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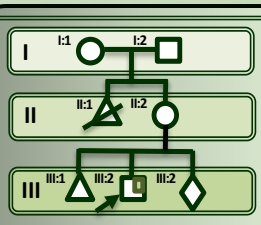
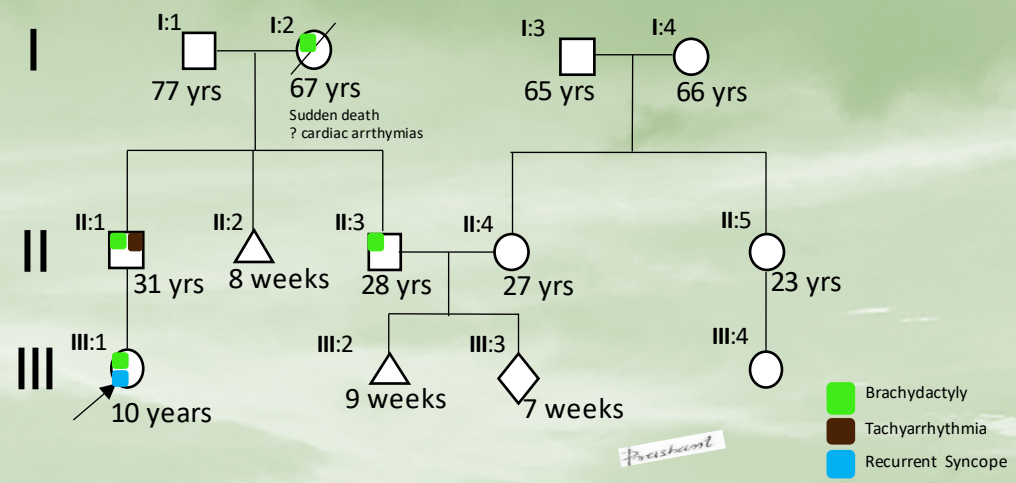
Progeroid Syndromes Like (PSL)-VI / LAMIN A/C related disorders / Heart and hand syndrome-IV, Slovenian type

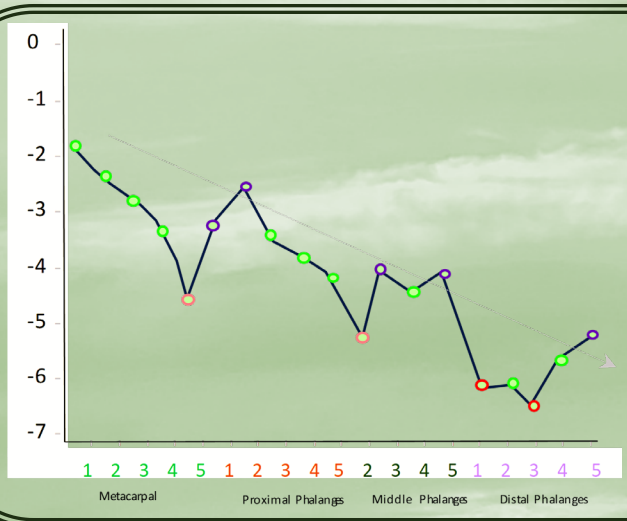
From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.





The metacarpophalangeal pattern (MCPP) profile



- **MCPP:** graphical representation of length of nineteen hand bones in an X-ray picture of a case with respected Z score against a control with the same age and sex.
- It has diagnostic value to recognize various genetic syndromes.

In HHS-IV, Slovenian type A

- Wavy pattern in appearance
- Generalized brachydactyly
- Grossly, shortening progresses from proximal to distal bones, and without any consistent pattern from the radial to the ulnar axis.

Insight:

1. What are the characteristic clinical phenotypes of HHS-IV?
2. What is the metacarpophalangeal pattern (**MCPP**) profile?
3. What are syndromes associated with consistent involvement of the heart and hand?
4. What are the possibilities of abortion for **Case III: 3**?
5. What are the various types of congenital limb malformations?

Plausible tenets:

Congenital limb malformations (CLMs):

- Approximately 1 in 500 live births, Very diverse: epidemiology, aetiology and anatomical changes.
- **50 % cases, CLMs are bilateral, while in unilateral CLM the right and left sides** are affected with approximately equal frequency.
- Surgical intervention can improve functional and aesthetic outcomes.
- **18% of children with a CLM die before the age of 6 years** (because of associated malformations).
- Most major limb anomalies (88%) had major associated anomalies involving other organ systems. These fetuses showed a high risk of chromosomal anomalies (28-32%) and an exceedingly high risk of non-chromosomal syndromic conditions (36-41%) responsible for an unfavorable outcome in almost all cases (98%)
- The first human disorder recognized to follow the principles of Mendelian inheritance - the limb malformation now termed brachydactyly type A1 (BDA1)

Heart- Hand syndrome: Specifically, syndromes reported with upper limb (Predominantly upper limb, and hand than lower limb) and CHD (structural and functional), historically four well-known entities in literature: Holt-Oram Syndrome I; HOS (Heart and Hand Syndrome), Heart-hand syndrome II (Tabatznik syndrome), Heart-hand syndrome III (Spanish type), Heart-hand syndrome, Slovenian type IV. But searching OMIM, there are 352 entries are reported with MeSH term ((+heart +hand)).

We have included eighty-seven monogenic disorders with cardiac structural or functional defects with congenital birth defects in hand as a common finding.

Excluded Two sixty-five entries those had inconsistent involvement of the heart or hand (in rare or in a few cases only), secondary deformities due to connective tissue disease, and non-monogenic genetic disorders.

Syndromes associated with various congenital birth defects of heart with of hand anomalies

Hand anomaly/CHD	Brachydactyly (16)	Limb hypoplasia and reduction defects (33)	Polydactyly (18)	Syndactyly (19)	Synostosis (1)
Structural cardiac birth defects	ALAGILLE SYNDROME 1; ALGS1 CARDIOFACIONEURODEVELOPMENTAL SYNDROME; CFNDS CORPUS CALLOSUM, AGENESIS OF, WITH FACIAL ANOMALIES AND ROBIN SEQUENCE KLEEFSTRA SYNDROME 1; KLEFS1 SHORT-RIB THORACIC DYSPLASIA 10 WITH OR WITHOUT POLYDACTYLY; SRTD10 SHORT-RIB THORACIC DYSPLASIA 12; SRTD12 DEVELOPMENTAL DELAY WITH OR WITHOUT DYSMORPHIC FACIES AND AUTISM; DEDDFA WEILL-MARCHESANI SYNDROME 1; WMS1 SMITH-MAGENIS SYNDROME; SMS PATENT DUCTUS ARTERIOSUS AND BICUSPID AORTIC VALVE WITH HAND ANOMALIES MYHRE SYNDROME; MYHRS JACOBSEN SYNDROME; JBS (5th clinodactyly also) CARDIOSPONDYLOCARPOFACIAL SYNDROME; CSCF CORNELIA DE LANGE SYNDROME 3 WITH OR WITHOUT MIDLINE BRAIN DEFECTS; CDLS3 COFFIN-SIRIS SYNDROME 2; CSS2	TETRAAMELIA SYNDROME 2; TETAMS2 ACROFACIAL DYSOSTOSIS 1, NAGER TYPE; AFD1 VERHEIJ SYNDROME; VRJS HUNTER-MACDONALD SYNDROME FANCONI ANEMIA, COMPLEMENTATION GROUP A; FANCA RABIN-PAPPAS SYNDROME; RAPAS COFFIN-SIRIS SYNDROME 3; CSS3 JOHANSON-BLIZZARD SYNDROME; JBS WARSAW BREAKAGE SYNDROME; WABS DIAMOND-BLACKFAN ANEMIA 11; DBA11 MICROCEPHALY-CAPILLARY MALFORMATION SYNDROME; MICCAP THROMBOCYTOPENIA-ABSENT RADIUS SYNDROME; TAR CRANIOECTODERMAL DYSPLASIA 1; CED1 COFFIN-LOWRY SYNDROME; CLS FANCONI ANEMIA, COMPLEMENTATION GROUP N; FANCN CATEL-MANZKE SYNDROME; CATMANS CLEFT PALATE, CARDIAC DEFECTS, GENITAL ANOMALIES, AND ECTRODACTYLY; CCGE GELEOPHYSIC DYSPLASIA 1; GPHYSD1 MULTIPLE JOINT DISLOCATIONS, SHORT STATURE, AND CRANIOFACIAL DYSMORPHISM WITH OR WITHOUT CONGENITAL HEART DEFECTS; JDSCD CLEFT LIP/PALATE WITH CHARACTERISTIC FACIES, INTESTINAL MALROTATION, AND LETHAL CONGENITAL HEART DISEASE HOLT-ORAM SYNDROME; HOS DIAMOND-BLACKFAN ANEMIA 1; DBA1 CHAR SYNDROME; CHAR ROBINOW SYNDROME, AUTOSOMAL RECESSIVE 1; RRS1 GILLESSEN-KAESBACH-NISHIMURA SYNDROME; GIKANIS SPONDYLOEPIPHYSEAL DYSPLASIA WITH CONGENITAL JOINT DISLOCATIONS; SEDCJD VACTERL ASSOCIATION, X-LINKED, WITH OR WITHOUT HYDROCEPHALUS; VACTERLX SPONDYLOEPIMETAPHYSEAL DYSPLASIA WITH JOINT LAXITY, TYPE 1, WITH OR WITHOUT FRACTURES; SEMDJL1 CARDIAC, FACIAL, AND DIGITAL ANOMALIES WITH DEVELOPMENTAL DELAY; CAFDADD	CARPENTER SYNDROME 2; CRPT2 AU-KLINE SYNDROME; AUKS SHORT-RIB THORACIC DYSPLASIA 8 WITH OR WITHOUT POLYDACTYLY; SRTD8 INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED 99, SYNDROMIC, FEMALE-RESTRICTED; MRXS99F SCHINZEL-GIEDION MIDFACE RETRACTION SYNDROME CRANIOECTODERMAL DYSPLASIA 2; CED2 PALLISTER-HALL SYNDROME; PHS OROFACIODIGITAL SYNDROME XX; OFD20 SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1 CARPENTER SYNDROME 1; CRPT1 MCKUSICK-KAUFMAN SYNDROME; MKKS SMITH-LEMLI-OPITZ SYNDROME; SLOS HYDROLETHALUS SYNDROME 1; HLS1 SHORT-RIB THORACIC DYSPLASIA 14 WITH POLYDACTYLY; SRTD14 PALLISTER-KILLIAN SYNDROME; PKS WOLF-HIRSCHHORN SYNDROME; WHS ACROCALLOSAL SYNDROME; ACLS MEGALENCEPHALY-CAPILLARY MALFORMATION-POLYMICROGYRIA SYNDROME; MCAP	CARPENTER SYNDROME 2; CRPT2 INTELLECTUAL DEVELOPMENTAL DISORDER WITH CARDIAC DEFECTS AND DYSMORPHIC FACIES; IDDCDF NEURODEVELOPMENTAL DISORDER WITH DYSMORPHIC FACIES AND DISTAL SKELETAL ANOMALIES; NEDDFSA SAETHRE-CHOTZEN SYNDROME; SCS OROFACIODIGITAL SYNDROME I; OFD1 NEUROCARDIOFACIODIGITAL SYNDROME; NCFD CORNELIA DE LANGE SYNDROME 1; CDLS1 TIMOTHY SYNDROME; TS RITSCHER-SCHINZEL SYNDROME 1; RTSC1 ELLIS-VAN CREVELD SYNDROME; EVC MICROPHTHALMIA, SYNDROMIC 2; MCOPS2 TOWNES-BROCKS SYNDROME 1; TBS1 PROGEROID FACIAL APPEARANCE WITH HAND ANOMALIES (+ other anomalies) ADAMS-OLIVER SYNDROME 1; AOS1 (brachydactyly) CONGENITAL HEART DEFECTS, HAMARTOMAS OF TONGUE, AND POLYSYNDACTYLY; CHDTHP SHORT-RIB THORACIC DYSPLASIA 15 WITH POLYDACTYLY; SRTD15 RUBINSTEIN-TAYBI SYNDROME 1; RSTS1 (polydactyly also) SPONDYLOEPIMETAPHYSEAL DYSPLASIA, GUO-CAMPEAU TYPE; SEMDGC PALLISTER-HALL-LIKE SYNDROME; PHLS	MESOMELIA-SYNOSTOSES SYNDROME
Functional cardiac birth defects	MANDIBULOACRAL DYSPLASIA PROGEROID SYNDROME; MDPS	MICROCEPHALY, CEREBELLAR HYPOPLASIA, AND CARDIAC CONDUCTION DEFECT SYNDROME; MCHCCD ANDERSEN CARDIODYSRHYTHMIC PERIODIC PARALYSIS KABUKI SYNDROME 1; KABUK1 ROBERTS-SC PHOCOMELIA SYNDROME; RBS SINGLETON-MERTEN SYNDROME 1; SGMRT1			

Counsel the family for Case III: 3 related for abortion- In case of paucity of the literature, it is always better to start with a positive part of counselling. In a multifactorial condition like the first trimester abortion, without knowing the detailed genotype, and case analysis, the abortion rate is quite similar to that in the control population.

Thought Riveting:

- ***What is the possible molecular mechanism to develop an HHS4 phenotype of the LMNA gene?***
- ***What is the clinical diagnostic yield of the metacarpophalangeal pattern (MCPP) profile?***