DOI: 10.13140/RG.2.2.28475.58403

Rishi vansh

All India institute of Medical Science Rishikesh (AIIMSR)

Volume 7, Issue 5, May 2026

Pulmogenetics-XVI/ Syndromes associated with Bronchiectasis / Periodic fever, immunodeficiency, and thrombocytopenia syndrome (PFITS)

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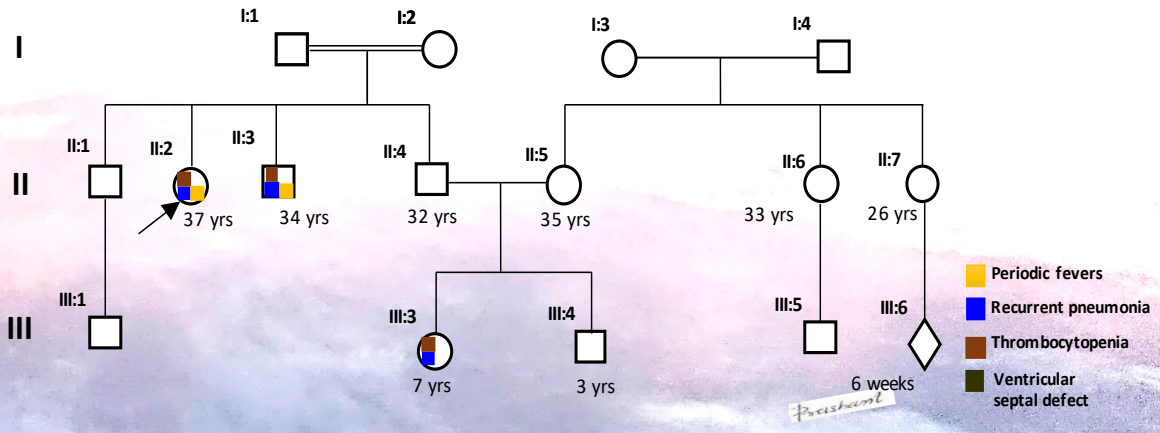
From the desk of Editor

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. What is the WD-repeat protein family?
2. What is the molecular pathology of PFITS clinical phenotypes?
3. What is the clinical utility of CADD scoring?
4. What are the genetic syndromes reported with "Periodic Fever"? How would you approach a case of hereditary periodic fever (**HPF**)?
5. Is there any need to perform a fetal echocardiogram beyond standard care, according to the available local guidelines, for Case II:7?

CADD (Combined Annotation Dependent Depletion) https://cadd.kircherlab.bihealth.org/

- A computational tool that **scores genetic variants** based on their predicted deleteriousness. It integrates multiple annotations (conservation, regulatory data, protein impact) into a single score, given as **C-scores (raw and PHRED-scaled).**
- **PHRED ≥10** → among top 10% deleterious variants; **≥20** → top 1% (more likely harmful).
- Helps in prioritizing variants in sequencing studies, especially rare variants. Applicable to both **coding and non-coding regions**.
- Does **not prove pathogenicity**—only predicts potential impact.
- It should always be interpreted in conjunction with ACMG criteria and the relevant clinical context.
- CADD is a powerful prioritization tool, but not a standalone diagnostic method—it guides, not decides, variant interpretation.

Plausible tenets:

Gene: WDR1 (WD Repeat Domain 1) 4p16.1, genomic coordinates (GRCh38): 4:10,074,339-10,116,799

- Discovered through studies of cell motility and cytoskeleton regulation in **1999 by H. J. Adler and colleagues at the Kresge Hearing Research Institute (University of Michigan); initially identified in chickens**.
- It belongs to **WD-repeat protein family**. It encodes AIP1 (Actin-Interacting Protein 1) protein, which regulates **actin filament dynamics**, controlling **cell shape, migration, phagocytosis, and division**.
- It is present inside the cytoplasm, particularly found in high-turnover areas of actin cytoskeleton, including the **cortical cytoplasm(gel-like, outer layer of cytoplasm, just beneath the plasma membrane), adherens junctions, and cell projections.** It controls actin turnover speed, so ensuring actin filaments are rapidly recycled.
- It plays an essential role in coordinating another protein (**cofilin**) to break down actin filaments as accelerator, and imperfectly disassembled actin filaments lead to significant cellular dysfunction.
- **Molecular pathology:** Impaired interaction with cofilin/actin → **Cytoskeleton becomes rigid and disorganized → Accumulation of F-actin → Cells become rigid and dysfunctional → leads to following consequences at cellular level:**
  - **Neutrophils:** Impaired chemotaxis and migration
  - **T cells:** Abnormal signaling and activation
  - **B cells:** Increased apoptosis and poor development
  - **Monocytes /macrophages (innate immune cells):** Cell damage signals (**DAMPs**) →triggers activation of the pyrin inflammasome (**esp. NLRP3**) → **activates caspase-1** →Increased IL-18 release, and (± IL-1β) →**Activation of innate immune pathways** →sterile inflammation (periodic fever, rash etc.)
  - **Platelets and hematopoiesis:** Decreased platelet shedding, and dysfunctional platelets
- Gene: Size ~48.9 kb, Number of 213 orthologues, Number of 40 splice variants
- Transcript: Total 15 exons & 15 coding exons; Number of 42 domains and features; transcript length 2993 bp
- Protein: Number of 606 AA with a molecular mass of 67 kDa
- Ubiquitously expressed, and overexpressed in the Immune-related cells (leukocytes) and tissues.

Phenotype: Periodic fever, immunodeficiency, and thrombocytopenia syndrome (**PFITS**), autosomal recessive **MOI** with highly variable manifestations.

Clinical phenotype spectrum:

- **Complex immunodysregulation phenotypes:**
  - **Autoinflammatory phenotype: Periodic fevers** (recurrent, self-limited episodes of fever occurring at irregular intervals, in the absence of infection), sterile inflammation (**raised inflammatory markers**), dermatological lesions (Oral ulcers / stomatitis/ abscesses/ pustular or neutrophilic dermatoses) with poor wound healing.
  - **Immunodeficiency**: Recurrent infections, and poor pathogen clearance (respiratory tract, skin, and soft tissue) but pus formation is less than expected, and increased susceptibility to viral infections (less than bacterial), and usually *overlapping with autoinflammatory component*
- **Thrombocytopenia:** Moderate to severe thrombocytopenia, normal or slightly reduced in size, defective functions, and normal or increased megakaryocytes
- **Management:** Symptomatic and preventive management
  Supportive online resources: Eurofever / PRINTO Criteria and Classification Work: **PMID: 31018962, and PMCID: PMC3194673.**

WD-repeat protein family (a highly conserved protein evolutionarily)

- Having **a WD (Tryptophan and Aspartic acid) repeat** is a short-conserved sequence **(~44–60 amino acids long),** that forms a **β-propeller.**
- **Main function:** Scaffolding proteins (**providing a platform for multiple proteins together into complexes**), and regulators of various cellular processes such as signal transduction, gene regulation, cell cycle control, apoptosis, cytoskeleton organization.
- The most commonly cited estimate WD-repeat proteins is approximately. 262; a few **examples include** β-TrCP (protein degradation), CDC20 (mitosis control), RACK1 (scaffold in signalling pathways), LIS1 (neuronal migration), and so on.

OMIM Entries with search tool- ("PERIODIC FEVER")

S. No.	Syndrome/ OMIM	Gene	MOI	Gene function	Other Phenotypes / key Clinical features (Possible mild overlapping features in other phenotypes)
1	HYPER-IGD SYNDROME /260920	**MVK**	AR	The MVK gene encodes mevalonate kinase which is involved in the biosynthesis of cholesterol and isoprenoid	**Mevalonic aciduria (610377)** Porokeratosis 3, multiple types / Failure to thrive, Hepato-splenomegaly, Oral ulcers, protein losing enteropathy
2	PERIODIC FEVER, FAMILIAL / 142680	**TNFRSF 1A**	AD	Preassembly or self-association of cytokine receptor dimers	Multiple sclerosis / Recurrent abdominal pain, variable age at onset, myalgias
3	PERIODIC FEVER, IMMUNODEFICIENCY, AND THROMBOCYTOPENIA SYNDROME/150550	**WDR1**	AR	WDR1 regulates cofilin-mediated actin filament turnover, enabling cellular tension, polarity, and dynamic shape changes required for normal cell function	Onset early childhood, aphthous ulcers, chronic lung disease, skin abscesses, immunodeficiency
4	PERIODIC FEVER, MENSTRUAL CYCLE DEPENDENT/614674	**HTR1A**	AD	The 5-HT1A receptor is a serotonin GPCR that regulates mood, cognition, and hippocampal neurogenesis, and is essential for the therapeutic effects of antidepressants	Fever recurrent with each menstrual cycle, symptoms relieved by ovarian suppression,
5	SIDEROBLASTIC ANEMIA WITH B-CELL IMMUNODEFICIENCY, PERIODIC FEVERS, AND DEVELOPMENTAL DELAY; SIFD/616084	**TRNT1**	AR	TRNT1 enables protein synthesis by adding the essential CCA tail to tRNA, allowing amino acid attachment and proper translation in both cytoplasm and mitochondria.	**Retinitis pigmentosa and erythrocytic microcytosis (616959)**
6	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME 2; FCAS2 / 611762	**NLRP12**	AD	NLRP12 is an innate immune regulator that suppresses NF-κB–mediated inflammation and maintains immune homeostasis, with a secondary role in inflammasome signaling	Age at onset from infancy to adult, episodic-urticaria, myalgias, and headache
7	YAO SYNDROME; YAOS / 617321	**NOD2**	Mu	NOD2 is an intracellular bacterial sensor that activates NF-κB, induces autophagy, and regulates immune responses, playing a key role in host defense and intestinal immune homeostasis.	Blau syndrome Inflammatory bowel disease 1, Crohn disease / dry eyes, dry mouth, serositis, oligopolyarthraligia of lower limbs predominantly
8	FAMILIAL COLD AUTOINFLAMMATORY SYNDROME 1; FCAS1 / 120100	**NLRP3**	AD	NLRP3 gene encodes a cytosolic receptor that forms the inflammasome, activating caspase-1 and promoting IL-1β/IL-18–mediated inflammation in response to cellular danger signals	CINCA syndrome, keratoendothelitis fugax hereditaria, muckle-wells syndrome/ variable age at presentation, **sensorineural hearing loss AD type 34(617772),** headache, systemic autoinflammation
9	AUTOINFLAMMATORY SYNDROME, FAMILIAL, BEHCET-LIKE 1; AIFBL1 / 616744	**TNFAIP3**	AD	TNFAIP3 (A20) is a ubiquitin-editing enzyme that shuts down NF-κB–mediated inflammatory signaling, maintaining immune balance and preventing excessive inflammation	Onset in first decade, oral ulcers, inflammatory bowel disease, uveitis, polyarthritis, genital ulcers
10	FAMILIAL MEDITERRANEAN FEVER; FMF / 249100	**MEFV**	AD	MEFV encodes pyrin, an innate immune regulator that controls inflammasome activation and IL-1β production, balancing host defense and inflammation	Onset in childhood or adolescent, acute attacks lasting 24 – 48 hours, nephrotic syndrome, serositis, orchitis
11	AUTOINFLAMMATION WITH INFANTILE ENTEROCOLITIS; AIFEC / 616050	**NLRC4**	AD	NLRC4 is an intracellular bacterial sensor that forms the inflammasome to activate caspase-1, inducing IL-1β/IL-18 production and pyroptosis for host defense	Familial cold autoinflammatory syndrome 4 / onset in neonatal or early infancy, enterocolitis remits with age, short stature, flares triggered with viral infection, overexertion and stress
12	NEURODEVELOPMENTAL DISORDER WITH LANGUAGE DELAY AND VARIABLE COGNITIVE ABNORMALITIES; NEDLC / 620502	**GABBR1**	AD	GABBR1 encodes a subunit of the GABA-B receptor that mediates inhibitory neurotransmission by reducing neuronal excitability and modulating synaptic signaling in the brain	-/ onset in early infancy, global developmental delay, dysmorphic facies, behavioural psychiatric manifestation
13	PROTEASOME-ASSOCIATED AUTOINFLAMMATORY SYNDROME 1; PRAAS1 /256040	**PSMB8**	AR	PSMB8 encodes LMP7, an immunoproteasome subunit that processes proteins into peptides for MHC class I presentation and regulates inflammatory immune responses	onset of autoinflammation in infancy, lipodystrophy later in life and lastly joint contracture, cardiac insufficiency and poor growth
14	AUTOINFLAMMATORY DISEASE, SYSTEMIC, X-LINKED; SAIDX / 301081	**IKBKG**	XL	IKBKG (NEMO) is an essential regulator of the IKK complex that enables NF-κB activation, coordinating immune responses, inflammation, and cell survival.	Autoinflammatory disease, systemic, X-linked, Ectodermal dysplasia and immunodeficiency 1, Immunodeficiency 33, Incontinentia pigmenti / onset in first month of life, chorioretinitis, hepatosplenomegaly, autoimmune anemia
15	AUTOINFLAMMATION WITH EPISODIC FEVER AND LYMPHADENOPATHY; AIEFL / 618852	**RIPK1**	AD	RIPK1 is a key signaling hub that integrates inflammatory and cell death pathways, controlling NF-κB activation, apoptosis, and necroptosis to maintain immune balance and tissue homeostasis	Immunodeficiency 57 with autoinflammation / onset in early infancy, hepatosplenomegaly, no rash, lymphadenopathy response to IL-6 inhibitors

Functional clusters: **Inflammasome / NLR proteins** → NLRP3, NLRP12, NOD2, NLRC4, MEFV; **NF-κB signaling** → TNFRSF1A, TNFAIP3, RIPK1, IKBKG; **Metabolism / stress** → MVK, TRNT1, PSMB8; **Neuro-immune modulators** → HTR1A, GABBR1; **Cytoskeleton / trafficking** → WDR1

Possible Functional Gene interaction:

MVK (Metabolism / Stress)→ MEFV (Inflammasome) → NLRP3 (Inflammasome) → NLRP12 / NLRC4 /NOD2 / TNFRSF1A → RIPK1 → TNFAIP3 → IKBKG → NF-κB **(Signaling Cascade)**

Peripheral Modulators:

WDR1, PSMB8, TRNT1, HTR1A, GABBR1 → NLRP3

A fetal echocardiogram for Case II: 7 – It is a better to perform a fetal ECHO as an additional test beyond standard care in caseII:7 **(recommended, not mandatory or legal guidelines).** The rationale behind that a fetal echo scan is often necessary for certain pregnancies, especially when there is a family history of heart disease (even for a sporadic multifactorial, or complex genetic diseases) in a previous child with heart defects, maternal health conditions, or if routine ultrasounds reveal concerns. Meanwhile, fetal ECHO with advanced techniques (3D/STIC imaging) has sensitivity (detecting CHD) up to 90% as compared to only 68 % sensitivity with the standard anomaly scan.

Thought Riveting:

- *What is the major site of the genomic site that needs to be targeted by genetic engineering to develop off-the-shelf stem cells that can be used for a wide range of inherited and acquired disorders?*
- *Are cofilin-1 gene defects incompatible with normal embryonic development?*
- *What could be the best strategy (approach) to build a phylogenetic tree for "WD-repeat" proteins?*
- *What is the clinical spectrum of Cytoskeleton-pathy?*