DOI: 10.13140/RG.2.2.30477.29923

Rishi vansh

All India institute of Medical Science Rishikesh (AIIMSR)

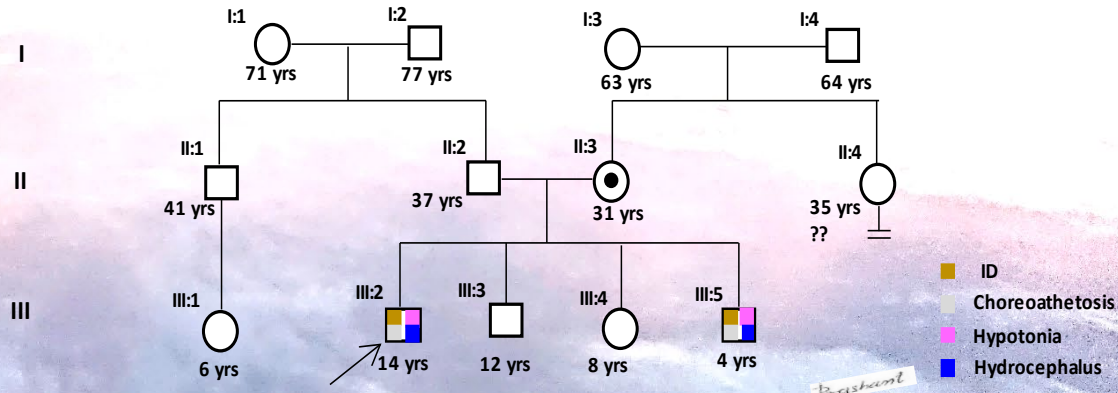
Volume 7, Issue 6, June 2026

Neurogenetics -XXIV/ Dysmorphic / Intellectual deficiency /X-Linked/ Intellectual developmental disorder, X-linked syndromic, Pettigrew syndrome

Author: Prashant Kumar Verma[1], Hitesh Poonia[2]
[1]Chairperson of Medical Genetic division, [2]Junior Resident in Pediatric, department of Pediatrics, AIIMS Rishikesh, Uttarakhand, India
Reviewer: Dr. Raksha Ranjan
1 Department of Pediatrics, AIIMS Bathinda, Punjab, India

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 should genetic counseling be approached for fetuses with **isolated posterior fossa abnormalities** in anomaly scan?
2. What are the possible differential diagnoses in a case with posterior fossa abnormalities associated with mild-to-severe intellectual disability and behavioral disturbances?
3. What are the adaptor protein complexes?
4. How can Rare Exome Variant Ensemble Learner **(REVEL)** scores from NGS data help determine whether a rare missense variant in a gene is likely pathogenic and clinically actionable?
5. What is the genotype and phenotype correlation of AP1S2 related ID?
6. What is **adaptor protein complexopathies (APC)**?

Rare Exome Variant Ensemble Learner (REVEL)

https:// revelgenomics/downloads

- REVEL is an ensemble computational tool used to predict (probabilistic rather than definitive) the pathogenicity of ONLY for rare missense variants identified through NGS-based tests (WES, WGS, & target gene panels)
- REVEL integrates outputs from multiple in silico prediction algorithms [integrates 13 individual prediction tools (sometimes described as 18 individual scores derived from those tools)] into a single score ranging from 0 to 1.
- <0.3 Likely benign
- 0.3–0.5 Uncertain significance
- >0.5 Possibly pathogenic
- >0.75 Stronger support for pathogenicity
- **The commonly listed integrated tools are:** **MutPred, FATHMM,** VEST, **PolyPhen-2**, **SIFT,** PROVEAN, **MutationAssessor,** MutationTaster, LRT, GERP++, SiPhy, phyloP, phastCons
- **Clinical Utilities of REVEL:**
  1. Variant Prioritization in NGS Pipelines (faster, decreased work burden, decreased turn over time, & improved workflow efficiency).
  2. Classification of Variants of Uncertain Significance (VUS) → help reclassify a VUS (PP3 → "Multiple computational tools support a deleterious effect").
  3. Clinical Decision-Making- patient surveillance, family screening, therapeutic planning, and cascade genetic testing.
  4. Rare Disease Diagnosis- cardiovascular genetics, neurogenetic disorders, metabolic diseases, and pediatric rare diseases.
  5. **Functional Interpretation Support.**
  6. Role in Cancer Genomics (Emerging Utility).

Steps: By using Ensembl VEP https://asia.ensembl.org/Tools/VEP : Run VEP with REVEL plugin:

```
vep -i input.vcf \
--plugin REVEL,/path/to/revel_data.tsv.gz
```

Minimal Input You Need: Chromosome Position Reference allele Alternate allele Genome build (hg19 or hg38);
for example: **chr7 140453136 A T hg19**

Plausible tenets:

Gene: AP1S2 (Adaptor Related Protein Complex 1 Subunit Sigma 2) Xp22.2, genomic coordinates (GRCh38): X:15,825,806-15,854,813

- It is a sigma-2 subunit of the Adaptor Protein Complex 1 (AP-1). It is important for normal receptor recycling, dendritic membrane trafficking, neurotransmitter receptor localization, lysosomal enzyme targeting, impaired autophagic flux, and neuronal membrane composition, causing a "neuronal intracellular trafficking disorder," where impaired protein sorting during embryonic brain development particularly disrupts cerebellar morphogenesis, basal ganglia integrity, and cortical neuronal function.
- Gene: ~29 kb, 295 orthologues, 6 paralogues and 14 splice variants.
- Transcript: 5 exons and 4 coding exons; 1 conserved domain and feature; transcript length 2,237 bp.
- Protein: 157 AA with a molecular mass of 17,700 Da.

Phenotype: X-Linked with the **most distinctive constellation**: Intellectual difference (below normal), seizures, movement disorder, basal ganglia abnormalities and Dandy–Walker/posterior fossa abnormalities. Females may have milder phenotype.

Clinical phenotype spectrum:

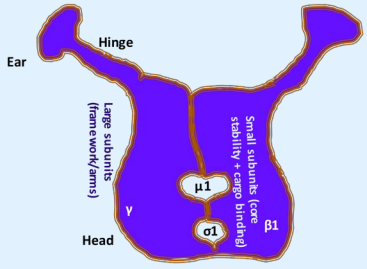
- **Neurological (Major):** ID (moderate to severe), early onset hypotonia, and delayed motor milestones(50%); brain structural abnormalities such as **Dandy-Walker malformation** (~17%), progressive **basal ganglia calcification** or iron deposition (~9–12%), and **hydrocephalus** (~76%); behavioral abnormalities (autistic traits, aggression, hyperactivity).
- **Dysmorphism:** a long face, high forehead, and prominent ears.
- Genotype-Phenotype Correlations:

Genotype / Variant Type		Reported Molecular Effect	Typical Phenotype
Nonsense variants (e.g., p.Arg52Ter, p.Gln66Ter)		Premature stop codon → truncated/nonfunctional protein	Microcephaly **(50% cases),** moderate–severe ID, delayed speech, hypotonia, aggressive behaviour, seizures
Splice-site variants	Non-leaky	Abnormal mRNA splicing and reduced protein production	ID with variable severity; hydrocephalus and basal ganglia calcification reported in some families, higher frequency of **seizures (~41%)** compared to nonsense variants
	Leaky	**Abnormal mRNA splicing and variable protein production**	Associated with **intrafamilial variability,** where some members have more severe verbal or motor impairments than others
Frameshift variants		Loss of normal sigma-1 subunit function	Developmental delay, impaired motor milestones, behavioral abnormalities
Missense variants (rarer)		Partial alteration of protein function	Usually milder or variable neurodevelopmental symptoms
Large deletions involving AP1S2		Complete loss of gene dosage	More severe syndromic presentation including epilepsy and structural brain abnormalities

Adaptor Protein Complex 1 (AP-1)

- **A heterotetrameric protein complex that helps in vesicular trafficking between the trans-Golgi network (TGN) and endosomes. It functions as a cargo adaptor that plays a key role in select membrane proteins for incorporation into clathrin-coated vesicles, ensuring proper sorting & distribution within the cell.**
- **Primary role: Cargo selection for clathrin-coated vesicles**
- **Localization: Trans-Golgi network and endosomes**
- **Subunit composition: γ, β1, μ1, and σ1 subunits**
- **Associated coat protein: Clathrin**
- **Functional process: Intracellular protein sorting and vesicle trafficking**

Organization of AP-1 clathrin adaptor complexes



A case of **"posterior fossa abnormalities"** with 'variable intellectual difference' (below normal), and 'behavioral disorders'

In OMIM, we selected out **24 entries from 80 entries with the search key (("posterior fossa" AND abnormalities)),** that have a triad of PFA with ID & BD +/- other additional key features to narrow down the DD

Disorder / Syndrome (OMIM)	Main Gene(s)	Key Clinical Findings	Characteristic Posterior Fossa / MRI Findings
Joubert syndrome, OMIM #213300	*AHI1, CEP290, TMEM67, CC2D2A* etc.	ID, hypotonia, ataxia, abnormal eye movements, autism/behavioral dysregulation	Vermian hypoplasia, molar tooth sign
Dandy–Walker malformation, OMIM #220200	Heterogeneous	Developmental delay, behavioral disorder, hydrocephalus, motor delay	Enlarged posterior fossa, cystic dilation of 4th ventricle, vermian hypoplasia
CASK-related intellectual disability, OMIM #300749	*CASK*	Severe DD/ID, microcephaly, autistic features, behavioral issues	Pontocerebellar hypoplasia
VLDLR-associated cerebellar hypoplasia, OMIM #224050	*VLDLR*	Moderate–severe ID, truncal ataxia, delayed ambulation	Cerebellar hypoplasia involving vermis/hemispheres
Lissencephaly 2, OMIM #257320	*RELN*	ID, epilepsy, autism-like behavior	Cerebellar hypoplasia with cortical malformations
PMM2-CDG (CDG-Ia), OMIM #212065	*PMM2*	ID, hypotonia, autism-like behavior, multisystem disease	Cerebellar atrophy/hypoplasia
PIGA deficiency, OMIM #300868	*PIGA*	Severe DD/ID, seizures, autistic behavior, hypotonia	Cerebellar atrophy/hypoplasia variably present
PIGN-related disorder, OMIM #614080	*PIGN*	Developmental delay, behavioral abnormalities, epilepsy	Cerebellar hypoplasia possible
OPHN1 syndrome, OMIM #300127	*OPHN1*	X-linked ID, aggressive/autistic behavior, hypotonia	Cerebellar hypoplasia, enlarged cisterna magna
Fragile X syndrome, OMIM #300624	*FMR1*	ID, autism, ADHD, anxiety, aggression	Mild vermian hypoplasia/structural cerebellar changes
PTEN hamartoma syndrome, OMIM #158350	*PTEN*	Macrocephaly, autism, behavioral dysregulation	Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos)
Phelan–McDermid syndrome, OMIM #606232	*SHANK3*	Autism, absent speech, behavioral dysregulation	Cerebellar volume loss/hypoplasia variably reported
FOXP1-related intellectual disability syndrome, OMIM #613670	*FOXP1*	Language impairment, autism spectrum disorder, ID	Mild cerebellar abnormalities occasionally
FOXP2-related speech-language disorder, OMIM #602081	*FOXP2*	Speech/language disorder, behavioral abnormalities	Cerebellar structural abnormalities reported
Pontocerebellar hypoplasia type 2, OMIM #277470	*TSEN54*	Severe developmental impairment, dystonia, behavioral features	Pontine and cerebellar hypoplasia
EXOSC3-related pontocerebellar hypoplasia, OMIM #614678	*EXOSC3*	Severe DD, hypotonia, respiratory issues	Pontocerebellar hypoplasia
Rett syndrome, OMIM #312750	*MECP2*	Regression, stereotypies, autistic behavior, ID	Cerebellar atrophy/volume loss
CAMTA1-related cerebellar dysfunction, OMIM #614756	*CAMTA1*	Ataxia, mild–moderate ID, behavioral symptoms	Cerebellar vermian atrophy
ATP1A3-related neurologic disorder, OMIM #182350	*ATP1A3*	Developmental delay, psychiatric/behavioral symptoms, movement disorder	Cerebellar atrophy variably present
CACNA1A-related neurodevelopmental disorder, OMIM #601011	*CACNA1A*	Autism, episodic ataxia, developmental delay	Cerebellar atrophy
Tuberous sclerosis complex, OMIM #191100	*TSC1, TSC2*	Autism, epilepsy, behavioral disorder	Occasionally cerebellar tubers/atrophy
Lhermitte–Duclos disease (Cowden Syndrome 1), OMIM #158350	*PTEN*	Autism, macrocephaly, cognitive impairment	Dysplastic cerebellar gangliocytoma
22q13 deletion syndrome (Phelan–McDermid syndrome), OMIM #606232	Terminal 22q13 deletion / *SHANK3*	Global DD, autism, hypotonia	Cerebellar vermian hypoplasia possible
COACH syndrome, OMIM #216360	*TMEM67* commonly	ID, autistic features, liver disease	Molar tooth sign + vermian hypoplasia

Adaptor protein complexopathies (APC)

- Adaptor Protein (AP) complexes are heterotetrameric vesicle-coat adaptor systems intricately involved in intracellular protein trafficking, endocytosis, lysosomal transport, and Golgi-endosome sorting. Five major AP complexes (AP-1 to AP-5) are known. Dysfunction of these complexes causes several neurological, pigmentation, immunological, and developmental disorders.
- Disorders involving clathrin-mediated trafficking ("clathrinopathies") can have very similar phenotypes because they disrupt the same intracellular transport pathway (cargo selection → AP complex recruitment → clathrin coat assembly → vesicle budding → endosomal/lysosomal trafficking).
- There are quite overlapping phenotypes across AP complex disorders:
  - Neurological Dysfunction (Most Universal Phenotype): Defective vesicle trafficking→ axonal degeneration→ progressive spastic paraplegia/neurodevelopmental disease.
  - Common Cytosolic phenotype: enlarged endosomes, accumulation of undegraded proteins, defective receptor recycling, and abnormal Golgi morphology.
  - Common Neuroimaging phenotypes: thin corpus callosum, cerebral atrophy, delayed myelination, ventriculomegaly, and leukodystrophy-like changes.

AP Complex	Major Function	Cellular Localization	Core Genes/Subunits	Important Diseases	Key Reference
AP-1	TGN ↔ endosome trafficking	Trans-Golgi network, endosomes	AP1G1, AP1G2, AP1B1, AP1M1, AP1M2, AP1S1, AP1S2, AP1S3	MEDNIK syndrome, Fried syndrome, pustular psoriasis	MEDNIK syndrome: PMID: 19859024; DOI: 10.1038/ng.454
AP-2	Clathrin-mediated endocytosis	Plasma membrane	AP2A1, AP2A2, AP2B1, AP2M1, AP2S1	Familial hypocalciuric hypercalcemia type 3, developmental epileptic encephalopathy	FHH3/AP2S1: PMID: 22508708; DOI: 10.1038/ng.1114
AP-3	Lysosomal and melanosomal trafficking	Endosomes/lysosomes	AP3B1, AP3B2, AP3D1, AP3M1, AP3M2, AP3S1, AP3S2	Hermansky–Pudlak syndrome type 2, neurological disorders	HPS type 2/AP3B1: PMID: 9973286; DOI: 10.1038/13935
AP-4	TGN-to-endosome trafficking	Trans-Golgi network	AP4B1, AP4E1, AP4M1, AP4S1	AP-4 deficiency syndrome, hereditary spastic paraplegia	AP-4 deficiency syndrome: PMID: 22265015; DOI: 10.1016/j.ajhg.2011.12.033
AP-5	Late endosomal trafficking	Late endosomes	AP5Z1, AP5B1, AP5M1, AP5S1	Hereditary spastic paraplegia type 48 (SPG48)	PG48/AP5Z1: PMID: 22305531; DOI: 10.1016/j.ajhg.2012.01.002

Genetic counseling approach for fetuses with isolated posterior fossa abnormalities (PFA) with a detailed targeted anomaly scan

1st – Confirm the anomaly and rule out other CNS anomalies – by Fetal MRI (usually best visualized at 22–24 weeks) normal developmental features can mimic abnormalities before that, so false-positive diagnoses are possible before 20–22 weeks.
2nd – Possible test yielding of fetal genetic testing: QF-PCR / karyotype (very less), QF-PCR / Chromosomal microarray (~5–10%), Exome sequencing (~5–15%)
3rd - Key counseling message: "Isolated" posterior fossa abnormalities are most often benign variants; however, small but real risk of chromosomal or subtle genetic syndromes remains. Hence, MRI + CMA/ +/- NGS are recommended even when everything looks isolated (as functional defects like ID and BD cannot be ruled out by scans).
Exact phenotype-wise prognosis in isolated posterior fossa abnormalities (Approx)

Lesion (Isolated)	Risk of Genetic/Chromosomal Abnormality	Neurodevelopmental Outcome	Key Counseling Point
Blake pouch cyst	<2–3%	>90% normal outcome	Usually benign; may regress or remain stable
Mega cisterna magna	<5%	90–95% normal outcome	Strongly favorable prognosis if truly isolated
Mild vermian hypoplasia	5–10%	80–90% normal or near-normal	Small risk of developmental delay; MRI confirmation important
Dandy–Walker variant (mild / partial forms)	5–15%	60–80% normal outcome	Prognosis varies; depends on vermis and ventricles
Isolated cerebellar hypoplasia (mild)	10–20% (higher than others)	Variable; 50–70% normal, rest may have delay	Higher uncertainty; consider genetic testing strongly

Thought Riveting:

- *What is a definitive cargo map that distinguishes between AP1S2-specific trafficking and redundant AP-1 pathways?*
- *How can trafficking pathway modulation drugs bring a revolution in precision therapeutics?*
- *Can somatic mutations of APC genes lead to various idiopathic autoimmune disorders?*
- *Are there any genotype and phenotype correlations for developing Dandy–Walker/posterior fossa abnormalities with AP1S2 variants?*