All India Institute of Medical Sciences Rishikesh (AIIMSR)
Department of Paediatrics

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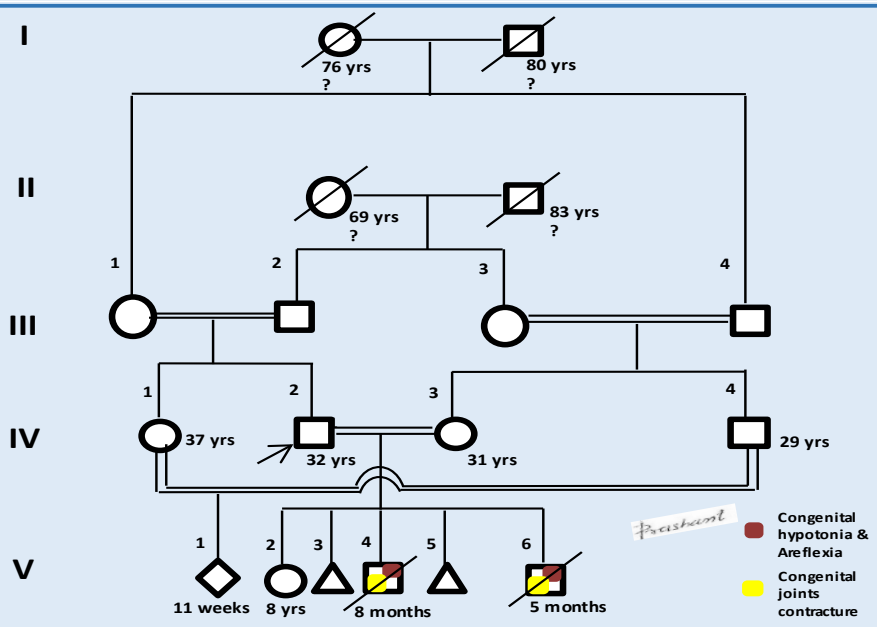
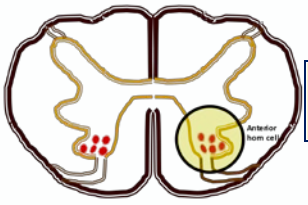
From the desk of Editor

The Department of Paediatrics is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and deliberate attempt to enhance awareness for genetic disorders with recent updates

Neurogenetics -III: NON-SMN related Spinal muscular atrophy (SMA)



Inherited Anterior Horn cells diseases



Spinal muscular atrophy (SMA)

- Proximal muscular weakness **(classical)**
- Distal **(LL>UL, Peripheral Neuropathy)**
- Lower extremity Predominant
- **Plus** (Epilepsy, arthrogryposis, fracture etc.)

Insight:

1. What is the inheritance pattern of distinct types of SMA?
2. What percentage of genetic material is shared between the double first cousins?
3. What is the scope and utility of clinical chronology in differentiating rare types of SMA?
4. What are the prime characteristic features & gene functions related to various rare types of SMA?
5. What is the inheritance pattern in [**Case V (4) and (6)**] and how is this information useful in genetic counselling of [**Case V (1)**]?

XL: NON-SMN SMA

S. No.	Disease	Gene	Function	Key features	Onset	Other Phenotype by gene
1.	Spinal and Bulbar MA, X-LINKED 1; SMAX1	AR	Androgen receptor	Testicular atrophy	30 to 50 years	Androgen Insensitivity, Hypospadias 1
2.	SMA, X-Linked 2; SMAX2	UBA1	In ubiquitin conjugation as the first step catalyzer	Infantile death, Arthrogryposis	Neonatal	VEXAS syndrome
3.	SMA, DISTAL, X-LINKED 3; SMAX3	ATP7A	Copper's subcellular transport and efflux	Distal involvement	variable	Occipital horn syndrome, Menkes disease

AR: NON-SMN SMA

S. No.	Disease	Gene	Function	Key features	Onset	Other Phenotype by gene
1.	DSMA1	IGHMBP2	A transcription regulator	Infantile death	3 months	CMTD, axonal, type 2S
2.	DSMA2	SIGMAR1	Regulation of lipid microdomains & different receptors	May become stable in young adulthood	6-12 years	Amyotrophic lateral sclerosis 16, juvenile (ALS16)
3.	DSMA3	??	??	Slowly progressive	6 months -19 years	
4.	DSMA4	PLEKHG5	Regulates autophagy of synaptic vesicles	Rapidly progressive	3 to 8 years	CMTD, recessive, intermediate C (CMTRIC)
5.	DSMA5	DNAJB2	Functions as a co-chaperone	Slowly progressive	18 to 23 years	

AR: NON-SMN SMA PLUS

S. No.	Disease	Gene	Function	Key features	Onset	Other Phenotype by gene
1.	SMA With Congenital Bone Fractures 1; SMABF1	TRIP4	Pre-mRNA processing & splicing regulator	Arthrogryposis, fractures & infantile death	In Utero	Muscular dystrophy, congenital, DC type
2.	SMA With Progressive Myoclonic Epilepsy; SMAPME	ASAH1	Steroidogenesis regulator	Progressive epilepsy, tremor, and weakness	2 to 5 years	Farber lipogranulomatosis
3.	SMA With Congenital Bone Fractures 2; SMABF2	ASCC1	Development of neuromuscular junction	AMC, fractures & infantile death	In Utero	Barrett esophagus & adenocarcinoma
4.	SMA With Microcephaly & Mental Subnormality: Progressive					
5.	SMA With Mental Retardation: Mitten-like syndactyly, microcephaly, infantile onset					
6.	SMA, Ryukyuan Type: Lower limb >> upper limb, infantile onset					

AD: NON-SMN SMA

S.No.	Disease	Gene	Function	Key features	Onset	Other Phenotype by gene
1.	SMALED1	DYNC1H1	Intracellular retrograde motility	Very slow or No progression	Onset in early childhood	CMTD axonal type 20, Mental retardation AD type 13
2.	SMALED2A	BICD2	A helping protein for dynein motor complex (DMC)	Severity variable & slowly progressive	3 to 8 years	***Severity of SMALED***: 2B> 2A>1
3.	SMALED2B			AMC, rapidly progressive	In utero	
4.	SMA, Late-Onset, Finkel Type; SMAFK	VAPBC	***Unfolded protein response (UPR)***	Lower limbs involve first	Onset after third decade	Amyotrophic lateral sclerosis type 8
5.	SMA, Jokela Type; SMAJ	CHCHD10	Mitochondrial & cristae organization	Hammertoes & slowly progressive neuropathy	Mid-adulthood	Frontotemporal dementia, ?Myopathy
7.	SMA, Infantile, James Type; SMAJI	GARS1	Mitochondrial translation & ***non-canonical*** role	Progressive, LL >UL, distal > proximal	Infantile	Neuronopathy, distal hereditary motor type VA; CMTD type 2 D
7.	SMA, Segmental: Sporadic & nonprogressive					
8.	SMA, Facioscapulohumeral Type: Onset in early adult life, face, and pectoral girdle muscular atrophy					

CMTD-Charcot-Marie-Tooth disease, **DC type**- Davignon-Chauveau type, **SMALED**- SMA, Lower Extremity-Predominant, **AMC** - Arthrogryposis multiplex congenita

Non-canonical- Not in standard or constitutive, **UPR:** a cellular signaling system that restores protein homeostasis by supervising folding of endoplasmic reticulum.

Genetic Counselling for [Case V (1)]:

- **Share** up to **25 %** genomic **sequence.**
- Proband phenotype & pedigree analysis**: X linked or AR.**
- **Panel test** include both **(XL & AR) genes**
- Carrier testing of couple **[IV (1) & IV (2)]**

Double first cousins: born to siblings marrying another set of siblings.

- **Couple [IV (1) & IV (2)], [IV (3) & IV (4)]**
- **Second degree of relationship**
- **Share 25% of nuclear genome.**

Thought Riveting:

- ***Why DSMA2 disease progression stops after certain time period?***
- ***Can incidence of NON-SMN SMA be predicted in the community, how attainable is it?***
- ***Is the option of fetus selection in sex linked severe phenotypes feasible & leads the path of genetic counselling, in the scenario of non-availability of genetic marker?***
- ***What are the common co-chaperonopathies and co-chaperonotherapy?***
- ***What are the functional similarities among the genes reported with SMA?***

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