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Neurogenetics -XXIII / Dysmorphic / Intellectual deficiency /X-Linked/ Intellectual developmental disorder, X-linked syndromic, Bain type (HNRNPH2-Related Neurodevelopmental Disorder)

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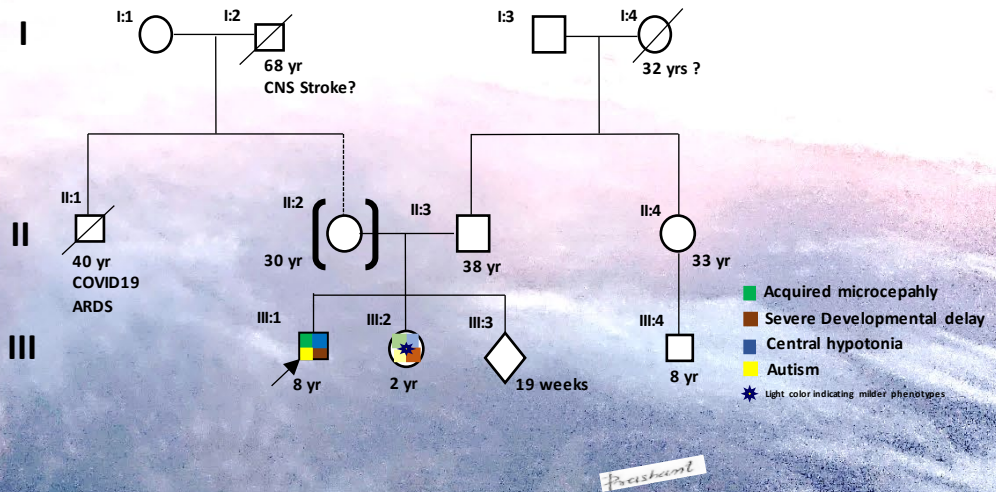
From the desk of Editor

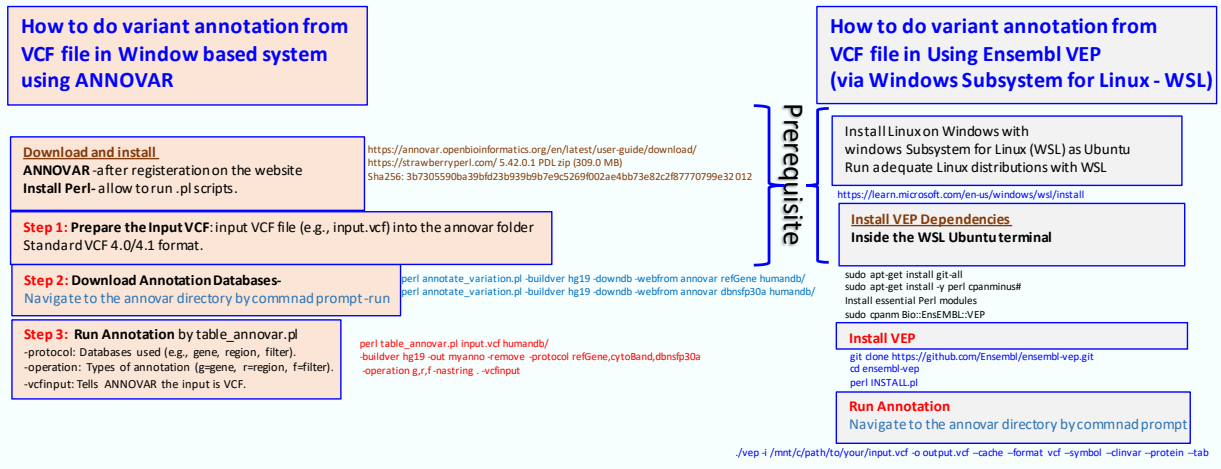
The Genetic Division of the Pediatric Department publishes a monthly newsletter for all medical professionals. The newsletter pertains to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.



Insight:

1. How to do variant annotation from VCF file in a Window based system?
2. What is the Karyopherinopathy?
3. What is the genotype and phenotype correlation of HNRNPH2-related neurodevelopmental disorder?
4. How shift to productive splicing happen with HNRNPH1?
5. When should you suspect, and how can you confirm germline mosaicism?
6. How would you counsel the Case III:3 regarding prenatal testing?

Variant annotation from VCF file



Tool	Best For	Windows Implementation
ANNOVAR	Fast annotation, Disease studies	Strawberry Perl + Command Line
VEP	Comprehensive/Official Ensembl	WSL (Ubuntu) or Docker
SnpEff	Rapid, gene-based annotation	Java-based (works in CMD)
VarAFT	Visual filtering (GUI)	Standalone Windows Installer

Plausible tenets:

Gene: HNRNPH2 (Heterogeneous Nuclear Ribonucleoprotein H2) Xq22.1, genomic coordinates (GRCh38): X:101,408,222-101,414,133

- Molecular cDNA cloning and **amino acid microsequencing** methods were used to discover the HNRNP H/F subfamily**)** in 1995 by Honoré et al. Its functional role was identified in 2016 before the discovery of its phenotypes. Having the three Quasi-RRM Domains (qRRMs) allows them to bind and recognize G tract sequences on RNA.
- A protein family of heterogeneous nuclear ribonucleoproteins (hnRNP), labeled A to U (over 20 proteins) as a major and numerous others as minors, and orchestrated the RNA metabolism (splicing, transport, stability, and translation).
- **HNRNPH2** is predominantly a nuclear protein, except mutations in PY-NLS lead to cytoplasmic accumulation as as toxic RNA granules, which are usually counted as more severe phenotype due to toxic gain of function, loss of compensatory mechanism as upregulation of >95% identical paralog **HNRNPH1**. **(PMID: 34907471, located on 5q35.3)**
- Gene: 6,024 bases, 127 orthologues, 10 paralogues and 2 splice variants.
- Transcript: 2 exons and 1 coding exon; 24 domains and features; transcript length 2,296 bps.
- Protein: 449 AA with a molecular mass of 49,264 Da.

Phenotype: X Linked Intellectual different (below normal), complex behavioral abnormalities, and dysmorphic features.

Clinical phenotype spectrum:

- **Neurological (Major):** a rapidly progressive complex neurodegenerative disorder with various psychiatric problems(attention deficit-hyperactivity disorder, anxiety, autism spectrum disorder, self-injurious behavior, and aggression), abnormalities in muscle tone (hypotonia or hypertonia), severe linguistic impairment, abnormal movements (ataxia, athetoid, tremors, and dyskinesia), late onset epilepsy (after preschool age), and acquired microcephaly (1/3 cases).
- **Dysmorphic features (Minor):** short palpebral fissures, almond-shaped eyes, long columella, micrognathia, hypoplastic alae nasi, full lower lip, and short philtrum.
- **Other systems:** (**mostly secondary**) progressive musculoskeletal deformities like contractures that can lead to spinal changes (scoliosis and lordosis), pectus carinatum, joint laxity (positive beighton criteria), short stature, and GERD.

Genotype-Phenotype Correlation Chart (HNRNPH2)

Genotype / Mutation Type	Associated Phenotype	Clinical Features
Missense (NLS-linked)	**Severe HNRNPH2-NDD** (Bain Type)	All major with variable minor features
Missense (Non-NLS)	**Variable / Milder Spectrum**	Milder major and minor features
Males (Hemizygous)	**Variable to Severe**	Depends on genotype
Females (Heterozygous)	**Highly Variable**	Mildly affected to highly variable phenotypes

Karyopherinopathy

- Karyopherins (Kaps) a nuclear transport receptor (95–145 kDa) family that guide the movement of RNA and proteins between the cytoplasm and nucleus through nuclear pore complexes (NPCs). **The Ran-GTPase** gradient helps Kaps in the regulation of importins (importing cargo into the nucleus) or exportins (exporting cargo out). Additionally, they prevent misfolding and aggregation of proteins, thus behaving like **a molecular chaperone**.

- Karyopherin abnormalities that lead to the disruption of the transport between the nucleus and cytoplasm. Excess accumulation in either side leads to protein mislocalization, aggregation, and cellular toxicity.

- Associated diseases: Spinocerebellar Ataxia Type 3 (SCA3), Huntington's disease, amyotrophic sclerosis, Alzheimer's and Parkinson's diseases, and Frontotemporal Dementia (FTD)

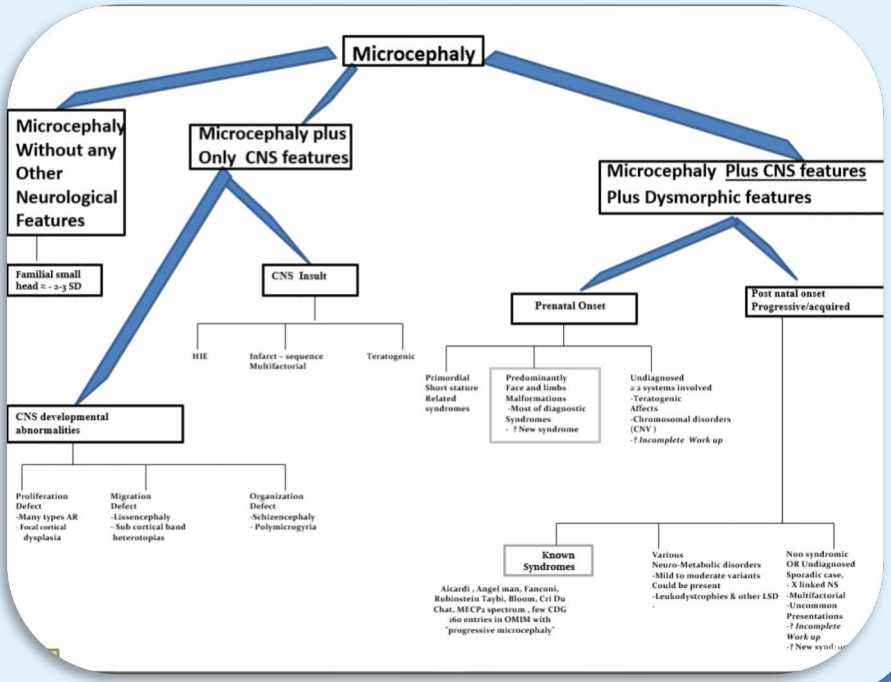
Clinical approach for a case with Microcephaly

Microcephaly

* ≥2 standard deviations (SD) below the mean (or < 3rd percentile) for a child's age, sex, and gestation at birth

Rationale for using < -3 SD as Significant Microcephaly

- Higher diagnostic yield by neuroimaging: up to 80 % versus (40 to 60 % with <-2SD)
- Defining severe phenotype (50-75 % LD) so more likely need urgent intervention (up to 89% normal development at – 2 SD)
- -2 SD considered as borderline in the fetus
- Less likely due to isolated environmental aetiologies
- -2 SD can be an isolated familial trait (up to 2.3%), so increased false positivity
- Strong correlation with brain volume with negative impact
- Constitutional: between -2 and -3 SD as "borderline" or "mild" microcephaly, which may still be benign (constitutional).



How does the Shift to Productive Splicing happen with HNRNPH1(>95% AA similarities with HNRNPH2)

HNRNPH2 protein availability regulates HNRNPH1 splicing coordination primarily through functional redundancy, transcriptional control, and co-regulation of common RNA targets. Although both work together to manage the splicing of G-rich motifs to a certain extent, HNRNPH1 may act as a more dominant, or "master," regulator of the family's total expression level. It acts as a "splicing coordinator." It ensures the correct inclusion or skipping of specific exons to produce functional, full-length protein-coding mRNAs rather than non-functional or unstable transcripts.

PGC for Case III: 3 –Both parents are phenotypically normal with negative blood tests, we should suspect germline mosaicism (often estimated up to 1% only). Testing for germline mosaicism must be tailored. It depends upon the particular disease databases, clinical decision, cost, and family willingness. Either sperm, or somatic tissue sampling is used for confirmation; however, the yield of the test is approximately low (4% to 8% or more of de novo variant cases). If test comes positive in either parent, recurrence risk is 50 %, and if it comes negative then it is estimated as 1%. Therefore, antenatal testing can be planned for target variants (if detected in proband) in case III:3.

Thought Riveting:

- *What are the genetic disorders associated with mutations in the Proline-Tyrosine Nuclear Localization Signal (PY-NLS)?*
- *Could Selective Stimulator of Nuclear Export (SSNE) modify the HNRNPH2 related phenotypes?*
- *Can regulating the "poison exon" mechanism be utilised as new therapeutic targets for various cancers, and inherited diseases?*
- *Why are HNRNPF/H family genes located on selected chromosomes (4, 5, 10, and X)?*