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Progeroid syndromes (PS)-VIII/ Fontaine progeroid syndrome (SLC25A24-related disorders)

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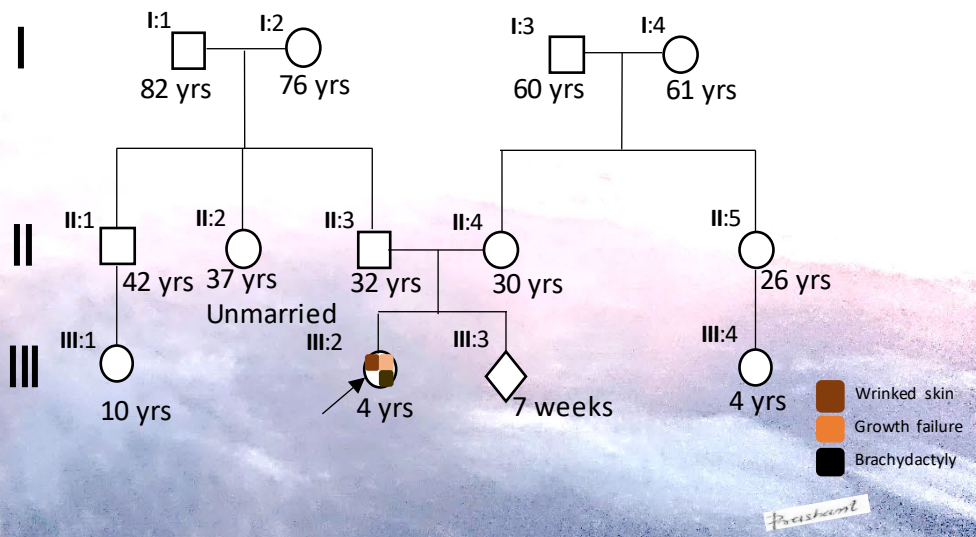

From the desk of Editor

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. How would you **select variants with pathogenicity** from annotated variants?
2. Discuss the **pleiotropy** of SLC25A24.
3. What do you understand about **antiporteropathies**?
4. How would you approach a case of **'turribrachycephaly'**?
5. What are the **key differences** between Fontaine progeroid syndrome and **mitochondrial proline synthesis defects?**
6. Is counseling about the possibility of a false negative test for a single gene of non-familial variant in antenatal invasive fetal sampling by NGS or Sanger sequencing needed?

Steps for prioritizing variants with pathogenicity from Annotated Variants

Steps for selecting of the variants with pathogenicity from Annotated Variants for Windows-based systems

1. **Before filtering, raw Whole Exome Sequencing (WES) data typically reveals an average of 20,000 to 30,000 variants (including non-synonymous, indels, splicing) per individual. This data is represents around 1/10 of the overall variants only after removing the functionally irrelevant variants.**

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

Step 1: Tool Selection (Windows-Based):
VCF.Filter: A Java-based tool providing a user-friendly GUI for interactive filtering.
PhenGenVar: A Windows-based application for visualizing and filtering VCF files based on phenotype.
IGV (Integrative Genomics Viewer): For visualizing filtered variants.
BCFtools (via Cygwin/WSL): Powerful command-line filtering

Step 2: Quality Control and Initial Filtering **(Removing Noise):**
Filter by 'PASS': Select only variants where the FILTER column is "PASS" (removes low-quality calls).
Coverage Filter: Retain variants with sufficient read depth (e.g., Depth > 10 - 20 X)

Step 3: Frequency Filtering **(Removing Common Variants):**
Pathogenic variants causing rare diseases are usually absent or extremely rare in the general population.
Filter by MAF: Filter out variants with a Minor Allele Frequency (MAF) or in databases like gnomAD, 1000 Genomes, or Exome Sequencing Project.

Step 4: Functional Impact Filtering **(Prioritizing Coding Changes):**
Impact Severity: Select high-impact variants such as: Stop-gain (nonsense), Frameshift deletions/insertions, Splice-site disruptions, Nonsynonymous missense mutations
Remove Synonymous: Remove synonymous variants (usually benign), unless splice-site prediction suggests otherwise.

Step 5: Pathogenicity and Conservation Scoring **(In Silico):**
CADD (Combined Annotation Dependent Depletion): Use a PHRED score cut-off between 10 and 20 (higher indicates more deleterious).
REVEL (Rare Exome Variant Ensemble Learner): Use a score (sensitive) or (specific) for missense variants.
ClinVar: Prioritize variants marked as "Pathogenic" or "Likely Pathogenic".

Step 6: Step 6: Variant Interpretation **(ACMG Guidelines):**
Segregation/Context: If working with trio data (affected child + unaffected parents), filter for de novo mutations.
Final Review: Evaluate if the variant matches the patient's clinical phenotype using tools like PhenGenVar

Plausible tenets:

Gene: SLC25A24 (Solute Carrier Family 25 Member 24) 1p13.3, genomic coordinates (GRCh38)- 1:108,134,043-108,200,343

- It belongs to the solute carrier family 25 (**SLC25**, **a total 53 members with highly conserved tripartite structure**), which is commonly known as the mitochondrial carrier family (**MCF, which are crucial for the transport of metabolites, nucleotides, cofactors, and ions across the inner mitochondrial membrane**). Specifically, it is an ATP-magnesium/inorganic phosphate **antiporter. Additionally, it also an adenyl nucleotide antiporter, so it acclimatizing mitochondria according to the callular energy needs.**
- As an electro-neutral and reversible exchange transporter, it exchanges ATP-Mg (or ADP) for phosphate (Pi) across the mitochondrial inner membrane. Its transport activity is highly sensitive to calcium levels, because it is a **"Short Calcium-Binding Mitochondrial Carrier" (SCaMC), protects cells against cellular stress through calcium binding.**
- It also acts as a tumor suppressor, promoting anti-tumor immunity by enhancing immune cell infiltration and inhibiting cancer cell proliferation and metastasis through the cGMP/PKG1 signaling pathway; its high expression is associated with better survival outcomes in **colorectal cancer (CRC)**, and is used as a potential independent prognostic biomarker.
- Gene: 66kb, 192 orthologues, 49 paralogues and 11 splice variants.
- Transcript: 10 exons & all of which are coding exons; 41 domains and features; transcript length 4,249 bps.
- Protein: 477 AA with a molecular mass of 53354 Da.
- No specific genotype-phenotype correlations have been identified (**hypomorphic variants may not be reported, or insufficient data due to an extremely rare genetics**) . Most of variants affecting **codon 217** have been reported with classical phenotypes, as this residue is **essential for the structural stability and its transportation function**. Variants such as p.Arg217Cys, and p.Arg217His, usually change the protein into a new conformation (**a gain of function**).

Phenotype: Fontaine progeroid syndrome, inherited as autosomal dominant

- A progeroid syndrome (**most severe in infancy, often improving with age**) with characteristic craniofacial anomalies, and bone dysplasias, and a multisystem connective tissue disorder. Gorlin-Chaudhry-Moss syndrome, Fontaine-Farriaux syndrome, and Petty syndrome are consolidated under this single genetic diagnosis.
- **Growth and Appearance: Severe pre-** and postnatal growth failure, and decreased subcutaneous fat (lipodystrophy).
- **Craniofacial/Skull:** Widely open anterior fontanelle, turribrachycephaly, , retruded hypoplastic midface, depressed nasal root with a convex nasal ridge, short palpebral fissures, microphthalmia, low anterior and posterior hairlines, dental dysplasia, and low-set dysplastic ears.
- **Ectodermal changes: Prominent subcutaneous veins** due to thin, sagging, transparent skin. Scalp hair transitios from sparse in early infancy to coarse, unruly in post infancy with multiple whorls; however generalized hypertrichosis in other body parts since birth, cutaneous syndactyly, hypoplastic external genitalia, and hypoplastic nipples.
- **Skeletal:** Craniosynostosis, short distal phalanges (**brachydactyly type B**) with nail dysplasia (hypo to **anonychia**), and **platyspondyly** with notching in vertebral bodies.
- Management: Conservative treatment of manifestations, and **standardized surveillnace**, with the need to follow updated guidelines. https://www.ncbi.nlm.nih.gov/books/NBK581082/#slc25a24-fps.Management

Key clinical clues to differentiate Hutchinson-Gilford Progeria Syndrome (HGPS)

- **Normal early infancy (appearance of symptoms after 1 year)**
- **Normal intelligence and neurodevelopment.**
- **Severe early cardiovascular disease/atherosclerosis.**
- **Alopecia and scleroderma-like tight skin; cutis laxa will not be seen**
- **No major eye abnormalities**
- **Early severe atherosclerosis is the major cause of death**

Antiporteropathies

- **Antiporters exchange two or more different molecules or ions across a membrane in opposite directions.** The dysfunction of antiporters leads to "Antiporteropathies", a type of transportopathies. ***(The term channelopathies used only defects related to ion channel subunits or the proteins that regulate them)***
- **Essential hypertension and diabetic nephropathy (Na+/H+ antiporter, NHE-1 isoform), osteopetrosis (Cl^-/H+ antiporter) and** various neurological disorders are well recognized Antiporteropathies.
- **Newer therapies for antiporteropathies:** lipid-modifying agents **(e.g., R3R01, hydroxypropyl-β-cyclodextrin),** dual-endothelin angiotensin receptor blockers **(e.g., Sparsentan, Atrasentan),** SGLT2 inhibitors **(e.g., dapagliflozin), and** chaperone therapy **(e.g., sodium 4-phenylbutyrate), as** molecular technologies **as CRISPR/Cas9 and so on.**

OMIM Entries with search MeSH term 'turribrachycephaly'

Turribrachycephaly: **Turricephaly** – "tower-shaped" skull with increased vertical height, and **brachycephaly** – shortened anteroposterior (front-to-back), caused by premature fusion of bicoronal craniosynostosis, which leads to the brain growth and causes compensatory upward expansion, producing the characteristic tower skull appearance.

DISEASE /OMIM NO.	GENE/MOI	GENE FUNCTION	CLINICAL FEATURES
RAINE SYNDROME (RNS)/ # 259775	FAM20C/ AR	key role in biomineralization of bones and teeth	Neonatal osteosclerotic bone dysplasia
GOMEZ-LOPEZ-HERNANDEZ SYNDROME (GLHS)/ % 601853	--/ Isolated cases	--	Triad of bilateral parietal or parietooccipital alopecia, rhombencephalosynapsis and trigeminal anesthesia
CRANIOECTODERMAL DYSPLASIA 1/ # 218330	IFT122/ AR	Part of IFT complex A (IFT-A), ciliogenesis and ciliary protein trafficking	Sagittal craniosynostosis (approx. 50%) with variable hair abnormality (sparse, fine and slow growing), with dental dysplasia, and progressive renal failure
CRANIOSYNOSTOSIS 2/ # 604757	MSX2/ AD	Regulates bone development, and in limb-pattern formation	Cloverleaf skull anomaly (Kleeblattschaedel deformity) a trilobular skull with craniosynostosis
APERT SYNDROME/ # 101200	FGFR2/ AD	Different cells patterning, differentiation for various tissue development	Cutaneous syndactyly in limbs with variable severity
PFEIFFER SYNDROME/ # 101600	FGFR1 and 2/ AD	Cell patterning, differentiation, skeletogenesis, and development of the GnRH	Cloverleaf skull, radiohumeral synostosis of elbow (ankylosis of the elbows), partial syndactyly in hands, broad thumb
AMINOPTERIN SYNDROME SINE AMINOPTERIN; ASSA/ % 600325	--	A folic acid antagonist aminopterin (methotrexate is a methyl derivative of the same drug)	Cleft lip/palate, facial asymmetry, hypertelorism, low-set and posteriorly rotated ears, upswept hairline, micrognathia, blepharophimosis, and ossification defects
CROUZON SYNDROME WITH ACANTHOSIS NIGRICANS/ # 612247	FGFR3/ AD	Cell patterning, differentiation, and regulation of chondrocytes	Acanthosis nigricans in flexural areas
PEROXISOME BIOGENESIS DISORDER 1A (ZELLWEGER)/ # 214100	PEX1/ AR	Peroxisomal protein import, PEX5 recycling	Down syndrome like features, stippled epiphyses, complex neurological problems, and lethal in infancy
BALLER-GEROLD SYNDROME/ # 218600	RECQL4/ AR	DNA helicase, and involved in DNA repair mechanisms	Craniosynostosis and radial aplasia
CRANIOSYNOSTOSIS 3/# 615314	TCF12/ AD	Helps in neuronal differentiation, and establishing GnRH axis	coronal synostosis bilateral (Bilateral > unilateral, right side >left side) with mild hands and CNS anomalies
CRANIOFRONTONASAL DYSPLASIA/ # 304110	FENB1/XLD	Signaling between contacted surrounding cells, a transmembrane ligand for Eph receptors	Frontonasal dysplasia leads to craniofacial asymmetry other facial features, and craniosynostosis

The differences between Fontaine progeroid syndrome and Mitochondrial Proline Synthesis Defects (De Barsy syndrome)

FEATURE	FONTAINE PROGEROID SYNDROME	MITOCHONDRIAL PROLINE SYNTHESIS DEFECTS (DE BARSY SYNDROME A/B)
GENETIC DEFECT	Mutation in **SLC25A24** gene	Mutations in **PYCR1** or **ALDH18A1** genes
INHERITANCE	Usually, **autosomal dominant**	**Autosomal recessive**
BASIC PATHOPHYSIOLOGY	Mitochondrial carrier protein defect affecting mitochondrial energy metabolism	Defect in **mitochondrial proline biosynthesis**, affecting connective tissue and mitochondria
AGE OF PRESENTATION	Present at birth or early infancy	Neonatal / early infancy
FACIAL APPEARANCE	Marked **progeroid face**, prominent forehead, midface hypoplasia	**Progeroid appearance** but often with **loose redundant skin (cutis laxa)**
SKIN FINDINGS	Thin, tight skin; reduced subcutaneous fat	**Cutis laxa**, wrinkled, redundant skin
OCULAR ABNORMALITIES	May occur but less prominent	**They are characteristic, which include** corneal clouding, cataract, myopia, optic atrophy
NEUROLOGICAL FEATURES	Developmental delay, intellectual disability	Severe developmental delay, hypotonia, movement disorders
MUSCULOSKELETAL FEATURES	Craniofacial dysmorphism, skeletal anomalies may be seen	**Joint laxity**, hypotonia
BRAIN IMAGING	May show structural abnormalities	Brain atrophy or delayed myelination
SKIN ELASTICITY	Skin thin but not markedly lax	**Marked skin laxity**
PROGNOSIS	May survive into childhood	Often progressive with severe neurological impairment

Counselling for the possibility of a false negative result for single gene testing: a non-familial (de novo) variant in antenatal invasive fetal sampling (amniocentesis or CVS) using Next-Generation Sequencing (NGS) or Sanger sequencing is typically estimated to be **less than 1%, but not zero in standard settings. Thus, counselling for the possibility of a false negative result is absolutely necessary before performing the test.**

Thought Riveting:

- ***What is the role of Mitophagy-Activating Compounds (MAC) in management of premature aging syndrome especially with mitochondriopathy?***
- ***How does "the negative stress" impact sirtuin protein activities (specifically SIRT1-7) as compared to "the positive stress" at cellular level?***
- ***Is long-term, moderate-to-high intensity aerobic training far superior to any drugs (like SRT2104) for promoting building a healthy physiological aging?***
- ***How does Reduced Nicotinamide Riboside (NRH) interact with antiporter proteins, can be used as medication against aging?***