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Abstract Topic: - Molecular and cytogenetic diagnostics

Abstract Title: - Genetic and epigenetic investigations in syndromic short stature patients.

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Aims: - Short stature with syndromic features is common among several genetic disorders. This study investigates the genetic and epigenetic causes in clinically suspected patients in order to provide molecular diagnosis to these patients.

Methods: - A total of 11 patients with short stature along with other syndromic features were screened for copy number variations and methylation changes of 11p15 region using methylation specific multiplex ligation-dependent probe amplification technique. Five patients along with there healthy parents were tested for genetic variants using whole exome sequencing. Bioinformatic analysis of the sequencing data was performed. In-silico analysis of the identified causal variants was also performed. All patients were recruited from the Postgraduate Institute of Medical Education and Research, Chandigarh, India with proper informed consent to the guardians. Molecular Diagnostic tests were performed at the Central University of Punjab, Bathinda, Punjab, India following the ethical approval from the institute's ethics committee.

Results: - Out of 11 patients screened for 11p15 CNVs and epimutations, CNVs were not identified in any of the patients while hypomethylation of H19 gene and promoter regions were identified in 2 patients providing diagnosis of Silver-Russell syndrome. Whole exome sequencing identified pathogenic variants in 2 cases. Compound heterozygous variants c.597_600del/c.342del (p.Gln200LysfsTer33/p.Thr116LeufsTer12) of LIG4 gene were identified in patient with severe microcephaly, delayed skeletal maturation, bilateral clinodactyly, and short stature providing molecular diagnosis of LIG4 syndrome. Also, compound heterozygous variants c.1942C>T/c.3907C>T (p.Gln648Ter/p.Gln1303Ter) CUL7 gene were identified in a patient with hip dysplasia, depressed nasal bridge, large globe, relative macrocephaly, frontal bossing, low-set ears, and short stature providing molecular diagnosis of 3M syndrome.

Conclusions: - Patients clinically suspected for Silver-Russell syndrome should be screened for methylation changes of the genes and imprinting control regions located on chromosome 11p15. Other patients with short stature and syndromic features suggesting clinical diagnosis of a genetic syndrome can be screened for genetic variants of the coding regions of the genome (exome) using whole exome sequencing which may provide the molecular diagnosis in these patients.

Keywords: - Out of 11 patients screened for 11p15 CNVs and epimutations, CNVs were not identified in any of the patients while hypomethylation of H19 gene and promoter regions were identified in 2 patients providing diagnosis of Silver-Russell syndrome. Whole exome sequencing identified pathogenic variants in 2 cases. Compound heterozygous variants c.597_600del/c.342del (p.Gln200LysfsTer33/p.Thr116LeufsTer12) of LIG4 gene were identified in patient with severe microcephaly, delayed skeletal maturation, bilateral clinodactyly, and short stature providing molecular diagnosis of LIG4 syndrome. Also, compound heterozygous variants c.1942C>T/c.3907C>T (p.Gln648Ter/p.Gln1303Ter) CUL7 gene were identified in a patient with hip dysplasia, depressed nasal bridge, large globe, relative macrocephaly, frontal bossing, low-set ears, and short stature providing molecular diagnosis of 3M syndrome.