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Presenting author name :- Shalini Dhiman

Presenting author institute:- Genetic Metabolic Unit, Department of Pediatrics, APC PGIMER

Co-authors name:- Dr. Inusha Panigrahi, Dr. Harvinder Kaur, Dr. Anupriya Kaur, Dr. Maryada Sharma, Karandeep Kaur

Co-authors institute:-Genetic Metabolic Unit, Department of Pediatrics, APC PGIMER, Growth Unit, Department of Pediatrics, APC PGIMER, Department of Otolaryngology , PGIMER

Aims:-To explore clinical, molecular and anthropometric basis of the congenital autopod malformation in North Indian Patients.

Methods:- In this study we enrolled patients and familial cases from Panjab, Chandigarh, Himachal Pradesh, Haryana and Utter Pradesh on visiting the Genetic Clinic. Clinical evaluation and radiographic analysis was performed for distinguish between the brachydactyly, syndactyly, polydactyly and complex autopod malformation patients. Molecular testing includes whole exome sequencing, targeted genes IHH, HOXD13, GLI3, WNT7A, GDF5 sanger sequencing. Anthropometric analysis with standard equipments and radiometric measurements was done by using digimatic calipers.

Results:- Firstly, we classified brachydactyly Types as A, B, C, D, E, syndactyly as cutaneous, bony syndactyly, preaxial and postaxial syndactyly in non-syndromic and syndromic patients on the basis of clinical phenotype and X-ray imaging. We enrolled (n=50) patients on the basis of clinical phenotype with different congenital autopod malformation (CAM). Brachydactyly A with short stature (n=14), isolated brachydactyly E (n=5), syndromic brachydactyly E (n=4), Isolated brachydactyly C (n=2). two families with isolated synpolydactyly (n=7), syndromic syndactyly (n=10). Preaxial and post axial syndromic polydactyly patients (n=8). For, Molecular analysis we performed Targeted gene IHH, HOXD13, GLI3, WNT7A, GDF5 Sanger sequencing for isolated cases and Whole exome sequencing was done on Illumina platform for complex syndromes. Complex syndromes include additional malformations as cardiac defects, craniosynostosis, eye abnormalities, dental anomalies, dysmorphism, and short stature. We identified novel SNV IHH: c.299A>C by targeted Sanger sequencing and CNV 6.4110 kb deletion on chromosome 7 GLI3: [c.(1497+1_1498-1)_(2103+1_2104-1)del] by WES. The WES variants in gene PTHR1, PTCH1, C8ORF37, EVC, FGFR2 were further validated by sanger sequencing. We also analysed lengths/ratios of hand metacarpals and phalanges of all patients and compare with normal hand X-rays. Variations in the different form of brachydactyly is identified in this study by anthropometric and radiometric analysis.

Conclusions:- This study is first study which focused on isolated and syndromic patient affected with congenital autopod malformations (CAM) in North Indian patients. We found likely pathogenic, and novel variants in various genes like IHH, HOXD13, WNT7A and PTCH1. A CNV was detected in the GLI3 gene in child with polysyndactyly. Metacarpal and phalanges ratios by radiometry in the CAM patients provided further insights into symmetrical/ asymmetrical, unilateral/bilateral variations in autopod malformations in hands and feet, which can implement in treatments by plastic surgery.

Keywords:- Congenital autopod malformation (CAM), brachydactyly, syndactyly, polydactyly, syndromic brachydactyly, dental anomalies, short stature