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From the desk of Editor

The Genetic Division of the Pediatric Department publishes a monthly newsletter for all medical professionals. The newsletter pertains to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Neurogenetics -XXIV/ Dysmorphic / Intellectual deficiency /X-Linked/ Intellectual developmental disorder, X-linked syndromic, Siderius type; MRXSSD

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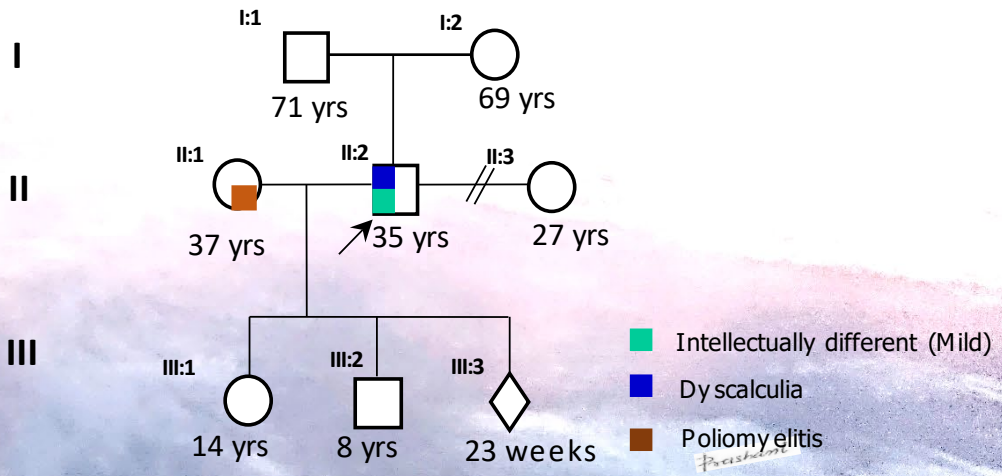


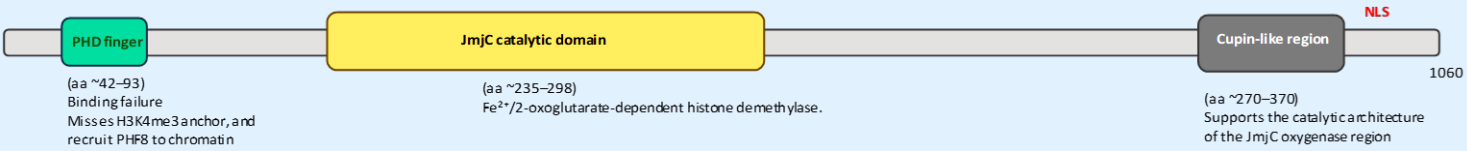
Insight:

1. Just after learning about her husband's hereditary disease, Case II:1 wants to terminate the current pregnancy (case III:3), even without conducting any genetic evaluation of this fetus. How would you counsel her?
2. What does a broad nasal tip mean, and how do you approach an XL ID case with BNT?
3. What are various PHF8 protein domains? Discuss their functions and the possible impact on phenotypic variability?
4. What is the **Sequence Variant Classification v4 (SVCv4)**? What are the newer changes in SVCv4?
5. How can dyscalculia help in approaching a case of syndromic intellectual difference?

Plausible tenets:

Gene: PHF8 (plant homeodomain (PHD) finger protein 8) Xp11.22,
Genomic coordinates (GRCh38): X:53,936,680-54,048,936

- As an epigenetic regulator, it belongs to the PHF protein family, which has small, zinc-binding protein domains (50–80 AA) act as epigenetic "readers" of chromatin by recognizing particular histone modifications (especailly histone H3) through histone lysine demethylase (KDM). There are many other PHF proteins with specialized functions.
- It is an Fe^{2+}/2-oxoglutarate-dependent histone lysine demethylase that preferentially removes mono- and dimethyl groups from specific histone lysine residues
- Histone mark → PHD-finger recognition → PHF protein recruitment → Chromatin regulation → Gene-expression changes.
- Disease state: Reduced or abnormal PHF8 function→lack of histone demethylation→abnormal regulation of developmental genes→ disrupted brain/developmental processes→intellectual/developmental disability.
- **PHF8 overexpression** has been reported in multiple cancers and is associated with increased tumor progression. This oncogenic role represents a somatic cancer-associated phenotype.
- Gene **PHF8 (ENSG00000172943):** 112.257 kb, 205 orthologues, 4 paralogues and 31 splice variants.
- Transcript **ENST00000338154.11 PHF8-202**: 22 exons and 21 coding exons; 34 domains and features; transcript length: 6,357 bps.
- Protein: 1,024 AA with a molecular mass of 113,913.43 Da.
- Conserved domains (**PHD_PHF8-** Chromatin/histone-mark reader, **JmjC-** Catalytic histone-demethylase domain, **Cupin-like-** contributes to the structural/catalytic architecture of the JmjC oxygenase region).



Phenotype: X-linked recessive with the **most distinctive constellation**: intellectual/developmental different, characteristic facial dysmorphism, with microcephaly and variable other craniofacial abnormalities.

Clinical phenotype spectrum:

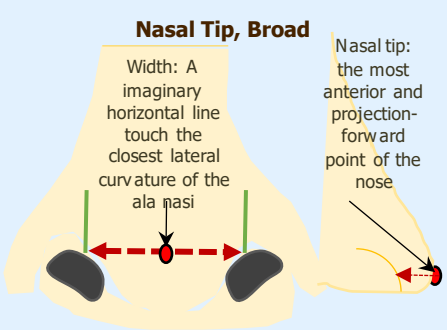
- **Neurological (Major):** ID (mild to severe), developmental delay (100%), ASD, ADHD, delayed speech and language development, delayed motor development, learning difficulties, dyscalculia (6%).
- **Craniofacial anomalies:** long/elongated face, broad nasal bridge, prominent supraorbital ridges, upslanting palpebral fissures, hypertelorism, ptosis, facial asymmetry, cleft lip, cleft palate, low set ears, and microcephaly.
- **Musculoskeletal**- large hands; variable skeletal findings
- Genotype-Phenotype Correlations:

Category	Genotype / variant type	Molecular consequence	Associated phenotype
Loss-of-function / truncating variants	Nonsense/stop-gain, frameshift, splice-site, early truncating variants	Premature termination, abnormal splicing, or truncated PHF8 → loss of PHD/JmjC function	Intellectual disability, developmental delay, speech/motor delay, facial dysmorphism, and variable cleft lip/palate
Catalytic / functional-domain variants	Missense variants in the JmjC catalytic region; variants affecting the PHD or JmjC domains	Reduced histone-demethylase activity and/or impaired histone-mark recognition and chromatin targeting	Neurodevelopmental abnormalities, including intellectual disability/developmental delay, with variable craniofacial and orofacial abnormalities
Partial-function / uncertain variants	Hypomorphic variants and variants with uncertain functional effects	Partial reduction or uncertain alteration of PHF8 function	Variable/milder phenotype, including mild intellectual disability, learning difficulties, dyscalculia, and variable facial features

- Management:
  - **Neurodevelopmental & Behavioral Management:** speech/language therapy, physiotherapy, occupational therapy, individualized education, behavioral/psychiatric management, seizure treatment when required.
  - **Craniofacial & Medical Management:** cleft lip/palate repair, dental/orthodontic care, feeding support, hearing/vision assessment, management of epilepsy and other associated complications
  - **Genetic & Long-term Support:** genetic counseling, family/at-risk relative testing, recurrence-risk counseling, reproductive counseling, multidisciplinary long-term follow-up

Nasal Tip, Broad

- Nasal tip width is measured at the spot where the outer sides of the nostrils (the alae) meet the tip of the nose
- Best Angle: This width is easiest to see when looking at the nose from underneath.
- Nose Shapes: It is much easier to measure on people who have a slightly square-shaped nasal tip.
- Measurement Tools: There are no exact measurement tools for this yet.
- Most of the genes related to impact the development of the frontonasal prominence.
- The Process: **Cranial Neural Crest Cells (CNCCs)** migrate from the developing brain area into the face during the **4th to 8th weeks** of embryonic development.



A X-Linked case of **"Broad nasal tip"** with 'variable intellectual difference' (below normal), and 'neurological/neurodevelopmental findings'

In OMIM, we have selected out **10 entries from 159 entries with the search key "broad nasal tip",** with broad nasal tip **as frequent finding with neurobehavioral features and X linked inheritance**.

Broad nasal tip is a nonspecific extended feature of craniofacial dysmorphism with marked genetic heterogeneity, and finding it alone has limited diagnostic specificity.

No.	OMIM	Disorder / Syndrome	Gene	MOI	Molecular Function	Key Clinical Features
1	300263	Intellectual Developmental Disorder, X-linked, Syndromic, Siderius Type (MRXSSD)	PHF8	XL-R	Histone demethylase / chromatin regulator; regulates histone methylation and transcription	Developmental delay, long face, **cleft lip/palate**, preaxial polydactyly, **large hands**, hypotonia, **behavioral abnormalities**
2	300148	MEHMO Syndrome	EIF2S3	XL-R	Translation initiation factor (eIF2γ); essential for protein synthesis and cellular stress responses	Microcephaly, epilepsy, **hypogonadism,** obesity, growth retardation, hypotonia, feeding difficulties, **characteristic facial features (diastema with long philtrum)**
3	309590	Intellectual Developmental Disorder, X-linked, Syndromic, Turner Type (MRXST)	HUWE1	XL	E3 ubiquitin-protein ligase; regulates protein stability and degradation, including developmental signaling proteins	Severe speech delay, short stature, **microcephaly/macrocephaly**, facial dysmorphism, hypotonia, seizures, **delayed bone age**
4	300844	Intellectual Developmental Disorder, X-linked 19 (XLID19)	RPS6KA3	XL	Serine/threonine protein kinase (RSK2); downstream effector of the RAS–MAPK/ERK pathway	Developmental delay, prominent forehead, **facial coarsening, hypotonia,** speech delay, skeletal abnormalities, **scoliosis,** short stature
5	300431	Atkin-Flaitz Syndrome	Unknown	XL-D	Molecular function not established	**Macrocephaly**, short stature, prominent forehead, **hypertelorism**, anteverted nares**, thick lower lip,** seizures, obesity, skeletal abnormalities
6	300166	Microphthalmia, Syndromic 2 / Oculofaciocardiodental Syndrome (MCOPS2/OFCD)	BCOR	XL-D	Transcriptional corepressor / chromatin regulator; component of BCOR/Polycomb-associated repression complexes	**Microphthalmia/anophthalmia, dental radiculomegaly, delayed tooth eruption**, cleft palate/bifid uvula, congenital heart defects, skeletal abnormalities
7	305600	Focal Dermal Hypoplasia / Goltz Syndrome	PORCN	XL-D	O-acyltransferase required for Wnt ligand secretion; essential for Wnt signaling	**Dermal hypoplasia, linear skin abnormalities,** pigmentary changes, papillomas, limb defects, syndactyly/ectrodactyly, abnormal nails, ocular and dental abnormalities
8	311450	Pallister-W Syndrome	Unknown	XL	Not established	Seizures, short stature, characteristic facies, **hypertelorism,** prominent forehead, **cleft/submucous palate,** dental abnormalities, **limb abnormalities**
9	300127	Oligophrenin 1 / OPHN1-related X-linked Intellectual Disability	OPHN1	XL	Rho-GTPase activating protein (RhoGAP); regulates cytoskeleton, neuronal morphology and synaptic development	Developmental delay, **cerebellar hypoplasia**, hypotonia, seizures in some individuals, facial dysmorphism, **genital abnormalities**
10	300373	Osteopathia Striata with Cranial Sclerosis (OSCS)	AMER1	XL	Wnt/β-catenin pathway regulator; interacts with β-catenin-associated signaling machinery	**Osteopathia striata**, **cranial sclerosis, macrocephaly**, hypertelorism, prominent forehead, **hearing loss**, dental abnormalities, skeletal abnormalities

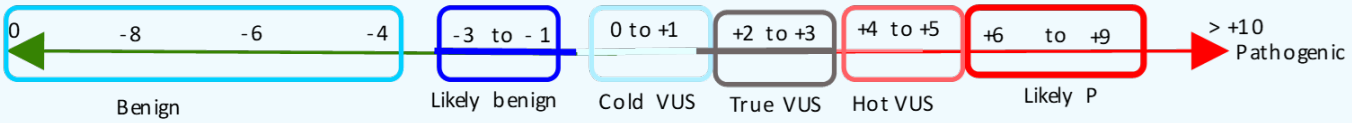
Sequence Variant Classification v4 (SVCv4)

https://hgsa.org.au/Web/Web/News/Articles/SVCv4_260731.aspx

- Development Phase: joint efforts by ACMG, AMP, CAP, and ClinGen.
- Testing: Expanded community pilot phases are underway
- Expected Publication: Oct 2026, **Genetics in Medicine**, for late stage piloting, and expected use for clinical laboratories in 2027.

Key Changes in SVCv4

- **Bayesian Points System:** Replaces rigid categorical combination matrices with structured point values
- **Evidence Reorganization:** Preventing double-counting of criteria by consolidating overlapping observations
- **VUS Sub-tiering:** Added a method to subdivide Variants of Uncertain Significance (VUS) based on the quantitative likelihood of pathogenicity ("Hot" VUS (4 to 5 points) / "Cold" VUS (0 to 1 points).
- **Decision Trees:** Structured flow diagrams and explicit gene-disease validity trees.



How Evidence Packages Assemble into Points

[+8 Points]	Very Strong Evidence	(e.g., Confirmed PVS1 Loss-of-Function)
[+4 Points]	Strong Evidence	(e.g., Confirmed PS2 De Novo mutation)
[+2 Points]	Moderate Evidence	(e.g., PM2 Rare Population Frequency)
[+1 Point]	Supporting Evidence	(e.g., PP3 Computational Predictor)

Dyscalculia

- **A specific learning disorder** characterized by persistent difficulty in acquiring age-appropriate **mathematical skills despite adequate education and normal opportunity to learn. (DSM-5-TR (Specific Learning Disorder with Impairment in Mathematics)**
- **Four core criteria irrespective of age: (PDOE)**
  - **Persistence:** for at least **6 months**
  - **Discrepancy:** substantially and quantifiably below **at least 1 standard** deviation below the mean on standardized
  - **Onset:** begin during **school-age years;** however, it is not fully manifest until **academic demands exceed the child's capacities**
  - **Exclusion:** cannot be better explained by other **sensorineural or environmental factors.**
- **Red flags include:** difficulty counting, recognizing quantities, comparing more/less, and learning number concepts.
- **It involves impaired number sense, counting, understanding quantities, calculation, arithmetic facts, and mathematical reasoning.**
- **Clinical relevance: OMIM search with "Dyscalculia" has very limited differential diagnoses; there are only eleven entries in clinical synopses: OMIM 618918:** Periventricular Nodular Heterotopia 9**, OMIM 141500:** Familial Hemiplegic Migraine 1**, OMIM 600795:** Frontotemporal Dementia and/or Amyotrophic Lateral Sclerosis 7**, OMIM 607485:** Frontotemporal Dementia 2, **OMIM 105550:** Frontotemporal Dementia and/or Amyotrophic Lateral Sclerosis 1, **OMIM 180849:** Rubinstein-Taybi Syndrome 1, **OMIM 616939:** Childhood-Onset Chorea with Psychomotor Retardation**, OMIM 607822:** Alzheimer Disease 3, **OMIM 300263:** X-Linked Syndromic Intellectual Developmental Disorder Siderius Type, **OMIM 615656:** Chromosome 15q11.2 Deletion Syndrome**, OMIM 618798:** Beck-Fahrner Syndrome.

Genetic Counseling a woman in this deeply complex and emotionally exhausting situation:

1st – Validate her circumstances and confirm her autonomy –Acknowledge that caring for a mentally handicapped husband presents immense emotional, financial, and logistical challenges. this validates her anxiety about her family's future. Clarify that under Indian law, her husband's consent is not legally required.

2nd – Explain the legal boundaries: within the 20-to-24-week statutory window, according the MTP Act, it legally requires the **similar opinion** of two registered medical practitioners **(RMPs).** There is **no need to conduct genetic testing to confirm fetal well-being** if continuing the pregnancy poses a grave risk to the woman's physical or mental health.

3rd – Essential counseling message- Ethically, there is no need to undergo genetic testing in this present scenario: "father affected with X linked recessive disease." All daughters will be carriers, and all male offspring will be unaffected, because they would inherit only Y from their father**.**

Thought Riveting:

- *Why is dyscalculia usually underreported in the community even having a similar frequency to dyslexia, and ADHD?*
- *How does high dose of folic acid interact with PHF8 gene function? Is there any protective role against cancer through this interaction?*
- *Can MS-8 (first-in-class, highly selective small-molecule allosteric activator of USP7) change the MRXSSD disease course?*
- *What could the phenotype be with germline gain of function variants of PHF8?*