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Department Of Pediatric Genetic -division

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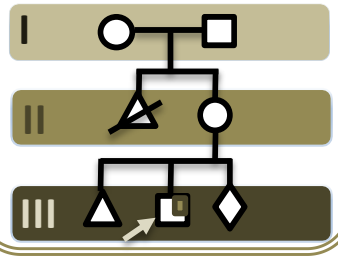
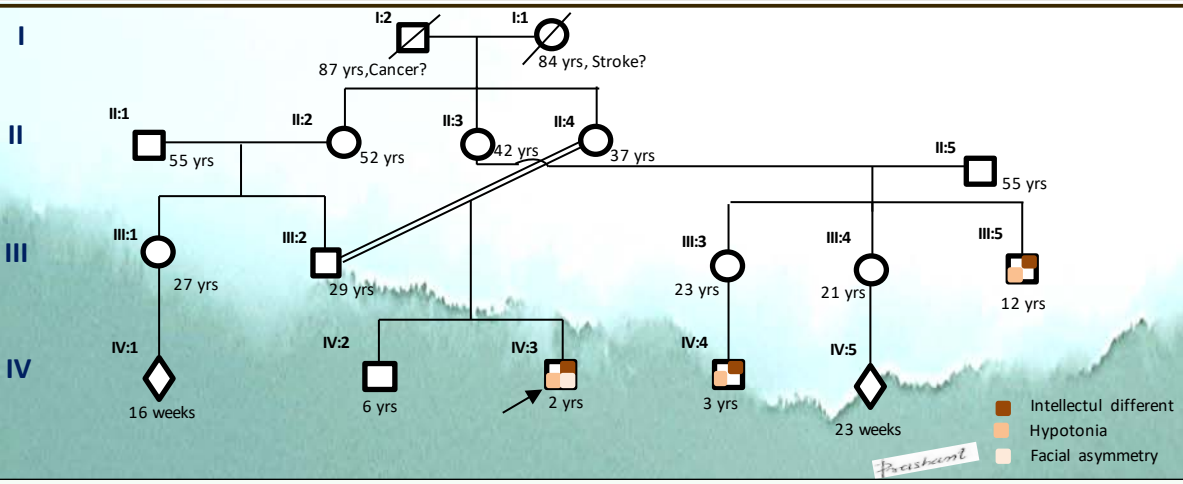


From the desk of Editor

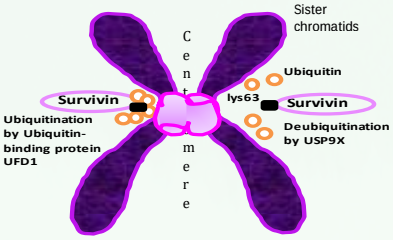
The genetic division of the Pediatric Department is publishing a monthly newsletter for faculty and residents. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Neurogenetics-(XI)

Intellectual Disability/ X-Linked/(IDXL)/ Intellectual developmental disorder, X-linked 99 /USP9X



Function of USP9X in metaphase spindle formation



- Ubiquitin – 8.5 kDa, regulatory protein, having 76 amino acids
- USP9X helps in disassociation of survivin with centromeres while UFD1 inverse it
- So, de/ubiquitination of proteins orchestral chromosomal segregation without protein loss

Insight:

1. How to approach a child with X-linked-facial asymmetry?
2. What are the characteristic features of USP9X?
3. What is the chromosome passenger complex (CPC)?
4. Does USP9X has any association with the phenotype of turner syndrome?
5. What could be the counseling plan for case IV:1 if the family wants to know the yielding of molecular testing?

Plausible tenets:

- **Gene: USP9X (Xp11.4):** a substrate-specific **"deubiquitylating enzyme";** a family member: "**the peptidase C19**" (≈ ubiquitin-specific protease family).
- Location on the forward strand of X: **41,085,445-41,236,579.** Locate in Turner syndrome-related critical region.
- Exons: 45, Coding exons: 44, **151,135 bps**, 39 domains and features, 227 orthologues, 18 splice variants or transcripts, 71 paralogues.
- Transcript length: **12,543** bps. Translation length: **2,554** residues protein has 2554 amino acids, with a molecular weight of 290463 Da. It escapes X-inactivation.
- Deubiquitinase removes ubiquitin from various proteins to protect them from proteolysis. Indirectly regulated protein intracelular activity.
- Decreased localization to the cilia? It may be a possible explanation for dysmorphology.
- Need for proper TGF-beta/BMP signaling cascade & mTORC2 complex assembly.
- Role in cancer: stabilized oncoproteins.

Clinical phenotypes:

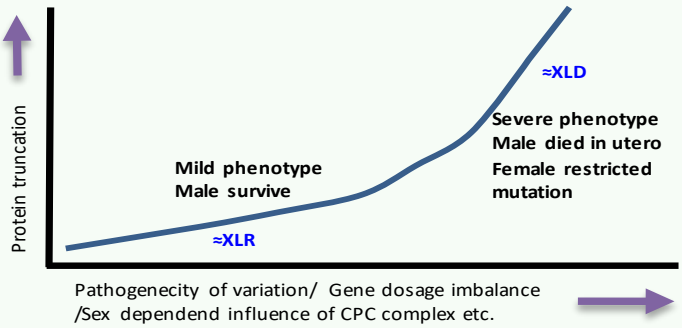
- **A. Intellectual developmental disorder, X-linked 99- XLR**
- **B. Intellectual developmental disorder, X-linked 99, syndromic, female-restricted- XLD**
- **Both are inherited in X linked manner,** with highly variable overlapping phenotype: hypotonia, Joint laxity, short stature, prominent forehead, facial asymmetry, nonspecific nasal anomalies, philtrum & ear anomalies, dental dysplasia, short and broad digits, developmental delay and intellectually different
- **XLD case has more obvious various** eye anomalies, including cataracts, Choanal atresia, brachycephaly, postaxial polydactyly, tapering fingers, Pigmentary abnormalities along the lines of Blaschko, Hypertrichosis, CHD, anal atresia, renal dysplasia, various types CNS anomalies (corpus callosum hypoplasia, dandy walker malformation, and abnormal gyral pattern)
- **Rx: Multidisciplinary symptomatic treatment, follow the surveillance guidelines and http://www.rehabcouncil.nic.in/ http://rehabcouncil.nic.in/writereaddata/mr.**

X linked - Facial *asym*metry

Syndrome	Gene & MOI	Key clinical features
Turner type of X-linked syndromic intellectual developmental disorder (MRXST)	**HUWE1 (XL)**	Delayed bone age, hypotelorism, hyperextensible joints, CHD, **intellectual different**
Spinal and bulbar muscular atrophy of Kennedy	**Androgen receptor gene Expansion of CAG(n) (XLR)**	Onset 3rd to 4th decade, slowly progressive muscular weakness (muscle atrophy), fasciculations, and gynecomastia
Intellectual developmental disorder, X-linked syndromic, Snyder-Robinson type	**SMS (XLR)**	Unsteady gait, intellectual different marfanoid habitus, nasal dysarthric speech, long great toes, chest deformity
Simpson-Golabi-Behmel syndrome, type 1	**GPC3(XLR)**	A primordial overgrowth syndrome, coarse facies, CHD
Hypogonadotropic hypogonadism 1 with or without anosmia (Kallmann syndrome 1)	**ANOS1(XLR)**	Hypogonadotropic hypogonadism (Congenital), micropenis, renal anomalies, hypo or anosmia
Craniofrontonasal dysplasia	**EFNB1(XLD)**	Coronal craniosynostosis, hypertelorism, & female more severe involvement
Orofaciodigital syndrome I	**OFD1(XLD)**	Lobulated tongue, variable intellectual differences and finger anomalies
Aicardi syndrome	**-- (XLD)**	Callosal agenesis, infantile spasms, and chorioretinal lacunae ('holes')
Focal dermal hypoplasia	**PORCN (XLD)**	Mucosal multiple papillomas, focal dermal atrophy, and linear pigmentation
Goeminne TKCR syndrome	**-- (XLR)**	Torticollis, cryptorchidism, varicose veins, renal dysplasia, keloid formation, and nevi

Note: First Need to evaluate for anatomical source of asymmetry

The chromosome passenger complex (CPC): survivin and the kinase aurora B regulate chromosome alignment and segregation by controlling both the dynamic association of survivin with centromeres and the proper targeting of survivin and aurora B to centromeres, which leads to the formation of bioriented chromosomes on the metaphase spindle.



Possible genotype and phenotype correlation for USP9X gene

Counsel plan for the family for case IV:1- Yielding (High/low) of a molecular test for an Intellectual different(ID) case depends upon the phenotype (syndromic /non-syndromic), severity (Severe/ Mild), family history (present/absent), Study plan (trio/ single). In this case scenario, yielding is quite high. First- try to collect molecular diagnosis of proband and send the maternal sample for carrier testing. Suppose none of the carrier females have clinical features (in the family pedigree). In that case, only the result is declared as affected or not affected to avoid the sex identity of the fetus. https://www.indiacode.nic.in/bitstream/123456789/8399/1/pre-conception-pre-natal-diagnostic-techniques-act-1994.pdf

Thought Riveting:

- ***What are other major proteins involved in intracellular protein turnover besides the ubiquitin-proteasome system (UPS) & chaperones?***
- ***How does a deubiquitinase inhibitor work as anticancer therapy?***
- ***What is the evolutionary value for skipping of selected genes' inactivation on the X chromosome?***
- ***What are the USP9X dependents proteins responsible for the phenotype of turner syndrome?***

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