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

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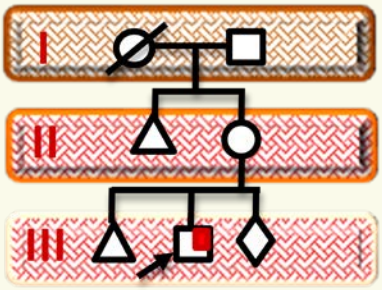
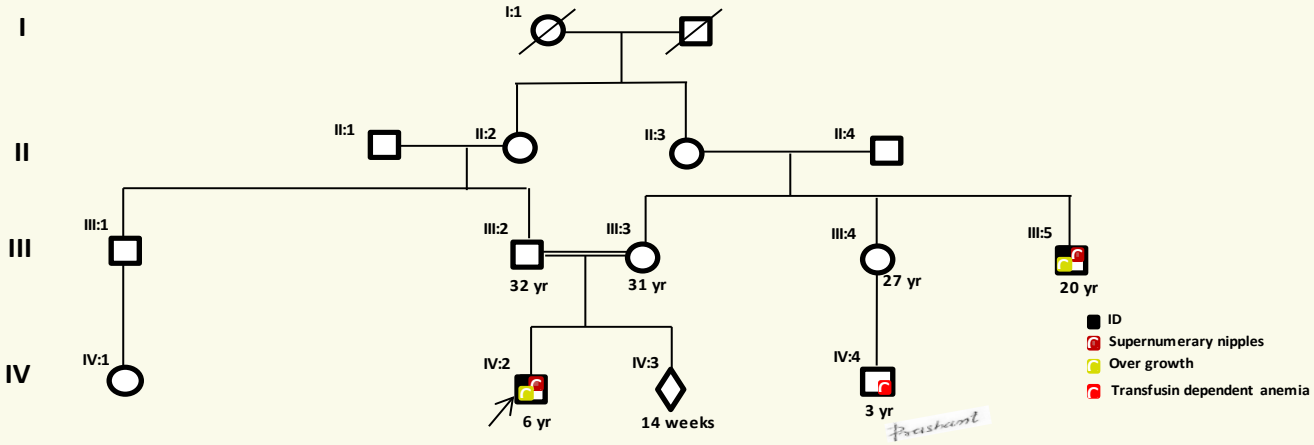
From the desk of Editor

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

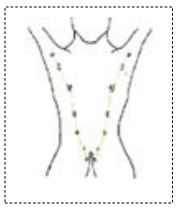


Neurogenetics -VII

Intellectual Disability/ ***X-Linked***/(**IDXL**)/ Simpson-Golabi-Behmel syndrome (**SGBS**)



Anatomical Location of non-ectopic supernumerary nipples (Embryonic Milk line)



- Additional Mammary glands & nipples develop from embryonic Milk line (a ventral epidermal ridge) extending from axilla to groin; which result from failure of regression during human embryogenesis.
- Atavism: presence of evolutionary regressed ancestor trait

Insight:

1. What are the key characteristic differences between SGBS type 1 & type 2?
2. What is the meaning of 'positional cloning' & 'overgrowth syndrome'?
3. Is there any genetic heterogenicity for SGBS?
4. How would you counsel III:2 & III:3 for case IV:3?
5. What are the surveillance guidelines for an overgrowth syndrome?

Plausible tenets:

Gene: GPC3 (Xq26.2); 451,356 bps & 8 Exons

- **Glypican3 belongs to the glypican-related integral membrane proteoglycan family (GRIPS)**
- Transcript length: 2267 bps, eight domains & features, thirteen splice variants, 205 orthologues, five paralogue
- Proteoglycan Protein of cell surface [(580 AA), Molecular mass: 65563 Da] carries heparan sulfate.
- Negatively regulator for hedgehog signaling(SHH) pathway by opposing for receptor while positively regulates the Wnt signaling pathway & do fine-tuning of BMP4, BMP2, BMP7, & FGF7 proteins in embryogenesis
- Might have a role in growth regulation & cell division

--- Clinical Phenotypes ---

- X Linked inheritance pattern (XLR)
- No clincial diagnositic criteria
- **Type 1 SGBS**: Primordial overgrowth syndrome(OGS), macrosomia craniofacial features with variable neurostructural & higher cognitive issues.
- **Other anomalies reported:** coarse facial features, supernumerary nipples, focal ectodermal defect(abdominal & diaphragmatic hernia), skeletal dysplasia (segmented vertebral defect & postaxial polydactyly), high risk for embryonal tumors (As ominous for the majority of OGS)
- **Management:** symptomatic with Multidisciplinary approach
- **Investigation: follow the protocol used for any dysmorphic case(**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4324078/)
- **Serum alpha fetoprotein (5-10 % risk for embryonic tumor)**

Type 2 SGBS (XLR): Gene **OFD**, brachydactyly, recurrent respiratory infection (**ciliary dysfunctions**) & short life span. (*likely to be reclassified soon*)
Genetic heterogeneity with type 1 SGBS: **30 %** SGBS fail to spot by GPC3/4 testing

Positional cloning (around the 1980s): localization of a gene (unknown functional activity) position in the genome by known polymorphic markers in a family having multiple affected cases.

Overgrowth syndrome: should be suspected if any two anthropometric parameters- head circumferences, height, & weight are > 2 SD from the mean

Imperative Counselling aspects for case IV:3

- Confirming the diagnosis: case IV:2, & IV:4 (in view positive of consanguinity need to rule inherited haemoglobinopathy especially thalassemia)
- **consanguinity could increase the risk of all types of mendelian MOI**

Thought Riveting:

- ***How do the cholesterol levels interact with GPC3 at the cellular level beyond the embryonal period?***
- ***Can CEmRNA (Carcinoembryonic microRNA panel) be used as the earliest biochemical marker for embryonal tumors?***
- ***What is the relation of GPC3 protein to the cellular aging process (CAP)?***
- ***How does the duplication of exons 1-9 in GPC4 alter GPC3 expression?***
- ***Which alternative splice variants of GPC3 have an active role in the regression of the embryonic milk line?***
- ***Does a genetic program or pathway regress or stimulate atavism & how does it help in evolution?***

Syndromes with supernumerary nipples

Syndrome	Gene (MOI)	Characteristic features
INTELLECTUAL DEVELOPMENT DISORDER X linked 106; XLID106	OGT (XLR)	ID + MRI changes & microcephaly
FOCAL DERMAL HYPOPLASIA	PORCN (XLD)	Focal skin aplasia or hypoplasia
INCONTINENTIA PIGMENTI	IKBKG (XLD)	Classical skin changes with stages
BRANCHIOOCULOFACIAL SYNDROME	TFAP2A	Branchial cleft sinus clefts, ocular anomalies, conductive hearing loss
OCULOECTODERMAL SYNDROME	KRAS (Somatic)	Epibulbar dermoid & aplasia cutis congenita
POSTAXIAL ACROFACIAL DYSOSTOSIS (Miller syndrome)	DHODH (AR)	Severe micrognathia, coloboma of eyelids, ulnar ray defects
DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 51; DEE51	MDH2 (AR)	Intractable Seizures, hypotonia, increased lactate, brain atrophy
CARPENTER SYNDROME 2; CRPT2	MEGF8 (AR)	Multisuture craniosynostosis, polysyndactyly & obesity
INTELLECTUAL DEVELOPMENT DISORDER WITH IMPAIRED LANGUAGE AND DYSMORPHIC FACIES; IDDILF	DDX6 (AD)	Abnormal philtrum, cardiac & urogenital anomalies & friendly behavior
TRICHOODONTOONYCHIAL DYSPLASIA WITH BONE DEFICIENCY	? (AR)	Ectodermal dysplasia, nevus pigmentosus, frontoparietal bone deficiency
BOHRING-OPITZ SYNDROME; BOPS	ASXL1 (AD)	Severe IUGR, trigonocephaly, nevus flammeus, forehead hirsutism
CHARCOT-MARIE-TOOTH DISEASE, TYPE 4A; CMT4A	GDAP1 (AR)	Peripheral neuropathy, gait difficulties, foot deformities
ANKYLOBLEPHARON ECTODERMAL DEFECTS-CLEFT LIP/PALATE; AEC	TP63 (AD)	Eyelids & alveolar synechiae, maxillary hypoplasia, ectodermal dysplasia
PALLISTER KILLIAN SYNDROME Tetrasomy of 12p	(Somatic mosaicism)	Streaks of hypo- or hyper-pigmentation, hypertelorism, short neck
NEURODEVELOPMENTAL DISORDER WITH HYPOTONIA, IMPAIRED LANGUAGE, AND DYSMORPHIC FEATURES; NEDHILD	CHAMP1 (AD)	Ophthalmologic anomalies, sleep disturbances, seizures
AGENESIS OF CORPUS CALLOSUM, CARDIAC, OCULAR AND GENITAL SYNDROME; ACOGS	CDH2 (AD)	ID, behavioral abnormalities, downslanting palpebral fissures, Hyposmia
BLEPHAROPHIMOSIS WITH FACIAL AND GENITAL ANOMALIES AND MENTAL RETARDATION	?(AR)	Midface hypoplasia, ear anomalies, Underdeveloped genitals, trigonocephaly
ECTODERMAL DYSPLASIA, HYPOHIDROTIC, WITH HYPOTHYROIDISM AND AGENESIS OF THE CORPUS CALLOSUM	?(? AR/ XL/ contiguous gene syndrome)	Ectopic or absent thyroid, Severe ID, midface hypoplasia, macrocephaly, hypotonia
INTELLECTUAL DEVELOPMENTAL DISORDER, AUTOSOMAL RECESSIVE 65; MRT65	KDM5B (AR)	Downslanting palpebral fissures, ear anomalies, thin lips, 4th or 5th finger Camptodactyly
CHAR SYNDROME	TFAP2B (AD)	Downslanting palpebral fissures, thick lips, hypertelorism, mild ID, Sleepwalking, Parasomnia
TYSHCHENKO SYNDROME	? (AD)	Short stature, flattened face, Prominent eye, congenital heart disease
OLIVER SYNDROME	?(AR)	Postaxial polydactyly, syndactyly, prominent jaw & eyebrows, ID

MOI- mode of inheritance, [**ID** +]- **Intellectual disabilities plus** - spastic gait, pyramidal syndrome & behavioral disorders, CP- cerebral palsy.

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