the potential to uncover novel disease-causing genes.

Cases

	Case 1 (9 days-old, boy)	Case 2 (7 days-old, girl)
Complaint	Bicytopenia, hypocalcemia	Hypocalcemia
Case History		
Prenatal	None	None
Natal	Term, 3130 g	Term, 3100 g
Family history	None	Elder brother died at the age of 4 months due to osteopetrosis
Parental consanguinity	No	Yes
Physical examination		
Weight	3060 g (25-50th p)	3045 g (25-50th p)
Height	46 cm (10-25th p)	47.5 cm (10-25th p)
Head circumference	36 cm (10th p)	37 cm (25th p)
Laboratory		
Hemoglobin (g/dL)	8.6	14
Leukocyte/mm3	13000	14100
Platelets/mm³	7700	139000
Calcium (mg/dL)	5.4	6.8
Phosporus (mg/dL)	4.4	4.4
ALP (U/L)	333	340
25(OH)D (ng/mL)	4.35	38.19
PTH (pg/mL)	445	437

Methods

Peripheral blood DNA was extracted from both cases. Exome data sequenced by Genotypic (India) Center using Illumina HiSeq 2500 sequencer were analyzed in Intergen Genetic Diagnosis Center with particular attention to the seven candidate genes.

Results

Case 1
31,382 variants were detected, one of which was a novel heterozygote mutation (c.718G>A) in ***CLCN7*** (Figure 1a).
Sanger sequencing revealed an additional mutation (c.398_401delTTGG, Figure 1b) resulting in compound heterozygosity.

Case 2
32,529 variants were detected including a known homozygote nonsense mutation in ***TCIRG1***: c.2236C>T. Sanger sequencing confirmed the mutation. (Figure 1c)

Genetic counselling was provided and pre-implantation genetic testing was recommended for both families.

Figure 1

Discussion

TCIRG1 gene mutations cause about 50% of cases of autosomal recessive osteopetrosis, while *CLCN7* mutations in 10-15%.

Whole exome analysis is a useful method for diseases in which multiple genes play role in the etiology. However, it should be kept in mind that Sanger sequencing/next generation sequencing may be needed when a heterozygous mutation is detected by whole exome sequencing in autosomal recessively inherited candidate genes.

References

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