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Department Of Pediatric Genetic -division

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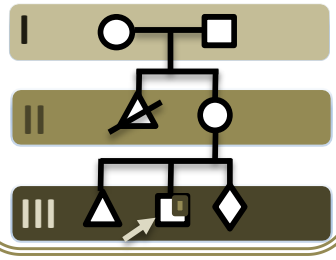
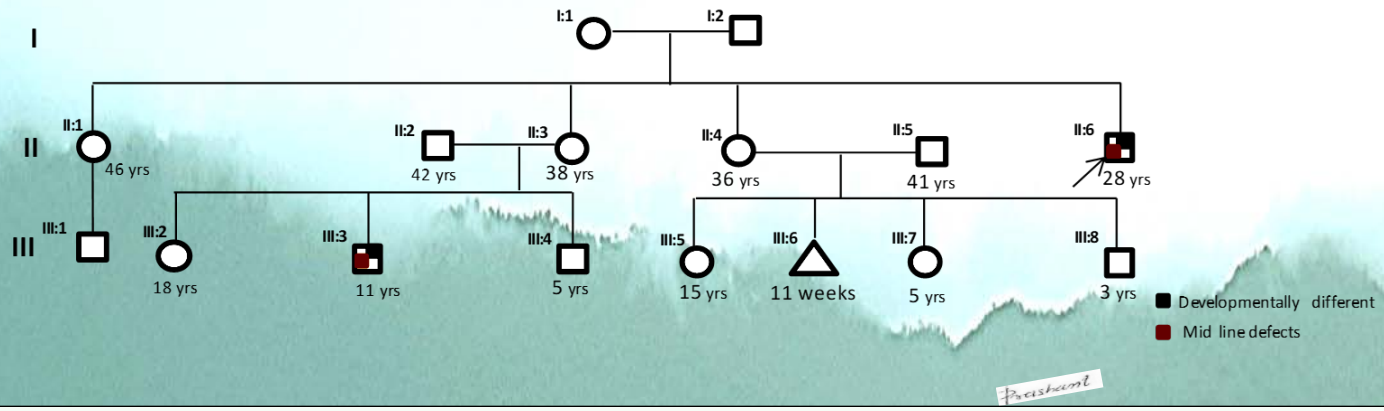


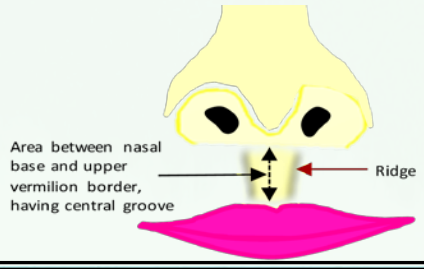
From the desk of Editor

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

Neurogenetics-(XII)/Intellectual Disability/ X-Linked/(IDXL)/ Intellectual developmental disorder, Opitz GBBB syndrome; (X-OS) GBBB



Philtrum, Smooth or Flat



- A variation in depths
- Shrunken ridge or a shallow groove
- Grading of variation used for Fetal Alcohol Syndrome
- Mandatory prerequisite: face must be in the neutral position

Insight:

1. How to approach a child with an imperforate anus who is X-linked-developmentally different?
2. What are the characteristic features of GBBB syndrome?
3. What is the molecular function of the MID1 gene?
4. Does Opitz G/BBB syndrome also inherited by autosomal dominant mode?
5. What are the principal differences in counselling steps between cases III:3 & III:5?

Plausible tenets:

- **Gene: MID1 (Xp22.2): Family:** tripartite motif (TRIM) also called 'RING-B box-coiled coil' (RBCC), **Subgroup**: RING finger proteins."
- Location on the forward strand of X: **X:10,445,310-10,833,683** An important paralog of this gene is MID2
- Exons: 10, Coding exons: 9, **388,374 bps**, 52 domains and features, 275 orthologues, 23 splice variants or transcripts, 80 paralogues.
- Transcript length: **6,168** bps. Translation length: **667** amino acids, with a molecular weight of 75251 Da. The TRIM motif: a RING, a B-box type 1, and a B-box type 2, three zinc-binding domains, and a coiled-coil region.
- **First identified in humans as a candidate gene of X inactivation although it escapes by this process in mice.**
- Various tissue-specific transcripts by alternative splicing and polyadenylation
- Homodimers of this protein coordinate with cytoplasmic microtubules & function like anchor points to microtubules for the formation of a multiprotein structure. The Core of a microtubule-associated mRNP complex is made by a **MID1/alpha-4 (IGBP1)** that associates with cytoskeleton-associated mRNA transport & translation control factors with members related to the **mTOR /PP2A signaling cascade.**
- **Its E3 ubiquitin ligase activity** → ↑ monoubiquitination of IGBP1(alpha-4) → ↓ protection of the catalytic subunit of protein phosphatase 2Ac (PP2AC) **and** its degradation by polyubiquitination**.**

Clinical phenotypes: X linked recessive inheritance - *The only sign in females: hypertelorism.*

- A syndrome with multiple midline birth defects from head to toe:
- **Midline brain defects**: Dandy-Walker malformation and agenesis or hypoplasia of the corpus callosum and/or cerebellar vermis
- **Midline head and neck anomalies**: widow's peak, prominent forehead, hypertelorism, broad nasal bridge, anteverted nares, cleft lip/palate, laryngotracheoesophageal anomalies
- **Midline anomalies in the trunk:** cardiac defects, hypospadias, cryptorchidism, hypoplastic/bifid scrotum, & imperforate anus
- Up to 50 % are only Intellectually different
- Wide intra and interfamilial phenotypical variabilities, **so no defined diagnostic criteria**
- Rx: symptomatic by a multidisciplinary team (https://www.ncbi.nlm.nih.gov/books/NBK1327/#opitz.Management)

X-linked-developmentally different child with imperforate anus

Syndrome / OMIM no.	Gene & MOI	Key clinical features
Opitz-Kaveggia syndrome or FG syndrome/ #305450	**MED12 (XLR)**	Relative macrocephaly, hypertelorism, down-slanted palpebral fissures, broad thumbs and halluces, hypotonia, constipation, and partial agenesis of the corpus callosum
Intellectual developmental disorder, X-linked syndromic, Armfield type/#300261	**FAM50A (XLR)**	Downslanting palpebral fissures, bulbous nose small hands and feet. Renal & ocular anomalies
Intellectual developmental disorder, X-linked, with skeletal dysplasia and abducens palsy/%309620	**--(XL)**	Skeletal dysplasia (vertebral), mental retardation, and abducens palsy
Linear skin defects with multiple congenital anomalies 1/#309801	**HCCS (XLD)**	Irregular linear areas of erythematous skin hypoplasia with included microphthalmia, corneal opacities, and orbital cysts
TARP syndrome/#311900	**RBM10 (XLR)**	Talipes equinovarus, atrial septal defect, Robin sequence (micrognathia, cleft palate, and glossoptosis), and persistent left superior vena cava +/- variable CNS, renal and cardiac abnormalities

Teebi hypertelorism syndrome-1 (TBHS1) also known as **GBBB2** inherited by autosomal dominant mode with very overlapping clinical features. The causative gene is a **Sperm Antigen With Calponin Homology And Coiled-Coil Domains 1 Like** (SPECC1L) which is located on 22q11.23 (just near Chromosome 22q11.2 deletion syndrome, distal**)**

Effects of duplication of a Gene in the same organism:

- If gene is functional, then it called the Paralog gene
- If it is not as perfectly functional – called pseudogene (PsG) or defective paralogous copy ≈14,000. PsG helps in regulation of functional gene through various way
- MID2- quite similar function & pathological phenotype- ? Intellectual developmental disorder. X-linked 101

Fundamental differences in counselling steps between cases III:3 & III:5- In Pediatric cases, Asymptomatic Carrier Status (ACS) testing is not mentioned if it does not provide any medical advantages (change in the disease's natural course) because of legitimate reasons & it leads to short or long-term psychological trauma, which affects their development. In the case of an adult, the patient wants to know the carrier status even after understanding its consequences, most specifically social and on personal life, carrier testing can be planed.

Thought Riveting:

- ***Why are midline anomalies common with GBBB syndrome?***
- ***What is the sequence initiator for smoothening the philtrum?***
- ***How does alcohol affect developmental pathway genes in the early embryonic period?***
- ***How many paralogous genes are present in the human genome?***
- ***What possible interaction exists between MID1 & MID2 gene products in the nucleoplasm or karyoplasm?***

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