Rishi Vansh

All India Institute of Medical Sciences, Rishikesh

Department of Paediatrics

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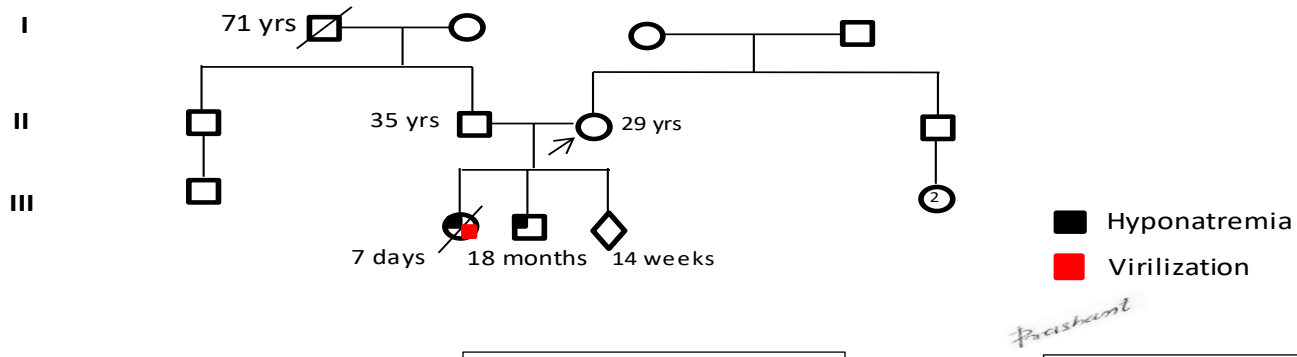
From the desk of Editor

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.

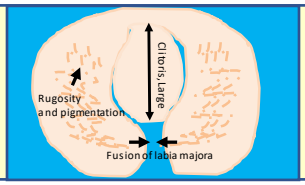
CYP21A2 (CAH1) Genetic Facts



Prashant

46, XX – Genital virilization

CAH1- 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia



Insight:

1. How important is it to do parents molecular testing along with the proband testing?
2. What is the percentage of carrier state in parents of a sporadic case?
3. What is the recurrence risk in proband's offspring and siblings?
4. Is there any genotype and phenotype correlation?
5. What is the crucial time for initiation of antenatal therapy for CAH?

Plausible tenets:

CYP21A2 CYTOCHROME P-450, FAMILY 21, SUBFAMILY- A, POLYPEPTIDE 2

- Molecular function: steroid 21-mono-oxygenase activity, steroid 21- hydroxylase activity and heme binding
- Cytogenetic Location is in the human leukocyte antigen (HLA) class III region in the major histocompatibility complex (MHC) on 6p21.33
- Possesses the highest gene density in human genome
- First De novo ***gene conversion** phenomenon identified in humans
- Has a corresponding highly homologous ***pseudogene** CYP21A1P
- Arranged in tandem repeats with 3 other genes in **RCCX module**(C4,RP,TNX)

CAH

- Most common disorder of sexual development , Most common cortisol production defect
- Autosomal recessive, Defective steroidogenesis
- CAH with DSD was first described in 1865 by De Crecchio, Dupont and coworkers in 1977 identified genetic linkage between HLA and 21-hydroxylase
- 90% to 95 % of CAH – due to deficient 21CYP21A2 (**CAH1**)
- **Phenotypes: 1.)** Non classical CAH (**NCCAH**) **2.)** Classical CAH(CCAH); Salt Wasting CAH (**SWCAH**)-75% **3.)** 25 % are Simple virilizing CAH (**SVCAH**)

*Gene conversion: homologous recombination; *Pseudogene: nonfunctional segments of DNA resembling functional gene

- Genetic diagnosis is complex, High variability of genomic region
- Targeted site-directed mutation analysis fails to identify mutations in approximately 10% of patients
- Need parent testing with proband
  - to investigate presence of mutations in different alleles and to determine if they are in the cis or trans configuration, and to verify de novo mutations.
  - 99 % Parents are Carrier - with sporadic case CAH & Carrier frequency in population 1/50

CAH Recurrence risk (RR) in offspring and siblings in each pregnancy				
Affected Offspring		**Siblings**	**Mutation Detection Rate**	
Spouse carrier	Spouse Not carrier	Empirical	Sequencing	Deletion/ Duplication analysis
50 %	<1%	25%	70-80 %	20-30 %

Genotype and phenotype correlation:

- **SW**CAH- 90.5% - Complete loss of enzyme function
- **SV**CAH-85.1 % - 1-2% normal enzyme activity - Due to variable CAG repeats of Androgen Receptor
- **NC**CAH-97.8% - 20-60 % normal enzyme activity - Can be missed on newborn screening by 17-hydroxyprogesterone (17OHP)

- Approximately 70% of mutations in CAH are pseudogene derived variants due to gene conversion (the transfer of deleterious pseudogene mutations to the active CYP21A2 gene)
- 25–30% are ***chimeric gene** due to large deletions (altered function)
  E.g. Contiguous gene deletion involving the adjacent CYP21A2 and TNXB genes in RCCX module in one or more alleles forming chimeric gene produce hypermobility type Ehlers-Danlos syndrome with CAH-**CAH-X syndrome**

***Chimeric gene: combination of two or more coding sequences of genes to produce new gene**

The time to initiate therapy in newborn is before 8 weeks (At indifferent stage of external genitalia)

Thought Riveting:

- *Why do testicular adrenal rest tumors (TART) develop from rete testis in later ages in CAH1?*
- *Can 17-OHP test be used for carrier status screening of CAH1?*
- *What are the genetic mechanisms for high incidence of CYP21A2 mutation*?
- *What is the current status for Gene therapy and IV Heme therapy for CAH1?*

Author: Dr Prashant Kumar Verma
Reviewers: Dr. Vyas K Rathaur and Dr. Raksha Ranjan