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AIIMSR Department of Pediatrics Genetic -division

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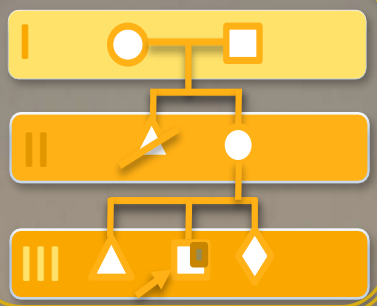

From the desk of Editor

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.

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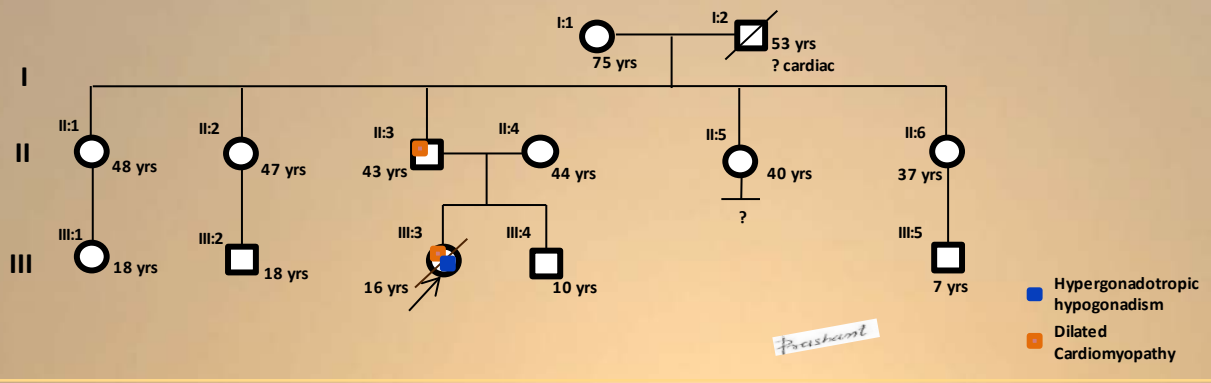
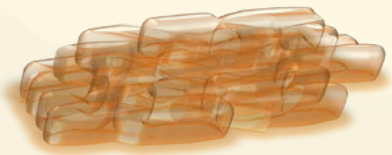
Progeroid Syndromes Like (PSL)-IV / LAMIN A/C related disorders/ Malouf syndrome / Najjar syndrome (Cardiogenital Syndrome)



Collagenoma



- Collagenoma Definition: A hamartomatous* collection of normal collagen fibers with variable elastic fibers. Collagenomas are classified according to number (single or multiple), position, and somatic or germline variation in the genome.

*A hamartoma is mostly a benign mass of disorganized tissue native to a particular anatomical location. While the presence of the normal tissue at an abnormal anatomical location is called heterotopic.

Insight:

1. What is the solitary collagenoma?
2. What is the phenotype spectrum of the Cardiogenital syndrome?
3. Does “Case III: 4” have any possibility for evolving the pathological phenotype of his sibling?
4. What is the possible differential diagnosis in a case with predominantly involvement of cardiac and gonadal tissue?
5. How would you predict the changes in protein structure for a novel single-point variant?

Plausible tenets:

Monogenic disorders having Hypogonadism PLUS Cardiac involvement as presenting features:

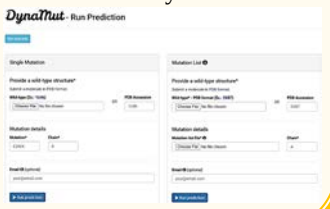
MIM Number	Phenotype (Syndrome)	Gene/MOI	Miscellaneous /Pointers
#212112	Cardiomyopathy, Dilated, With Hypergonadotropic Hypogonadism	LMNA/AD	Mild progeria features present
#602390	Hemochromatosis, Type 2A; HFE2A	HJV/ AR	Increase Iron levels
#212720	Martsolf Syndrome 1; MARTS1	RAB3GAP2/ AR	Severe MR, nail dysplasia
#176670	Hutchinson-Gilford Progeria Syndrome; HGPS	LMNA/AD	Classical progeria syndrome
#235200	Hemochromatosis, Type 1; HFE1	HFE/ AR	Increase Iron levels
#614921	Congenital Disorder Of Glycosylation, Type It; CDG1T	PGM1/ AR	Highly variable phenotype , exercise intolerance, hypoglycemia, episodic
#619422	Spinocerebellar Ataxia, Autosomal Recessive 31; SCAR31	ATG7/AR	Ataxia
#203800	Alstrom Syndrome; ALMS	ALMS1/AR	Eye-renal involvement
#616541	Short Stature, Microcephaly, And Endocrine Dysfunction; SSMED	XRCC4/ AR	Hypotelorism, acanthosis nigricans, severe attention deficit
#608540	Congenital Disorder Of Glycosylation, Type IK; CDG1K	ALG1/AR	Nephrotic syndrome, contractures
#212065	Congenital Disorder Of Glycosylation, Type IA; CDG1A	PMM2/AR	Abnormal isoelectric focusing of serum transferrin (type 1 pattern)
#258450	Progressive External Ophthalmoplegia With Mitochondrial DNA Deletions, Autosomal Recessive 1; PEOB1	POLG/ AR	Severe mitochondrial myopathy
#613313	Hemochromatosis, Type 2B; HFE2B	HAMP/AR	Increase Iron levels
#160900	Myotonic Dystrophy 1; DM1	DMPK/ AD	Myotonia, progressive disorder, cataract
#615084	Mitochondrial DNA Depletion Syndrome 11; MTDPS11	MGME1/AR	Emaciation, profound growth failure, exercise intolerance
#607426	Coenzyme Q10 Deficiency, Primary, 1; COQ10D1	COQ2/AR	Muscle weakness, progressive, Exertional fatigue, lipid accumulation
#182900	Spherocytosis, Type 1; SPH1 with deletions (p21p11.1)	ANK1/AD	Hyperbilirubinemia, increased osmotic fragility
#163950	Noonan Syndrome 1; NS1	PTPN11/ AD	Downslanting palpebral fissures Ectodermal changes
#615981	Bardet-Biedl Syndrome 2; BBS2	BBS2/ AR	Polydactyly, Retinitis pigmentosa obesity
#602668	Myotonic Dystrophy 2; DM2	ZNF9/ AD	Myotonia, proximal muscle weakness, Cataracts, posterior, subcapsular, iridescent
#253250	Mulibrey Nanism; MUL	TRIM37/ AR	Pericardial constriction
#146255	Hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome; HDRS	GATA3/ AD	Hypoparathyroidism, sensorineural deafness
#609286	Progressive External Ophthalmoplegia With Mitochondrial DNA Deletions, Autosomal Dominant 3; PEOA3	TWNK/AD	Late onset, muscular weakness, psychomotor retardation
#309801	Linear Skin Defects With Multiple Congenital Anomalies 1; LSDMCA1	HCCS/XLD	Microphthalmia, microcephaly, short stature
#230740	GAPO Syndrome; GAPOS	ANTXR1/ AR	Skeletal dysplasia, ectodermal changes
#604250	Hemochromatosis, Type 3; HFE3	TFR2/ AR	Increased iron levels
#222300	Wolfram Syndrome 1; WFS1	WFS1/ AR	Sensorineural hearing loss with optic atrophy
#277700	Werner Syndrome; WRN	RECQL2/ AR	Atypical progeroid features

Predicting the changes of protein structure for a novel single-point variant:

1. Get the wild protein structure in PDBfile format by
2. AlphaFold Protein Structure Database https://alphafold.ebi.ac.uk/entry/

3. Get the PDB file; Download it, and upload it in **DynaMut software** with mutation submission https://biosig.lab.uq.edu.au/dynamut/prediction

4. DynaMut analysis and prediction of protein stability changes upon mutation using Normal Mode Analysis



Classical cardiac manifestation of LMNA with HGPS

- Advanced atherosclerosis, which leads to heart failure with or without cardiac infarction (a median age of 13).
- Degenerative changes in smooth muscles and basement membrane (arterial smooth muscle dystrophy) are the peculiar findings in vessels besides atherosclerotic plug.
- Unexplainable significant reduction of type I collagen in basement membranes, adventitia, and media.

Possibilities for age dependent penetration of sibling phenotype in Case III: 4 - Pedigree analysis shows vertical transmission and, there is 50% possibility for carrying the pathological variant. However, prediction of exact phenotype without molecular testing is not possible, additionally somatic and germ-line mosaicism have been also reported with LMNA gene.

Thought Riveting:

- *What is the specific LMNA protein domain change associated with Malouf syndrome?*
- *What are the evolutionary changes in LMNA protein of the longest-living animals?*
- *How does the LMNA protein interact with SMC complex gene expression in cardiomyocytes?*
- *Would you like to recommend cardiac ECHO for an apparently asymptomatic sporadic case of hypogonadism?*