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Progeroid syndromes (PS)-VIII / Wiedemann- Rautenstrauch syndrome

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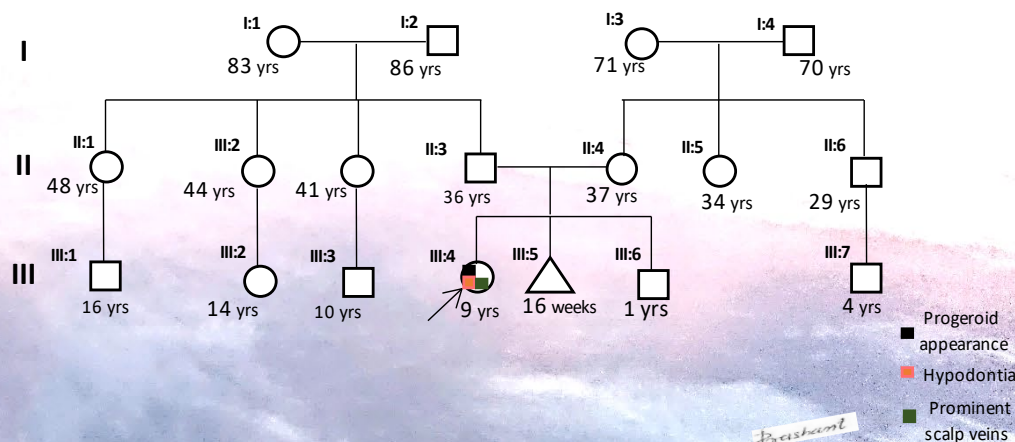
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From the desk of Editor

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.

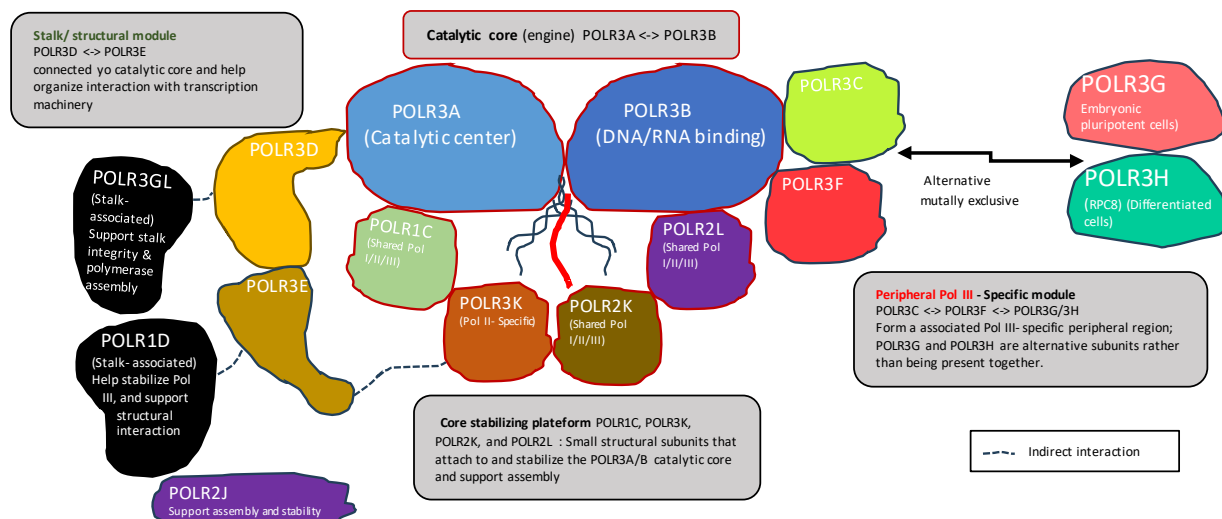
Insight:

1. Case III:6 was not tested antenatally, and now parents want to know the genotype. How would you counsel the family?
2. Why is the research on POLR3A critically important for geroscience?
3. Does any definite POLR3A genotype–phenotype correlation exist?
4. What is the subunit composition and genetic architecture of eukaryotic RNA polymerase III?
5. What are various phenotypes and modes of inheritance of subunit proteins of RNA Polymerase III complex?

RNA Polymerase III (Pol III): 17 Subunits, Their Role and Interaction

- RNA Polymerase III (Pol III) is a multi-subunit protein complex consisting of 17 distinct subunits. Genetically, it is **the largest and most complex** of the eukaryotic RNA polymerases. Its genetic composition is highly conserved across eukaryotes, from yeast to humans, and the subunits are encoded by independent, nuclear genes. It can be divided into three distinct categories:
 1. Unique Pol III Subunits (10 Subunits)- POLR3A, POLR3B, POLR3G / POLR3GL, POLR3C, POLR3F, POLR3D, POLR3E, POLR3H, CRCP (stalk partner of POLR3H/RPC8), and POLR3K.
 2. Subunits shared among all three eukaryotic polymerases (5 Subunits)- POLR2E, POLR2F, POLR2H, POLR2L, POLR2K
 3. Subunits shared by Pol I and Pol III- POLR1C, and POLR1D

Assembled POL III complex – A 17-units multiprotein complex that transcribes of tRNA, 5S rRNA, U6 snRNA, and other small RNAs



- Although the unit work together, but their disease phenotypes are not exactly the same; however the key characteristic phenotypes reported with this unit dysfunction are hypomyelination, ataxia, abnormal dentition, hypogonadotropic hypogonadism, progressive myopia, and increased varicella zoster virus susceptibility.

Reported Phenotype and MOI of RNA Polymerase III (Pol III)

Gene	Phenotype & OMIM	MOI	Key Clinical Features
POLR3A 614258	Leukodystrophy, Hypomyelinating, 7 (HLD7 / 4H Syndrome) #607694	AR	Progressive cerebellar ataxia, spasticity and motor regression, hypodontia / oligodontia, hypogonadotropic hypogonadism, progressive severe myopia, and short stature (GH deficiency)
	Wiedemann-Rautenstrauch Syndrome (WRS) #264090	AR	Neonatal progeroid appearance, severe intrauterine growth restriction, generalized lipoatrophy (lack of fat), prominent scalp veins and macrocephaly
	Spastic Paraplegia / Ataxia / Striatal Forms PMID 21855841, 25655951	AR	Adult-onset gait disorders, mild-to-severe striatal necrosis, dysarthria and central tremors
POLR3B 614366	Leukodystrophy, Hypomyelinating, 8 (HLD8) #614381	AR	Motor delay and cerebellar atrophy, oligodontia and missing teeth, endosteal sclerosis / hyperostosis, T2-weighted capsule hypodensity, hypogonadotropic hypogonadism
	Charcot-Marie-Tooth Disease, Type 1I (CMT1I) #619742	AD	Demyelinating peripheral neuropathy, Distal muscle weakness and wasting, childhood generalized epilepsy, variable vertical gaze palsy
POLR3C 614367	Varicella Zoster Virus Infection Susceptibility PMID 28783042	AR	High susceptibility to VZV, severe viral pneumonitis, CNS varicella encephalitis
POLR3D 187280	POLR3D-related Leukodystrophy PMID: 37915380	AR	Hypomyelinating leukodystrophy, delayed neurological milestones, altered tRNA transcription profiles
POLR3E 617815	-	-	Impaired Type I interferon responses, severe central nervous system virus infection
POLR3F 617423	? Immunodeficiency 101 (varicella zoster virus-specific) #619872	AD	Target immunodeficiency to alpha-herpesviruses, severe respiratory or neurological viral load
POLR3G 617456	-	-	-
POLR3H 619801	Primary Ovarian Insufficiency (POI)/ 46,XX gonadal dysgenesis/ PMID 30830215	AR (Biallelic)	Hypergonadotropic hypogonadism, premature ovarian failure / infertility, reduced structural transcription of small non-coding RNAs
POLR3K 606007	Hypomyelinating leukodystrophy 25 (HLD25) 619310	AR	Early childhood-onset hypomyelination, cerebellar ataxia and motor decline, variable dental or ocular manifestations
POLR3GL 617457	Short stature-oligodontia-dysmorphic facies-motor delay (SOFM) 619234	AR	Severe growth restriction / short stature/oligodontia, progeroid-like facial profile in some patients, endosteal hyperostosis
POLR1C 610060	Hypomyelinating leukodystrophy 11 (HLD11) 616494	AR	Cerebellar ataxia and tremors, delayed motor development, mild intellectual disability
	Treacher Collins syndrome 3 (TCS3) 248390	AR	Mandibulofacial dysostosis, malar hypoplasia and cleft palate, external ear abnormalities / hearing loss
POLR1D 613806	Treacher Collins syndrome 2 (TCS2) 613717	AD / AR	Downslanting palpebral fissures, micrognathia and mandibular hypoplasia, conductive hearing loss
POLR2K 606033	-	-	-
POLR2L 601189	-	-	-

Plausible tenets:

Gene: POLR3A (Polymerase III, RNA, Subunit A; POLR3A) 10q22.3,

Genomic coordinates (GRCh38): 10:77,975,149-78,029,515

- It encodes the largest catalytic subunit (RPC1) of the DNA-dependent RNA Polymerase III complex. It is responsible for transcribing essential non-coding RNAs, including transfer RNAs (tRNAs), 5S ribosomal RNA (rRNA), U6 small nuclear RNA (snRNA), 7SL RNA, 7SK RNA, Y RNAs, RNase P/RNase MRP-related RNA species, and other small regulatory RNAs. Thus, **its defects affect entire RNA homeostasis network → DNA damage and proteostasis stress → cellular senescence → tissue dysfunction, and progeria. Malfunctioning of non-coding RNAs likely produces tissue-specific effects as defective adipogenesis.**
- **Able to sense a foreign AT rich microbial DNA, and incite interferon (IFN) based innate immunity.**
- Complete null variants are typically embryonically lethal. Although it is expressed constitutively and ubiquitously in all human tissues, but it is highest in the nervous system (cerebellum), followed by cerebral cortex and white matter; that is why clinically presents as severe neurological disorders.
- Gene: 76.4 kb, 235 orthologues, 26 splice variants; 2 paralogues.
- Transcript: 31 exons & 31 coding exons; 10 domains and features; transcript length 6,610 bps.

Phenotypes: Wiedemann-Rautenstrauch syndrome (WRS), and leukodystrophy, hypomyelinating, 7, with or without oligodontia and/or hypogonadotropic hypogonadism, **AR-MOI, Severity – WRS >> leukodystrophy, hypomyelinating, 7**

- In WRS, diagnosed **at birth or in early infancy**, while classical POLR3A/4H leukodystrophy: onset usually in early childhood, with diagnosis commonly made during childhood or adolescence. (**more rapid progression than POLR3B-associated disease**)
- **Neurological:** progressive ataxia, tremor, dysarthria, dystonia, abnormal eye movements and sometimes cognitive impairment, in MRI: hypomyelination, often with cerebellar atrophy and/or a thin corpus callosum.
- **Dental:** delayed dentition, hypodontia or oligodontia.
- **Endocrine:** short stature and hypogonadotropic hypogonadism, causing delayed or absent puberty.
- **Ocular:** progressive myopia, which can become severe.
- **WRS phenotype:** severe growth restriction, lipodystrophy, progeroid features. Neurological manifestations such as ataxia, tremor, and other movement abnormalities may develop later in some patients, if survive.
- **Management guidelines:** https://www.ncbi.nlm.nih.gov/books/NBK99167/?utm_source=chatgpt.com
- **Social support sites for families:** https://yayafoundation4hl.org/?utm_source=chatgpt.com, <https://rarediseases.org/organizations/progeria-research-foundation/>

Geroscience and the Relationship with POLR3A

- **Geroscience:** study of the mechanisms of aging and their relationship to age-related diseases.
- **Pol III acts** downstream of mTORC1, and partial Pol III inhibition extends lifespan in yeast, worms and flies while improving tolerance to proteostatic stress (PMID: 29186112; PMID: 39436952). Human evidence comes from POLR3A-related progeroid disease (PMID: 30446582), and POLR3A/Pol III is a promising geroscience research target, but its exact role as a therapeutic anti-aging target in humans remains to be proven (PMID: 34295356).
- POLR3A, besides a housekeeping gene, is a highly dynamic regulator of cellular lifespan. Research is going on the ways to **modestly inhibit or modulate Pol III activity** in adults to mimic the lifespan-extending, **proteome-protecting benefits of caloric restriction** and rapamycin without the systemic side effects (PMID: 34295356).

POLR3A Genotype–Phenotype Correlation

POLR3A Genotype	Phenotype	Correlation
Biallelic hypomorphic/missense variants	HLD7 / 4H syndrome (#607694)	Residual function → hypomyelinating leukodystrophy
Biallelic truncating/splice LoF variants	Wiedemann–Rautenstrauch syndrome (#264090)	Marked loss of function → neonatal progeroid phenotype
Specific hypomorphic/intronic alleles, e.g. c.1771-7C>G, depending on allele in trans	Spastic ataxia / striatal phenotype	Partial residual function → later or atypical neurological phenotype
LoF + severe splice defect, particularly c.1771-7C>G (a leaky splice-altering intronic variant)	Severe early-onset POLR3-related leukodystrophy	Very low residual function → severe neurological disease

Two leaky splice alleles → milder phenotype

Leaky splice allele + missense/splice allele → intermediate phenotype

Leaky splice allele + amorphic/truncating allele → severe phenotype

Counsel the family for Case III: 6 – Till one year; he is asymptomatic, likely he has either heterozygous (carrier-50%) pathological variant or wild variants (normal genotype-25%), However analysis of variants by a geneticist must be completed before further planning for this case. Therefore, identification of exact genotype status is important if genotype identification would change his medical management in childhood. Thus, the answer is no for this case scenario.

Thought Riveting:

 *Do POLR3 related gene expression alterations relate to paraneoplastic syndrome and autoimmune disorders?*

 *Why is the study of POLR3 gene family crucial for understanding the aging process?*

 *Are the following subunits: POLR3E, POLR2K, and POLR2L of RNA polymerase III homozygous variants embryonically lethal?*

 *Is ML-60218 compound truly a selective POLR3A inhibitor?*