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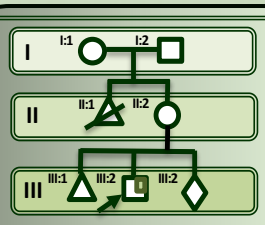
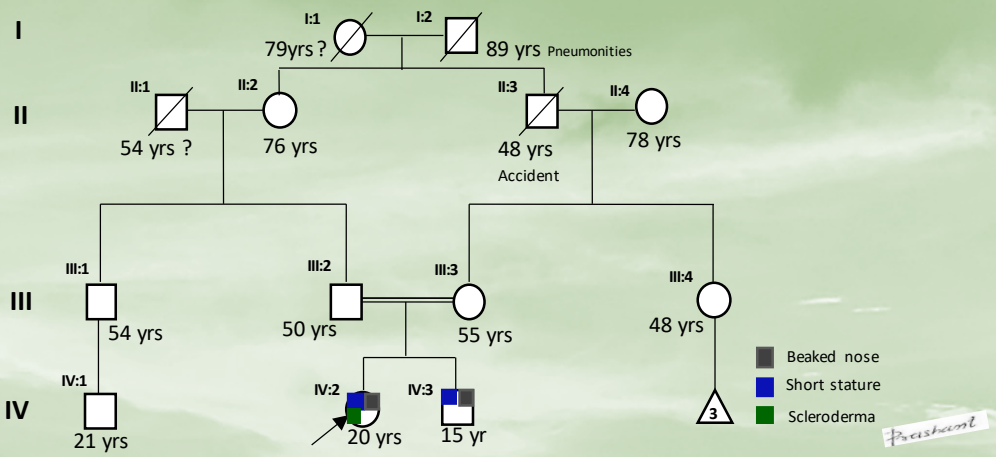
Progeroid syndromes (PS)-VII / Werner syndrome (RECQL2)

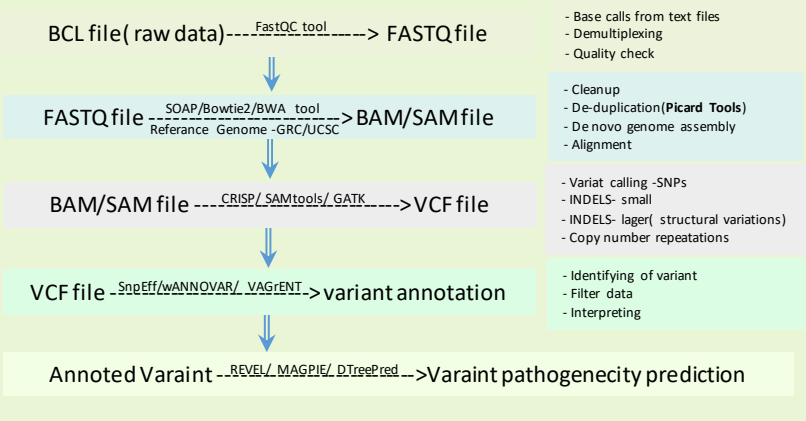
From the desk of Editor

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.





Basic Bioinformatics Steps for variant analysis



Insight:

1. How would you do counselling of **Case III: 4**?
2. What are the basic bioinformatics steps for variant analysis?
3. What are differences between segmental progeroid syndrome and non-segmental progeroid syndrome?
4. What is a beaked nose?
5. What is the current status of the clinical trial for Werner syndrome?

Protein sequence

MSEKKLETTAQQRKCPEWMNVQNKRCAVEERKACVRKSVFEDDLPFLEFTGSIVYSYDAS
DCSFLSEDISMSLSDGDVVGFDMEWPPLYNRGKLGKVALIQLCVSESKCYLFHVSSMSVF
PQGLKMLLENKAVKKAGVGIEGDQWKLLRDFDIKLKNFVELTDVANKKLKCTETWSLNSL
VKHLLGKQLLKKDKSIRCSNWSKFPLTEDQKLYAATDAYAGFIIYRNLELLDDTVQRFAIN
KEEEILLSDMNKQLTSISEEVMDLAKHLPHAFSKLENFRRVSILLKDISENLYSLRRMII
GSTNIETELRPSNNLNLLSFEDSTTGGVQQKQIREHEVLIHVEDETWDPFLDHLAKHDGE
DVLGNKVERREDGFEDGVEENKLKENNERACLMSLDITEHELQILEGQGDQREYLSDIAYK
STEHLSPNDNENDTSYVIESDEDLEMEMLKHLSPNDNENDTSYVIESDEDLEMEMLKSLE
NLNSGTVEPTHSKCLKMERNLGLPTKEEEEDDENEANEGEEDDDKDFLWPAPNEEQVTCL
KMYFGHSSFKPVQWKVIHSVLEERRDNVAVMATGYGKSLCFQYPPVYVGKIGLVISPLIS
LMEDQVLQLKMSNIPACFLGSAQSENVLTDIKLGKYRIVYVTPEYCSGNMGLLQQLEADI
GITLIAVDEAHCISEWGHDFRDSFRKLGSLKTALPMVPIVALTATASSSIREDIVRCLNL
RNPQITCTGFDRPNLYLEVRRKTGNILQDLQPFLVKTSSHWEFEGPTIIYCPSRKMTQQV
TGELRKLNLRCGTYHAGMEFSTRRDIHHRFVRDEIQCVIATIAFGMGINKADIRQVIHYG
APKDMESYYQEIGRAGRDGLQSSCHVLWAPADINLNRHLLTEIRNEKFRLYKLKMMAKME
KYLHSSRCRRQIILSHFEDKQVQKASLGIMGTEKCCDNCRSRLDHCYSMDDSEDTSWDFG
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QLITEGFLVEVSRYNKFMKICALTKKGRNWLHKANTESQSLILQANEELCPKKLLLPSSK
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IGDVSEGKAAMLAPLLEVIKHFCQTNSVQTDLFSSTKFQEEQKTSLVAKMKICTLSQSMA
ITYSLFQEKKMPLKSIAESRILPLMTIGMHLSQAVKAGCPLDLERAGLTPEVQKIIADVI
RNPPVNSDMSKISLIRMLVPENIDTYLIHMAIEILKHGPDSGLQPSCDVNKRRCFPGSEE
ICSSSKRSKEEVGINTETSSAERKRRLPVWFAKGSDTSKKLMDKTKRGGLFS

Key differences between segmental progeroid syndrome (SPS) and non-segmental (unimodal) progeroid syndrome (NSPS):

Feature	SPS	NSPS
Premature aging	Multiple organs or systems	Single organ or system
Lifespan	Decreased significantly	Less significantly
Major system	Not- specific, including derma	More neural and metabolic
Dysmorphology	Grossly visible	Not specific
Genomic instability	Yes	No
Examples	Werner, HG syndrome	familial Alzheimer's disease & Parkinson's disease

Plausible tenets:

Gene: RECQL2 (DNA helicases RECQ-Like) 8p12,
Genomic coordinates (GRCh38): 8:31,033,810-31,176,138

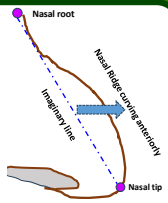
- A member of the **RecQ subfamily of the DNA helicases family**. It has 3'-5' DNA-helicase & 3'->5' exonuclease activity. It helps in gamma-irradiation-induced double-strand break repair, and DNA repair after homologous recombination.
- Participate in the following genomic stability and DSBs repair pathways: homologous DNA pairing and strand exchange, and resolution of D-loop structures through Synthesis-Dependent Strand Annealing (SDSA).
- Gene: 142,351 bases, 151 orthologues, and 6 splice variants.
- Transcript: 35 exons and 34 coding exons; 59 domains and features; transcript length: 1,432 bps.
- Protein: 1432 AA with 162461 Da molecular mass.
- **Gene tree** (**a pedigree of gene**) ENSGT00940000159168, ***Number of*** (#) genes - 152, # Speciation nodes - 147, # duplication - 0, # ambiguous - 2, # gene split events - 2 https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000165392;r=8:31033788-31176138;t=ENST00000298139

Phenotype: Werner syndrome, autosomal recessive mode of inheritance

- A premature ageing features, including primary and secondary phenotypical changes. It has a high risk for developing malignant or benigh tumors, especially nonepithelial types. (**1:1** proportion for epithelial to nonepithelial cancers against **10:1 in the population**)
- Issue with fibroblast growth potential due to abnormal response of FGF (**defective growth factor-mediated pathways**), which leads to **significant problems postopertiave healings**.
- **Cytogenetic abnormalities:** consider as a 'mutator' syndrome, because various numerical and structural chromosomal changes are noticed in the cultured lymphocytes. The mutagenesis pathways lead to cell lines resistent to 6-thioguanine (8 times more than control).
- Management: conservative, treatment of manifestation, **standardized surviellnace**; need to follow updated guidelines. https://www.ncbi.nlm.nih.gov/books/NBK1514/#werner.Management
- Avoid: sun exposure, trauma, fractures, and carcinogenic agents such as **smoking, processed meat**, **tobacco, alcohol (group 1 carcinogen)**. https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/known-and-probable-human-carcinogens.html

Nasal Ridge, Convex:
has been replaced terms such as beaked, hooked nose

- It is not specific dysmorphology.
- Familial form also reported.
- More than eighty entries in OMIM.



Summary of latest PUBMED articles related WRN research

Year	Authors & Topic	One-Line Summary
2023	Phan et al.	Clinical implications of sclerosing epithelioid fibrosarcoma (a rare sarcoma) in a Werner syndrome patient
2024	Orren & Machwe et al.	WRN protein functions to preserve telomeric genome stability under replication stress.
2024	McGrath et al.	Diabetic foot complications in a consanguineous Werner syndrome family.
2024	Monnat et al.	Reflects on the contributions of James German toward understanding Werner and related RECQ helicase disorders
2025	Zhang et al.	Possible therapeutic potential of targeting WRN protein via synthetic lethality strategies

Differences between LMNA associated progeroid syndrome and Werner syndrome

Feature	LMNA-Associated Progeroid Syndrome	Werner Syndrome
Genetic Cause	Caused by mutation in the LMNA gene	Primarily caused by mutation in WRN gene
Inheritance	Usually, Autosomal Dominant	Autosomal Recessive
Onset of Symptoms	Symptoms often begin to manifest in childhood and adolescence	Symptoms typically become apparent during the third and fourth decades of life.
Facial Appearance	Includes a beaked nose and thin lips	Described as "bird-like," with a pinched or beaked nose and prominent eyes
Voice	No specific voice changes are commonly reported.	A distinctive high-pitched or hoarse voice is a characteristic feature
Skin Manifestations	Characterized by skin atrophy	The skin often appears thin, hardened, and tight due to the loss of underlying fat. **(+ in 96%)**
Hair	Hair changes are not a defining feature.	Early greying **(+ in 100%)** and premature hair loss (alopecia) are common, starting with the scalp and eyebrows.
Metabolic Abnormalities	Features partial lipodystrophy, which is the loss of fat from the face and limbs.	Involves abnormal fat deposition, leading to a thick trunk with thin arms and legs. Type 2 diabetes is a common complication
Cardiovascular Feature	Arrhythmia, valvular disease, and cardiomyopathy	Atherosclerosis of coronary arteries
Skeletal Features	short clavicles and generalized joint stiffness are common feature	Osteoporosis is a common manifestation
Eyes	Generally, not involved	Development of cataracts in both eyes. **(+ in 99%) ***
Cancer Risk	Mesenchymal tumors (osteosarcoma, liposarcoma) are more common	sarcomas, thyroid, melanoma, hematologic cancers.
Life Expectancy	Life expectancy is reduced averaging to 30-40 yrs	Average death in 40s–50s (mainly from malignancy or cardiovascular disease).

*** 91% patients have four cardinal features, including short stature (95%) (Oshima et al. 2017). Clinical diagnosis established: four cardinal signs plus any two additional signs; probable diagnosis with three cardinal signs with two additional signs.**

Ten additional signs: Thin limbs (present in 98%), Pinched facial features (96%), Osteoporosis (91%), Voice change (89%), Hypogonadism (80%), Type 2 diabetes mellitus (71%), Soft tissue calcification (67%), Neoplasm(s) (44%), Skin ulcers, usually of distal legs (40%), and Atherosclerosis (30%).

Counsel the family for Case III: 4 – She has **three** spontaneous abortions (a case of **R**ecurrent **S**pontaneous **A**bortions). A carrier (a heterozygous state) does not have additional risk for the RSA. Although Werner syndrome patients have a high risk for RSA, she does not have any abnormal phenotype. RSA is a complex disease and need to be evaluated by a multidisciplinary team.

Thought Riveting:

- ***Does the aging process have a programmed LCR (locus control region) to suppress RecQ synthesis after reaching a particular age?***
- ***How do antioxidant and superfoods interact with RecQ proteins at the cellular level to increase cell longevity?***
- ***Could overexpression of 'Ku complex' slow down the normal aging process?***
- ***Can VVD-133214 (covalent allosteric inhibitor of WRN) be used locally for keloid?***
- ***What is the biological role of direct interaction between WRN and wild-type lamin A protein?***