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Progeroid syndromes (PS)-IX/ Cockayne syndrome

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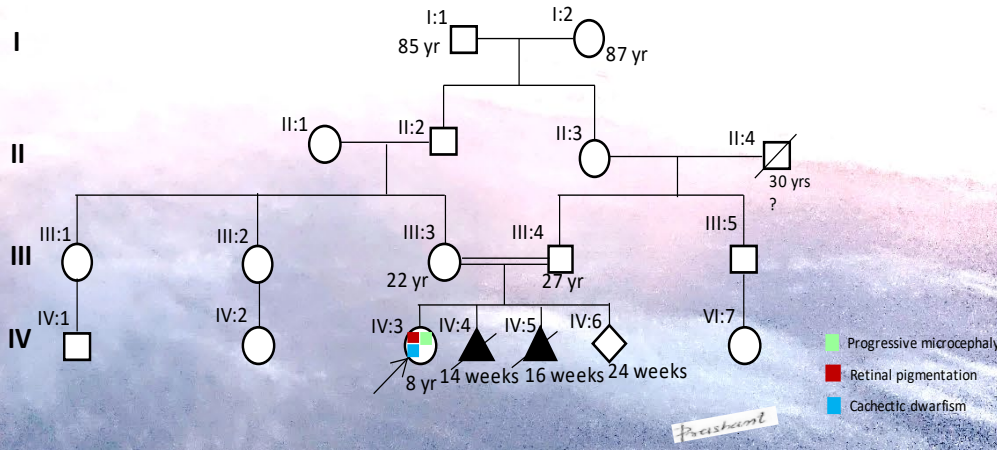
From the desk of Editor

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. How would you counsel the family regarding spontaneous abortions?
2. What are the clinical phenotypes of Cockayne syndrome?
3. What are the possible phenotypes of ERCC related disorders?
4. What is Trimmomatic?
5. How do you approach a hereditary cachexia case?

Trimming and Trimmomatic

Trimming of sequence data: A step before alignment and assembly, it helps to filter out sequences with errors [as adapter sequences (**Adapter Trimming**), and low-quality errors (**Quality-Based Trimming**), etc.] from individual reads without any changes to original reads.

Available tools for trimming:

1. **Trimmomatic** is a licensed program under GPL V3. http://www.usadellab.org/cms/index.php?page=trimmomatic https://pmc.ncbi.nlm.nih.gov/articles/PMC4103590/
2. **Cutadapt** is a free, open-source software tool that helps error-tolerant matching. https://cutadapt.readthedocs.io/en/stable/, https://cutadapt.readthedocs.io/en/stable/guide.html
3. **Trim Galore** internally uses Cutadapt and autonomously processes multiple samples in parallel to identify adapters and low qualities reads without losing valuable unpaired reads. https://github.com/FelixKrueger/TrimGalore, https://www.bioinformatics.babraham.ac.uk/projects/trim_galore/

Steps to run the Trim Galore command for DNA Whole Exome Sequencing (WES) data in WSL

Install Linux on Windows with windows Subsystem for Linux (WSL) as Ubuntu
Run adequate Linux distributions with WSL

Step 1: Download and install Biconda
First install Anaconda/Miniconda
1. **Update Packages and Install**
2. **Download the Installer Script (Anaconda/Miniconda)**
3. Run the Installation Script
4. Activate the Installation and Verify

```
sudo apt-get update && sudo apt-get upgrade -y
sudo apt-get install wget -y
cd /tmp wget https://repo.anaconda.com/archive/Anaconda3-2024.06-1-Linux-x86_64.sh -O anaconda_installer.sh
cd /tmp wget https://repo.anaconda.com/miniconda/Miniconda3-latest-Linux-x86_64.sh -O miniconda_installer.sh
bash miniconda_installer.sh
source ~/.bashrc
conda list
conda config --set auto_activate_base false
```

Step 2: Use Bioconda for installation dependencies
1. Configure Bioconda channels
2. Create and activate a new Conda environment
3. Install trim-galore, cutadapt, and fastqc
4. Verify Installation

```
conda config --add channels defaults conda config --add channels bioconda conda config --add channels conda-forge
conda create --name wes_env
conda activate wes_env
conda install trim-galore cutadapt fastqc
cutadapt --version
fastqc -v
```

Prerequisite

Step 3: Organize Data

Ensure assessability of FASTQ files

Step 4: Running the Trim Galore Command

```
trim_galore [options] <forward_reads.fastq.gz> <reverse_reads.fastq.gz>
```

ERCC related Disorders

Gene OMIM number	Phenotype
ERCC1 (126380)	Cerebrooculofacioskeletal syndrome 4
ERCC2 (126340)	? Cerebrooculofacioskeletal syndrome 2 Trichothiodystrophy 1, photosensitive Xeroderma pigmentosum, group D
ERCC3 (133510)	Trichothiodystrophy 2, photosensitive Xeroderma pigmentosum, group B
ERCC4 (133520)	Fanconi anemia, complementation group Q Xeroderma pigmentosum, group F Xeroderma pigmentosum, type F/Cockayne syndrome XFE progeroid syndrome
ERCC5 (133530)	Cerebrooculofacioskeletal syndrome 3 Xeroderma pigmentosum, group G Xeroderma pigmentosum, group G/Cockayne syndrome
ERCC6 (609413)	? De Sanctis-Cacchione syndrome {Lung cancer, susceptibility to} {Macular degeneration, age-related, susceptibility to, 5} Cerebrooculofacioskeletal syndrome 1 **Cockayne syndrome, type B** Premature ovarian failure 11 UV-sensitive syndrome 1
ERCC8 (609412)	**Cockayne syndrome, type A** UV-sensitive syndrome 2

Majority of pathological variants of ERCC genes have **overalpping phenotype that related to premature aging and increase susceptabilty for carcinogenic agents**.

Plausible tenets CS-A:

Gene: ERCC8 (Excision Repair Cross-Complementation Group 8) 5q12.1, genomic coordinates (GRCh38): : 5:60,866,454-60,945,070

- A WD* repeat protein of the **nucleotide excision repair (NER) pathway and is a subunit of the CSA ubiquitin ligase complex**. It interacts with a p44 subunit of the **TFIIH complex** that has essential role in DNA repair**.**
- CSA complex engages in transcription-coupled nucleotide excision repair (TC-NER) and degradation of ERCC6 by inducing the ubiquitination. It also plays a role in DNA double-strand breaks (DSSBs) repair.
- Gene: 79 kb, 201 orthologues, 9 paralogues and 37 splice variants.
- Transcript: 12 exons & 12 coding exons; 42 domains and features; transcript length 9,414 bps.
- Protein: 396 AA with a molecular mass of 44055 Da.
- **Gene tree** (**a pedigree of gene**) ENSGT00390000009065, ***Number of*** genes - 209, speciation nodes - 197, duplications -6, ambiguous - 5, gene split events - 0 https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000049167;r=5:60866454-60945073

Phenotype: Cockayne syndrome, autosomal recessive MOI

- CS types on the basis of clinical phenotype:

Type	Severity	Age of onset	Major	Minor
II	Severe	Antenatal	Later no physical & neurological growth	Congenital cataract
I	Classical	Childhood	Both present	≥ 3 criteria +
III	Mild	Teenagers	Progressive with ataxia	+/- Photosensitivity

Major criteria	Minor Criteria
1.Growth failure 2. Acquired microcephaly and neuroregression with MRI brain changes leukodystrophy with atrophy	1.Deafness: sensorineural type 2.Peripheral neuropathy 3.Cataract +/- retinopathy 4.Photosensitivity 5.Dental dysplasia 6.Cachectic dwarfism

Cerebro-oculo-facio-skeletal syndrome (COFS) – (most severe) besides type II phenotype, additional eye anomalies with arthrogryposis

Genotype and phenotype correlation: Usually, the severity of the phenotype matches with protein truncation

- Management: conservative, treatment of manifestations, and **standarded surviellnace**; need to follow updated guidelines. https://www.ncbi.nlm.nih.gov/books/NBK1342/#cockayne.Management
- Avoid: sun exposure, methotrexate, metronidazole(**acute liver failure**), sedatives and neuromuscular blocking 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
- Social support site for families: https://www.thecockaynesyndromefoundation.org/

TFIIH complex

-TFIIH has **ten subunits** (**seven core complex**: XPB, XPD, p62, p52, p44, p34, and p8, and **three CDK-activating kinases**: CDK7, Cyclin H, and MAT1) with versatile biological roles besides regulation of RNA polymerase II transcription.

*__WD (Tryptophan-Aspartic acid) repeat proteins__ have a common structural motif: 40-60 amino acids repeating units, which have terminal ends of a tryptophan-aspartic acid (W-D) dipeptide. They form a beta-propeller structure (**a β protein architecture characterized by 4 to 8 highly symmetrical blade-shaped beta sheets arranged toroidally around a central axis**) that provides a platform for many crucial complex proteins in eukaryotic cells only.

Cachexia: an asthenic condition with significant loss of weight (≥5 % within 12 months or BMI < 20 kg/m^2) and muscle mass with or without fat mass loss. It is multifactorial by aetiologies, and might be part of a syndrome.

In OMIM searching with "cachectic" , we found only ten clinical synopses.
(https://omim.org/search?index=entry&search=%22cachectic%22&sort=score+desc%2C+prefix_sort+desc&start=1&limit=10&retrieve=clinicalSynopsis&cs_exists=true)

S. No.	Syndrome	OMIM/MOI	Gene	Key phenotypic features
1.	Cockayne Syndrome A; CSA	#216400/AR	ERCC8	Cachectic dwarfism, sensorineural hearing loss, knee contracture, plus*
2.	Cockayne Syndrome B; CSB	#133540/AR	ERCC6	Severe form of CSA
3.	Xeroderma Pigmentosum, Complementation Group B; XPB	#610651/AR	ERCC3	Variable form of CSA, dermatological cancers with normal stature
4.	Congenital Myopathy 3 With Rigid Spine; CMYO3	#602771/AR	SELENON	Hypotonia, amyotrophy, progressive deforming scoliosis, distal hyperlaxity
5.	Mitochondrial DNA Depletion Syndrome 1 (MNGIE Type); MTDPS1	#603041/ AR	TYMP	Late onset (after 2nd decade) with ptosis, pseudoobstruction, scattered leukoencephalopathy
6.	Surfactant Metabolism Dysfunction, Pulmonary, 1; SMDP1	#265120/AR	SFTPB	Infantile onset respiratory distress refractory to surfactant therapy, cyanosis, alveolar proteinosis
7.	Multicentric Carpotarsal Osteolysis Syndrome; MCTO	#166300/AD	MAFB	Juvenile rheumatoid arthritis mimic with CKD (chronic kidney disease)
8.	Immunodeficiency 125; IMD125	#620926/AR	FLT3LG	Chronic cough and diarrhea, serious HPV and HSV infections
9.	Achalasia-Progeroid Syndrome; ACHPS	#621123/AR	BUD13	Early onset lipodystrophy, corneal clouding, hearing loss
10.	Lambotte Syndrome	%245552/AR	None	Microcephaly, holoprosencephaly, and intrauterine growth retardation (IUGR)

Difference between Cockayne syndrome type A (CSA) and Cockayne syndrome type B (CSB)

Feature	**Cockayne Syndrome Type A (CSA)**	**Cockayne Syndrome Type B (CSB)**
Gene involved	*ERCC8* gene mutation	*ERCC6* gene mutation
Protein affected	CSA protein	CSB protein
Inheritance	Autosomal recessive	Autosomal recessive
Severity	**Milder** form	**More severe** form
Age of onset	Symptoms usually begin **after 1 year of age**	Symptoms often present **at birth or early infancy**
Growth failure	Present but less severe	Marked growth failure, more pronounced
Neurological impairment	Progressive but slower	**Severe**, rapid neurodegeneration
Photosensitivity	Mild to moderate	**More severe form**
Hearing loss	Common	Common (may be more severe)
Vision problems	Progressive cataracts, retinal degeneration	Similar but typically earlier and more severe
Life expectancy	Survival into **teens or early adulthood** possible	Often **childhood** (more reduced lifespan)
Facial features	Characteristic "cachectic dwarfism"	More pronounced classic progeroid features
Developmental milestones	Delayed, but less severe	Very limited developmental progress

Counsel the family for Case III: 4 – She has two spontaneous abortions (SA). There is no additional risk for SA to have a carrier status for RECQL2. Although Werner syndrome patients have a high risk for RSA, however she does not have any abnormal phenotypes. SA is a complex disease and needs to be evaluated by multidisciplinary team.

Thought Riveting:

- *What could be the additional extranuclear functions of ERCC8 be?*
- *Why is there no human ERCC7 gene nomenclature in the literature?*
- *Are there any possible etiological, and therapeutic roles of ERCC8 polymorphism in melanoma?*
- *How do the LMNA proteins and ERCC genes interact with each other?*