PRENATAL DIAGNOSIS OF SPINAL MUSCULAR ATROPHY TYPE 0

Dr. Sujatha Jagadeesh
Consultant Clinical Geneticist
Mediscan

Dr. Subapriya Kandasamy, M.S(O&G)
Fellow in fetal medicine
Mediscan
&
Ms. Gayathri Jayaraman
Fellow in Genetic Counseling
Mediscan

Types of SMA

- 5 subtypes based upon onset of symptoms and progression of weakness:
  - Type 0 – Most severe, prenatal onset by usually 30-36 weeks
  - Type 1 – Severe, Onset by 6 months and succumb by 1-2 years
  - Type 2 – Intermediate severity. Onset 6-18 months. Survive upto around 3 years
  - Type 3 – Mild, Onset anytime after 18 months. Normal lifespan
  - Type 4 – Adult onset with normal lifespan

Review of literature…

- Kirkinen et al (PND, 1994)- presented a case of SMA type 1 presenting antenatally with history of decreased fetal movements at 36 weeks but had reactive CTG and normal breathing movements. Target scan showed normal fetal activity.
- In 1999, Dubowitz – “Type 0 is an expanding clinical phenotype of Type 1 SMA”

- Nuchal edema, hydrops, body wall edema in second trimester may represent severe variant of SMA – Asha R et al (PND, 1997)
- Nuchal translucency increase in fetus with normal karyotype - Robert J. Stiller et (1999 PND)

Case history

- 30 yrs old Mrs. J who P2L1 came for pre-pregnancy counseling
- 3rd degree consanguineous marriage
- 1st child died ? Cause
- 2nd child – floppy, hypotonia, feeding difficulty
- No significant anomalies noted in family pedigree

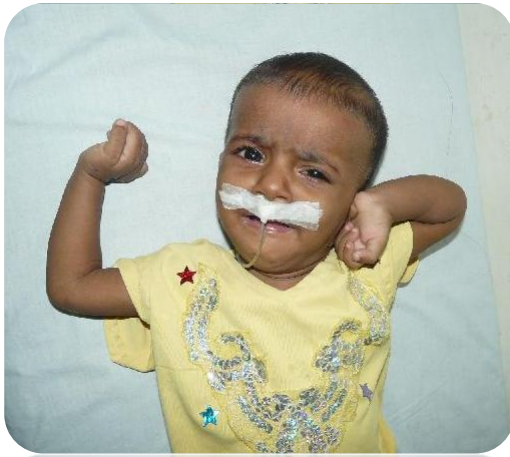
Obstetric history

- Gravida 1: Male baby born at term. 3.7 kg bw. Lethargic at 3 months, h/o recurrent respiratory infection. No h/o aspiration. Diagnosed as floppy infant -? Congenital myopathy ? SMA. Baby succumbed at 13 months ? Cause of death. No confirmatory tests done.

Obstetric history

Gravida 2:

- 1 yr old female child .
- Diagnosed as a case of spinal muscular atrophy
  - Born at term
  - Was normal upto 1 month.
  - Subsequently developed weakness
  - Recurrent aspiration requiring NG feeds.
- Mutation analysis of this child and mother were already done and referred for pre-pregnancy counseling to Mediscan.



Mutation analysis

Mutation analysis of proband showed deletion of exon 8 of SMN 1 gene

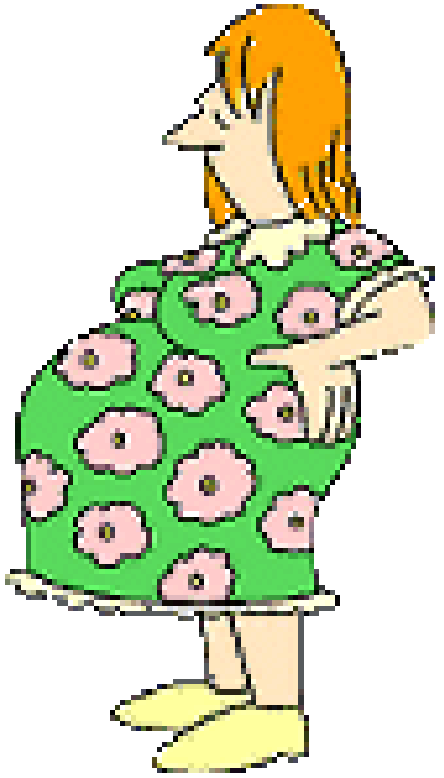
Mutation analysis of mother showed that she is carrier of exon 8 deletion of SMN 1 gene

Counseling

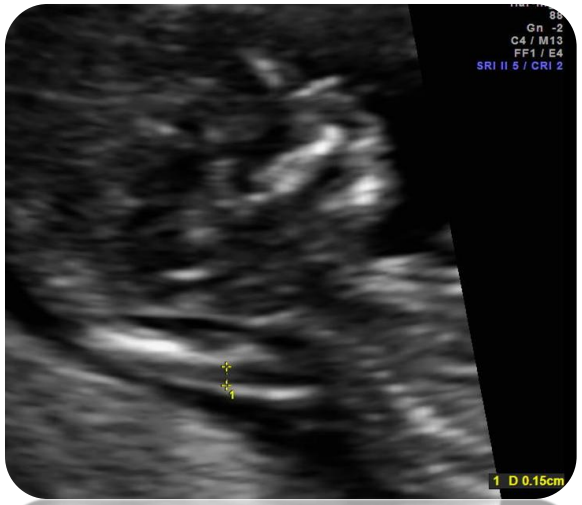
The couple was explained that

- SMA is an AR disorder with 25 % chance of recurrence.
- As mutation analysis was done for index child, prenatal diagnosis is possible in subsequent pregnancy.

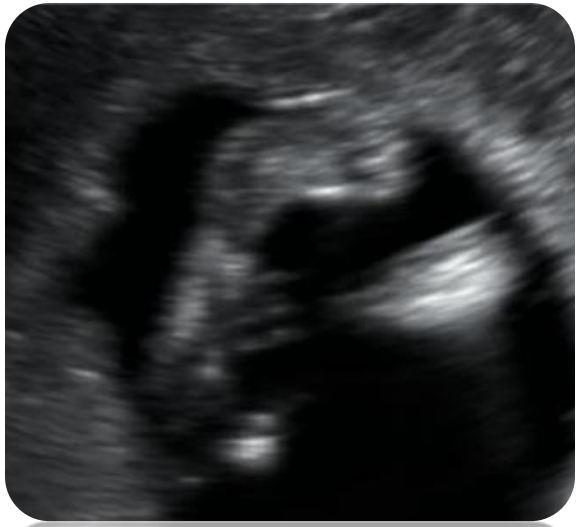
The patient came for first trimester screening of next pregnancy…

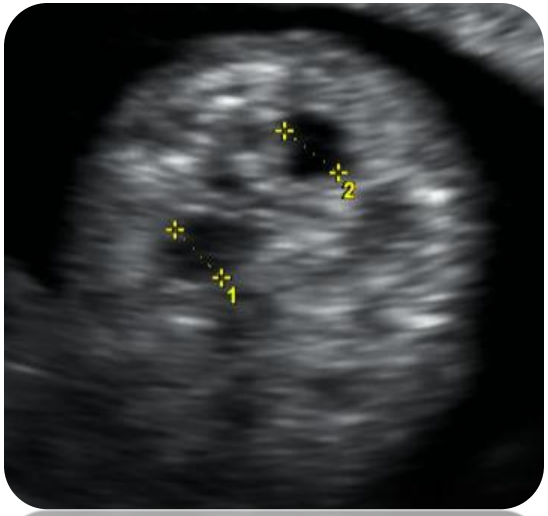


USG at 13 -14 wks



Decreased fetal activity



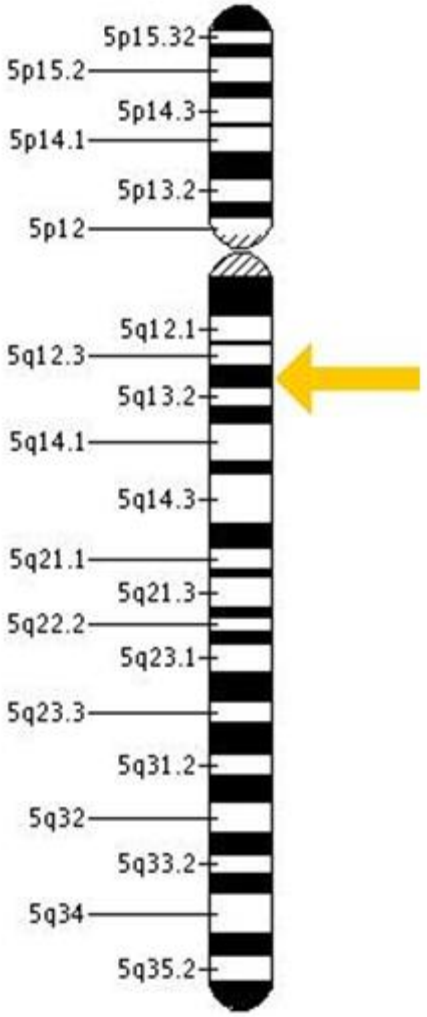


- CVS done to rule out chromosomal abnormality and SMA

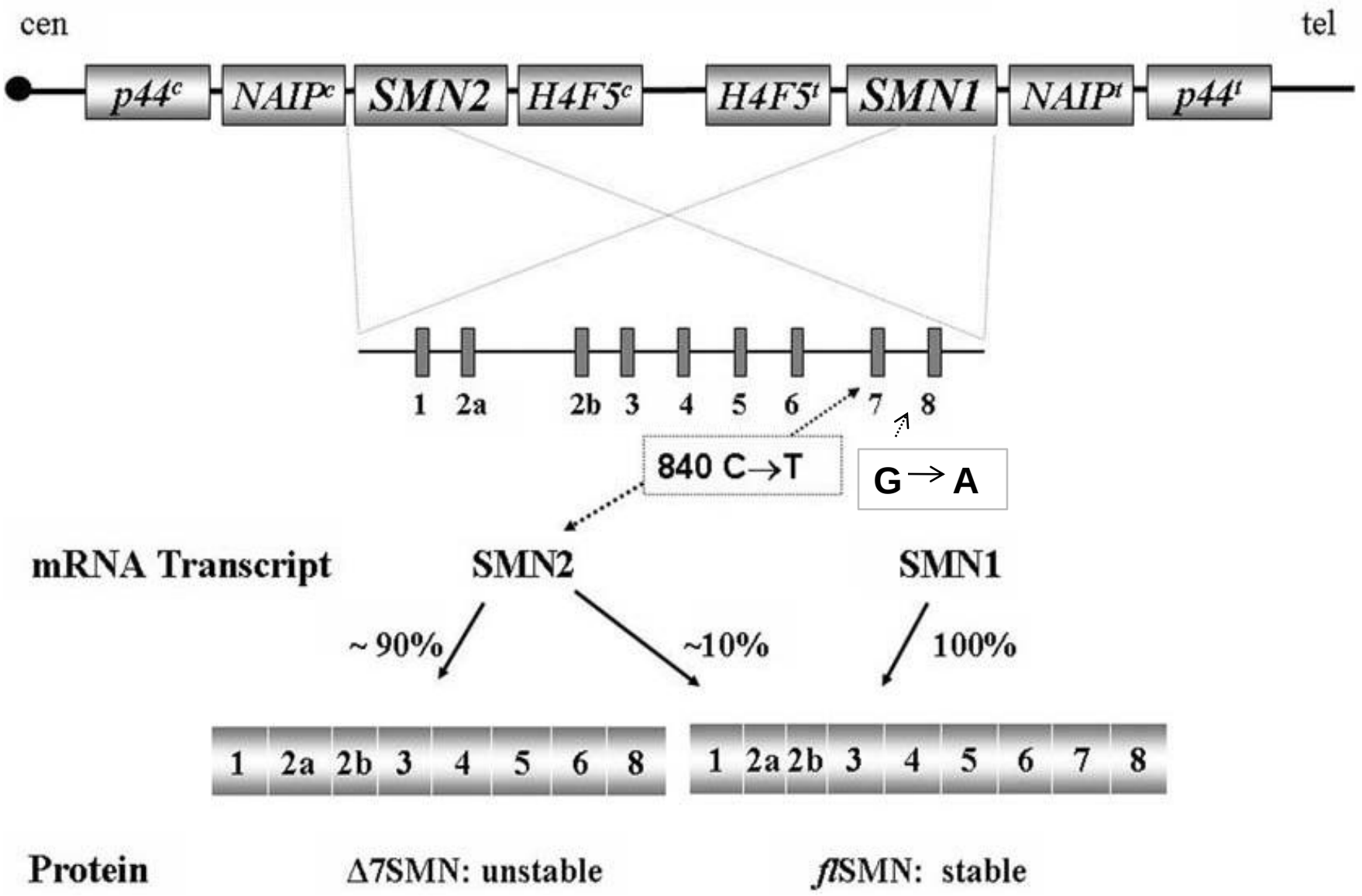
Mutation analysis showed deletion of exon 8 of SMN 1 gene, similar to previous child

Spinal Muscular Atrophy

- Autosomal recessive
- Lower motor neuron disease causing muscle weakness and atrophy
- Causative gene : SMN (Survival Motor Neuron) gene
- Located on chromosome 5q
- Carrier frequency about 1:50 in general population



Structure of *SMN* Gene Region on 5q



SMN1

- Multiple copies of SMN1 can be present
  - Normally (94.3%) - 2 copies
  - 2.1% - 3 copies
  - 0.7% - 4 copies
  - 2.9 % - 1 copy

- One copy of SMN is sufficient for normal functioning

SMN1

- Disease caused by :
  - Homologous deletion of SMN1 gene
  - Intragenic mutation in SMN1 gene when only one copy is present

- 2% of affected SMA individuals is due to *denovo* deletion/mutation wherein parents are not carriers

SMN2

- Deletion of SMN2 does not cause disease
- However it can act as a modifier – More copies of SMN2 gene can decrease severity
- Also sequence variants in SMN2 can modify severity. Eg .859G>C in exon 7 of *SMN2* creates new exonic splicing enhancer (ESE)

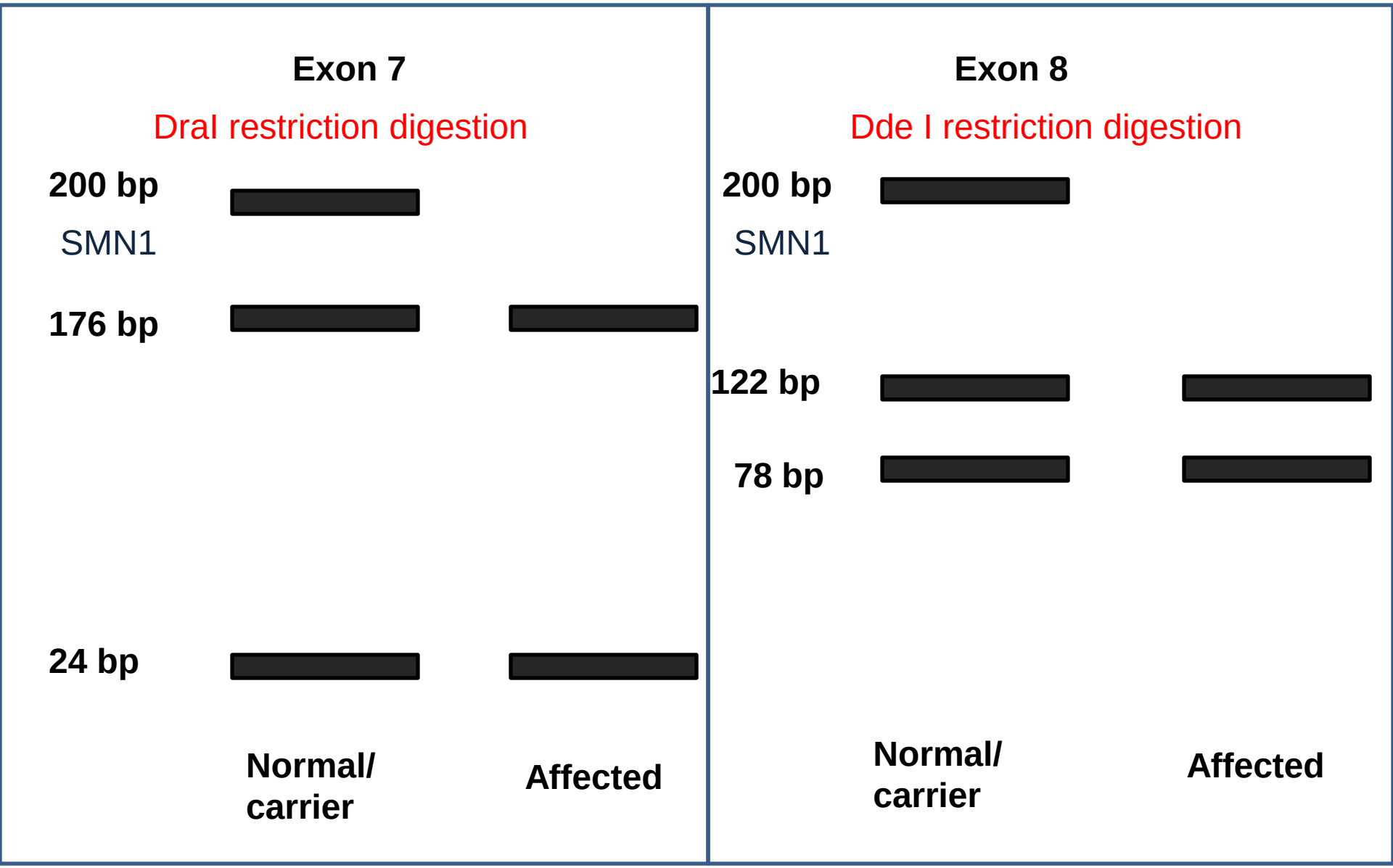
Other genes

- Neuronal Apoptosis Inhibitory Protein (NAIP) gene
- P44 gene
- Their role in the disease is controversial
- Present close to SMN gene
- Many patients with SMN1 deletion have NAIP deleted also
- NAIP more often deleted in Type 1 than Type 2 and 3 – Hence increases disease severity

Molecular diagnosis

- PCR-RFLP
  - Detects homozygous exon 7 and exon 8 deletions
- Sequencing for point mutations
- Quantitative PCR
  - for carrier detection

PCR-RFLP


Exon 7
DraI restriction digestion
200 bp
SMN1
176 bp
24 bp
Normal/ carrier
Affected
Exon 8
Dde I restriction digestion
200 bp
SMN1
122 bp
78 bp
Normal/ carrier
Affected

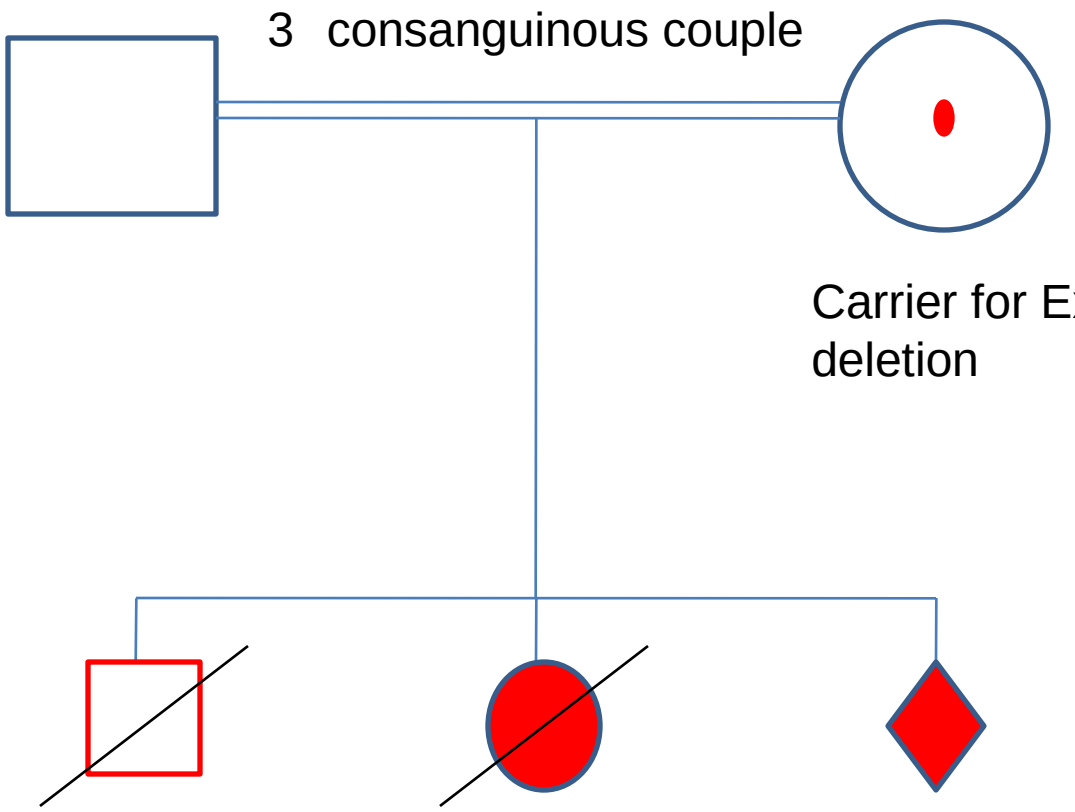
SMA Type 0 clinical presentation

- Intrauterine onset
- Present with asphyxia or severe respiratory distress in the neonatal period
- Usually need immediate intubation and artificial ventilation
- Profound hypotonia and facial weakness
- Death within the first 3 months

SMA type 0 genetics

- Consistent homozygous deletion of exon 7 and 8 of SMN1
- A case report of 3 cases with SMA type 0 (Barzegar et al, 2010) – Additionally exon 5 of NAIP deleted
  - Further implicating this gene as a factor for disease severity
- However, none of these studies have reported prenatal diagnosis

Our case


3 consanguinous couple
Carrier for Exon 8 deletion
No mutation analysis done
Exon 8 deletion
Exon 8 deletion

- First case wherein prenatal diagnosis has confirmed SMA type 0 with exon 8 deletion with severe and early presentation

- SMN2 and NAIP exon 5 and exon 11 as modifiers are being looked into

Acknowledgements

- Dr. V. Vishwanathan for referring the index case to us
- Dr. A.Prema for referring the patient for prenatal diagnosis
- Dr. Chandak of CCMB, Hyderabad for performing molecular testing in the index child, mother and fetus.

Thank you…