RISHI VANSH

DOI:10.13140/RG.2.2.24435.69922

All India institute of Medical Science Rishikesh (AIIMSR)

Volume 7, Issue 7, July 2026

Progeroid syndromes (PS)-VIII / Nestor-Guillermo progeria syndrome (NGPS)

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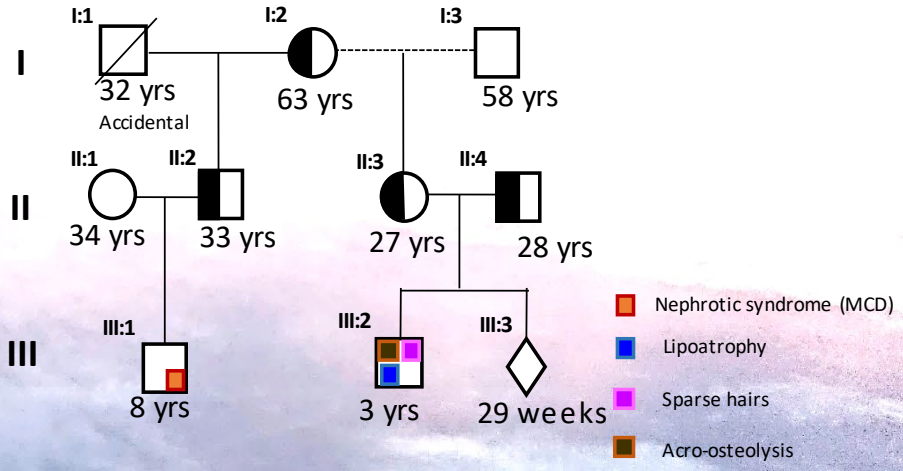

From the desk of Editor

The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.

Insight:

1. If the case III:3 comes out positive in an antenatal test, how would you counsel the family?
2. What does the network-level reference framework for nuclear envelope systems biology contain?
3. What are the clinical utilities of Multimodal Annotation Generated Pathogenic Impact Evaluator (MAGPIE)?
4. What is the most characteristic hallmark feature of NGPS?
5. What is the functional molecular anatomy of BANF1/BAF?

Nuclear Envelope Gene–Disease Atlas

The nuclear envelope (NE) is a highly organized double-membrane structure that separates the nucleus from the cytoplasm while coordinating genome organization, mechanotransduction, chromatin regulation, nucleo-cytoskeletal coupling, and nucleocytoplasmic transport.

- **Components of the NE:** Nuclear lamina; Inner nuclear membrane (INM); Outer nuclear membrane (ONM); Nuclear pore complexes (NPCs); LINC (Linker of Nucleoskeleton and Cytoskeleton) complexes; Chromatin tethering systems; Nuclear envelope repair and quality-control machinery.
- **Diseases Associated with NE Defects:** Aminopathies; Nuclear envelopathies; NPC disorders (nucleoporopathies); Mechanotransduction disorders; Progeroid syndromes; Chromatin tethering disorders.
- **Tissues Commonly Affected:** Skeletal muscle; Cardiac muscle; Brain; Adipose tissue; Bone; Kidney.
- **Structural Organization: Cytoplasm** → Cytoskeleton → Nesprins (SYNE proteins) → Outer Nuclear Membrane (ONM) → LINC Complex (SUN1/SUN2 proteins) → Inner Nuclear Membrane (INM) → Emerin, LBR, LAP2, LEMD proteins → Nuclear Lamina → Lamin A/C, Lamin B1/B2 → Chromatin / Genome → Nucleus
- **A network-level reference framework for nuclear envelope systems biology contains:** a mechanical organelle ("Mechanical Stability Network"), a signaling hub, a chromatin organizer, a transport interface, and a genome-protection system.

Category	Subcategory / Role	Gene Symbol(s)	Key Function	Associated Disease Phenotypes
Nuclear Lamina	Structural scaffold	LMNA	Lamin A/C – nuclear stability, genome organization	Hutchinson–Gilford progeria syndrome; Emery–Dreifuss muscular dystrophy; dilated cardiomyopathy; lipodystrophy
	Structural scaffold	LMNB1	Lamin B1 – structural integrity	Adult-onset leukodystrophy
	Structural scaffold	LMNB2	Lamin B2 – brain development	Neurodevelopmental defects (rare)
Inner Nuclear Membrane (INM)	LEM-domain proteins	EMD	Emerin – lamina binding	Emery–Dreifuss muscular dystrophy
	LEM-domain proteins	LEMD3 (MAN1)	TGF-β regulation	Osteopoikilosis; Buschke–Ollendorff syndrome
	LEM-domain proteins	LEMD2	NE integrity/repair	Cardiomyopathy; nuclear envelope rupture syndromes
	Lamin-associated proteins	TMPO (LAP2)	Chromatin anchoring	Cancer-associated dysregulation
	Lamin-associated proteins	LBR	Chromatin tethering	Pelger–Huët anomaly; Greenberg dysplasia
	SUN-domain proteins	SUN1	LINC complex	Muscular dystrophy (modifier role)
	SUN-domain proteins	SUN2	LINC complex	Cardiomyopathy (reported)
	Other INM proteins	ANKLE2	NE reassembly	Microcephaly
	Other INM proteins	TMEM43	Structural support	Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Outer Nuclear Membrane (ONM)	Nesprins	SYNE1	Nuclear–cytoskeletal linkage	Cerebellar ataxia; muscular dystrophy
	Nesprins	SYNE2	Cytoskeleton linkage	Emery–Dreifuss–like disease
	Nesprins	SYNE3	Actin linkage	Limited/unclear disease association
	Nesprins	SYNE4	Microtubule linkage	Hearing loss
LINC Complex	Core components	SUN1, SUN2	Nucleus–cytoskeleton bridge	Myopathies; cardiomyopathies
	Core components	SYNE1–4	Force transmission	Neuromuscular disorders
	Regulators	TOR1A	AAA+ ATPase	Early-onset torsion dystonia
	Regulators	TOR1AIP1	LAP1 – torsin regulator	Muscular dystrophy; progeroid features
Nuclear Pore Complex (NPC)	Scaffold NUPs	NUP205, NUP188, NUP155	NPC structure	NUP155: atrial fibrillation; sudden cardiac death
	NUP107 complex	NUP107, NUP133, NUP160	NPC assembly	Nephrotic syndrome (NUP107 mutations)
	Central channel	NUP62, NUP58, NUP54	Transport	Neurological disorders
	Cytoplasmic filaments	NUP214, NUP88	Nuclear transport	Leukemia (fusion proteins)
	Nuclear basket	NUP153, TPR	Nuclear organization	Cancer associations
	Membrane anchors	POM121, NDC1, NUP210	NPC anchoring	Autoimmune disease; cancer links
NE Assembly / Disassembly	Chromatin linker	BANF1 (BAF)	Chromatin–NE bridging	Néstor–Guillermo progeria syndrome
	Kinase	VRK1	BAF regulation	Microcephaly; neuropathy
	Phosphatase	PPP2CA	NE reassembly	Cancer (broad role)
	ESCRT machinery	CHMP7, CHMP4B	Membrane sealing	Cataracts (CHMP4B); NE rupture defects
	AAA ATPases	VPS4A, VPS4B	ESCRT recycling	Developmental disorders (rare)
Lipid Metabolism (Indirect)	Phospholipid synthesis	PCYT1A	Membrane formation	Spondylometaphyseal dysplasia
	Phospholipid synthesis	CEPT1	Phospholipid synthesis	Limited data
	Lipid modification	AGPAT2	Lipid metabolism	Congenital lipodystrophy
	Lipin proteins	LPIN1, LPIN2	Lipid regulation	Myopathy (LPIN1); Majeed syndrome (LPIN2)
	Transcription factors	SREBF1, SREBF2	Lipid homeostasis	Metabolic syndrome
Chromatin Organization	DNA linker	BANF1	Chromatin tethering	Progeroid syndrome
	Histone modifier	HDAC3	Gene repression	Cancer; developmental defects
	Heterochromatin	CBX1, CBX3, CBX5	HP1 proteins	Genome instability; cancer
	Tethering factor	PRR14	Heterochromatin anchoring	Cancer-associated dysregulation
	Epigenetic regulator	MECP2	DNA methylation binding	Rett syndrome
Cytoskeleton Coupling	Actin	ACTB	Nuclear mechanics	Baraitser–Winter syndrome
	Myosin	MYH9	Force transmission	MYH9-related disorder (macrothrombocytopenia)
	Dynein	DYNC1H1	Nuclear positioning	Spinal muscular atrophy-like disease
	Kinesins	KIFs	Transport	Neurological disorders
NE Quality Control / Repair	Torsin system	TOR1A, TOR1AIP1	NE integrity	Dystonia; muscular dystrophy
	DNA damage	ATM, ATR	Genome surveillance	Ataxia telangiectasia (ATM); Seckel syndrome (ATR)
	Autophagy	MAP1LC3B, SQSTM1	Nuclear turnover	Neurodegeneration (ALS; Paget's disease)

Multimodal Annotation Generated Pathogenic Impact Evaluator (MAGPIE)

MAGPIE is a machine learning-based bioinformatics tool designed to predict the pathogenicity of various human genome variations, and it bridges critical gaps in medical genetics by automating complex multi-scope variant evaluations:

a. VUS Resolution: It dramatically improves the prioritization and classification of Variants of Uncertain Significance (VUS).
b. Mendelian Disease Diagnosis: accurately identifying causal mutations in highly complex or imbalanced clinical sequencing datasets.
c. Broad Mutation Screening: interprets multiple exonic mutation types, including stop-gain, stop-loss, and frameshift variants.

Steps: 1. [Input Variant Data "Processed standard VCF format"] ➔ [Select Reference Genome- (ShenLab MAGPIE Webtools Server) (http://tools.shenlab-genomics.org/tools/MAGPIE) or pull the source code from GitHub] ➔ [Submit "target variant list" Run Automated Multimodal Analysis] * ➔ [Interpret Pathogenicity Score] **

* 1. Fetch and bundle the variant's features across 6 functional modalities.
2. Run automatic feature selection to isolate high-impact metrics.
3. Pass the data through its LightGBM gradient-boosting classifier.
**
1. Scores closer to 0: Indicate benign variations.
Scores closer to 1: Highlight highly pathogenic impacts.

Step-by-Step VCF Pre-processing on WSL before feeding to MAGPIE

Install Linux on Windows with
https://learn.microsoft.com/en-us/windows/wsl/install
windows Subsystem for Linux (WSL) as Ubun
Run adequate Linux distributions with WSL

Step 1: Convert Windows CRLF to Linux LF Line Endings
bash
sed -i 's/\r$//' your_input.vcf

Step 2: Deconstruct Multiallelic Sites into Biallelic Rows
Use bcftools to split and normalize multi-ALT records into individual rows:
bcftools norm -m -any your_input.vcf -o normalized_biallelic.vcf

Step 3: Verify VCF Syntax Integrity
Validate the file structure before passing it to the machine learning framework:
bash
bcftools view -H normalized_biallelic.vcf | head -n 10

Plausible tenets:

Gene: BANF1/BAF (Barrier to Autointegration Nuclear Assembly Factor 1) 11q13.1, genomic coordinates (GRCh38): 11:66,002,503-66,004,149

- It is a foundational member of the BANF gene family**.** It has a a critical role in cross-linking/compacting DNA, **regulating** gene expression, **repairing** the nuclear envelope, and acting as **an innate immune sensor** especially for viral defense. Total loss of this gene is embryonically lethal in model organisms.
- It bridges chromosomes to the inner nuclear membrane during telophase, and it rapidly recruits nuclear transmembrane proteins and ESCRT machinery following interphase nuclear membrane rupture. The protein is regulated by phosphorylation, particularly by VRK1 kinases, which impair DNA binding.
- It also helps in maintianing nuclear compartmentalization, and immune silence toward self-genomic DNA. **BANF1 shields nuclear DNA from cGAS, and additionally it promotes clearance/sequestration of cytoplasmic self-DNA, thus supressing spontaneous basal interferon signaling, and autoimmune-like interferonopathies.**
- It can self-assemble into a stable **obligate homodimer (monomer misfolds and loses its stability; that is why it does not behave like AD)** in solution and utilizes two distinct **helix-hairpin-helix (HpH)** structural domains to attach non-specifically to the phosphate backbone of double-stranded DNA, while simultaneously **binding to DNA and nuclear envelope proteins (like LEM-domain proteins and lamins)** to maintain chromatin organization.
- Gene: 1,942 bp, 230 orthologues, 8 splice variants; BNAF2 (14q24) is primary paralogue.
- Transcript: 3 exons & 2 coding exons; 6 domains and features; transcript length 1,155 bp.
- Protein: 89 AA with 10,059 Da molecular mass.

Phenotype: Néstor–Guillermo Progeria Syndrome (NGPS), also called progeria syndrome, childhood-onset, with osteolysis; **PSCOO**, **AR**-MOI

- Normal early infancy; symptom onset around 2 years; failure to thrive; severe short stature; chronic slowly progressive course; survival into adulthood
- **Most characteristic ("Hallmark") features: severe generalized osteolysis**; mandibular/maxillary destruction causing micrognathia and pseudosenile facies; generalized lipoatrophy with prominent veins; premature aged appearance with preserved cognition; **absence of accelerated atherosclerosis despite progeroid phenotype**; slowly progressive course with survival into adulthood; normal cognitive development and intelligence; and **eyebrows and eyelashes preserved; scalp hair retained until adolescence (later alopecia than classic progeria).**
- Management: conservative, treatment of manifestations, and **standardized surveillance**, need to follow updated guidelines.
- **There is no clear evidence for a markedly increased cancer risk.** Avoid: **(group 1 carcinogen**) https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/known-and-probable-human-carcinogens.html
- Social support site for families: https://www.progeriaresearch.org/

Counsel the family for Case III: 3 – In India, for a pregnancy beyond 24 weeks with significant fetal anomalies (**severe, substantial, or incompatible with life**), first approval from authorized a state-level medical board (**gynecologist, a pediatrician, a radiologist/sonologist, and other state-nominated members**) is required for termination of pregnancy. Parents have to sign for feticide (stoppage of heartbeat) before induction of abortion (**to avoid fetal distress or ethical dilemmas for surviving outside the womb**). It is essential to maintain confidentiality for all procedures.

Thought Riveting:

- ***Why is there a descending (top-to-bottom) pattern followed in progressive graying of hair?***
- ***What is the possible epistasis for notably absent or minimal coronary atherosclerosis in NGPS?***
- ***How can MAGPIE be used for non-genomic studies?***
- ***What is the non-canonical function of BNAF2?***