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

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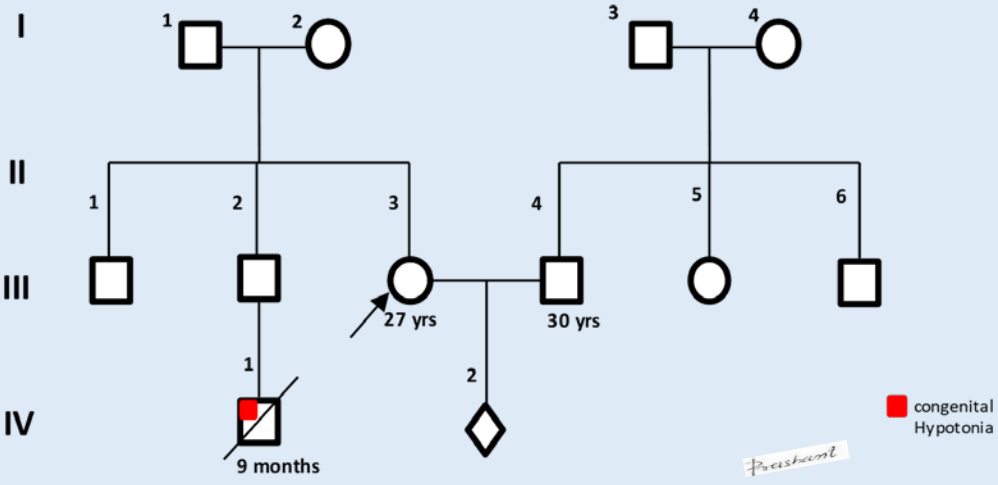
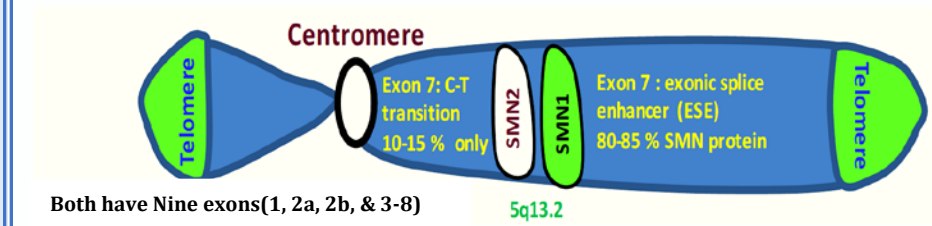
From the desk of Editor

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 -II: SMN1 related Spinal muscular atrophy (**SMA**)



SMN1 & SMN2 Gene cytogenetic location



Functional full length (FL) SMN protein– SMN1 >>> SMN2
DNA single nucleotide substitution: Transition- A ↔ G or C ↔ T & Transversions – A or G ↔ C or G

Insight:

1. What will be the counseling plan if only one of the couple has one SMN1 copy (positive carrier screening)?
2. Is it possible to eliminate SMA by population screening from the community?
3. Should India adopt NBS (newborn screening) for SMA?
4. What are the current treatment guidelines for SMA?
5. What are the available drugs and their role in management of SMA?

Plausible tenets:

Genes related to SMA: SMN1 & SMN2(homologous SMN1 & SMN2 genes (a product of inverted duplication)

SMN 1 gene

- **The most common cause for SMA & CNV (**deletion>>>/duplication**)(95-98%) is the most common type of** mutation
- **FL-SMN protein consists of 294 amino acids, ubiquitously expressed**
- **Role in housekeeping - snRNP biogenesis & pre-mRNA splicing**

SMN 2 gene

- Phenotype {Spinal muscular atrophy, type III}
- Pre mRNA processing defect(lack Exon 7) of SMN2 is the cause for truncated & a lesser stable protein

Disease phenotypes:

- **Proximal SMA**: Lower motor neuron(LMN) degeneration, occasionally bulbar motor neurons, genetically heterogenous group; **2nd most common AR** disorder. Incidence : 1 in 6000; carrier frequency: 1 in 35. It is also **the most common** genetic cause of infant mortality.

Clinical classification on the basis of disease onset:

- Types: **0**(congenital), **I** (**Werdnig-Hoffmann disease**, < 6 months, no sitting), **II** [**Dubowitz disease**, 6-18 months, no independent ambulation(IA)], **III**(**Kugelberg-Welander disease**, >18 months, IA) & **IV**(adult, excess fatigue)

Disease Modifiers causing milder phenotype: [**α** = propotionate]

1. More than one SMN2 gene copy **α** more SMN protein **α** survival of LMN **α** 1/ disease severity
2. New **ESE** element a single-base substitution – c.859G>C (p.Gly287Arg) – in exon 7 of SMN2
3. Xq23 locus PLS3 or plastin 3- high expression has protective role

Exon splicing enhancer (ESE): Distinct intra-exonic sequence which enhances correct splicing of **pre-mRNA into**

Specific therapy should be started before the appearance of disease phenotype (Asymptomatic state)
So newborn screening is the essential part of therapy, other key issues are cost, side effects, long term safety & efficacy.

Drug	Mechanism	Key Issue	Indication#
Nusinersen	ASO target SMN2 pre-mRNA & enhance FL SMN protein synthesis	Needed lifelong by intrathecal route	All SMA types
AVXS-101	Single IV dose AAV based delivery of SMN1 gene therapy	Adverse events up to 72 %	Type 1
Risdiplam	First oral drug, Splicing modifier of SMN2(increase exon 7 inclusion)	Effect splicing of FOXM1 & MADD	All SMA type Age > 2 months

AAV: Adeno-associated virus, ASO: Antisense oligonucleotide, #- FDA approved.

If the mother is a carrier & husband 's screening (CNV based) is negative or vice versa: Antenatal testing should be discussed with family because of:

a. The risk of affected child is 1/1,340 because there is a 1/670 probability of being a carrier (4 % chance of two copy of SMN1 on same chromosome & risk of non CNV mutations)
b. 2 % chance of de novo mutation

Elimination is difficult by Population Screening for SMN1 disease – as nearly 6 % parents with negative screening test may have a child with SMA

Ethics for Population screening should follow Wilson and Jungner criteria in three major fields:
Disease characteristics: definitive diagnostic criteria, treatment availability, disease course well defined, presence of latent stage
Population aspects: public health concern & social acceptability for the test
Administrative policies: availability of investigation & treatment facilities, acceptable and affordable test, assured continuation of treatment, clear strategies, and definition for population screening

Thought Riveting:

- ***What could be the different mechanisms for housekeeping proteins exclusively affecting a specific cell line or system more severely in the nonfunctional state?***
- ***How does the SMN-Gemins complex work as 'assemblysome'?***
- ***What is the exact cellular pathway responsible for motor neuron death in SMA?***
- ***Can drugs like hydroxyurea enhance Plastin 3 expression and alter the disease course?***
- ***What would be the molecular testing strategy if there are more than two homologous gene copies?***

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