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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.

Pulmogenetics-XVII/ Syndromes associated with Bronchiectasis / WHIM syndrome

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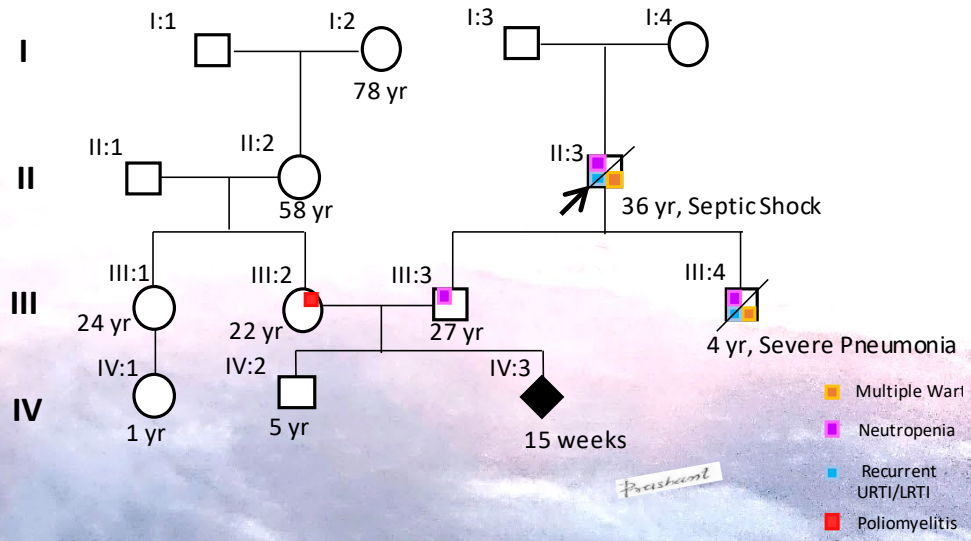

Insight:

1. Why WHIM syndrome does not classify as 'severe congenital neutropenia (**SCN**)' or Severe Combined Immunodeficiency (**SCID**)?
2. What is the DTreePred?
3. What are the clinical phenotypes of WHIM syndrome?
4. How would you approach a patient with myelokathexis?
5. Even though highly effective therapies are (orphan drugs) available, how should society, and parents balance the ethics of bringing case IV:3 into the world?

DTreePred (https://danhfg.github.io/dtreepred/)

- It is a free open-source online tool and has integrated multiplatform application (e.g., allele frequency, conservation scores, protein impact, and functional annotations) and can classify variants into categories such as pathogenic, likely pathogenic, benign, likely benign, or variant of uncertain significance (VUS).
- **Input features:** Allele frequency, mutation type, evolutionary conservation, functional prediction scores (SIFT, PolyPhen-2, CADD), protein domain, gene–disease associations, and clinical evidence (e.g., ClinVar).
- **Clinical utility:** Identifies pathogenic variants, genetic counseling, precision medicine, and faster, more consistent variant interpretation.
- **Limitation:** Predictions should complement—not replace—clinical assessment, including phenotype, family history, laboratory/functional studies, and established variant interpretation guidelines.

Plausible tenets:

Gene: CXCR4 (C-X-C Motif Chemokine Receptor 4) 2q22.1, genomic coordinates (GRCh38): 2:136,114,349-136,118,149

- In the early 1990s, it was discovered as an orphan receptor, and in 1996, Edward A. Berger and colleagues identified **fusin** as the **major co-receptor for T-cell-tropic HIV-1**. In the same year, Thomas J. Schall et al. identified **CXCL12 as the natural ligand for the receptor.** Around 2001, Isaiah J. Fidler and teammates showed that many cancers overexpress it.
- It belongs to G protein-coupled chemokine receptor (CXCR1–CXCR7) family that binds CXC chemokines to regulate leukocyte migration, immune responses, inflammation, and cell trafficking. G protein-coupled receptors (GPCRs) are the **largest family of cell-surface membrane** proteins in eukaryotes.
- It is present inside the cytoplasm, particularly found in high-turnover areas of actin cytoskeleton, including the **cortical cytoplasm(gel-like, outer layer of cytoplasm, just beneath the plasma membrane), adherens junctions, and cell projections.** It controls actin turnover speed, so ensuring actin filaments are rapidly recycled.
- Knockout mice lacking CXCR4 died before birth because of multiple congenital malformations indicating its role as one of the most important developmental signaling receptors. They are also known as seven-transmembrane (7-TM) or serpentine receptors
- **Molecular pathology:** Bone marrow and lymphoid tissue stromal cells produce CXCL12→ Bind with CXCR4→ Stimulate signaling pathways that increase cell adhesion (α4β1 integrin binds VCAM-1, and αLβ2 integrin binds ICAM-1) and reduce WBCs motility→ **once WBCs mature, CXCR4 signaling decreases, allowing them to leave the bone marrow and enter the bloodstream → gain-of-function mutation of CXCR4→ leads to following consequences at cellular level:**
  - Persistent signaling:**the receptor is not efficiently desensitized and internalized after binding CXCL12.**
  - Neutrophils and other multiple mature leukocytes (WBCs) receive a signal: **persistent have high adhesion.**
  - Mature neutrophils(**degenerative hypersegmented)** & WBCs **stay** in the bone marrow: **myelokathexis**
  - Fewer neutrophils circulate in the blood: **neutropenia** and lymphopenia.
  - The combined deficiency of neutrophils and lymphocytes: **impairs both innate and adaptive immunity →This weakens the immune system → recurrent infections and the features of WHIM syndrome.**
  - Neutropenia is the hallmark of WHIM syndrome because **neutrophils have the highest turnover and continuous release from the bone marrow** depends critically on tightly regulated CXCR4 signaling**.**
- Gene: Size 4.83 kb, Number of 729 orthologues, 44 paralogues, and 7 splice variants.
- Transcript: Total 2 exons & 2 coding exons; 1 GPCR domain containing seven transmembrane helices; transcript length 1,668 bp.
- Protein: Number of 352 AA with a molecular mass of 39.7 kDa.
- CXCR4 is ubiquitously expressed, and overexpressed in the immune-related cells.

Phenotype: W (warts), **H** (Hypogammaglobulinemmia), **I** (Infections), **M** (Myelokathexis).

Clinical phenotype spectrum: **AD - Mode of inheritance**

- **Human papillomavirus infection (HPV)-related manifestations:** Persistent cutaneous and anogenital warts, chronic HPV, increased risk of HPV-associated dysplasia and malignancies
- **Immunological abnormalities**: hypogammaglobulinemia, impaired antibody responses, defective leukocyte trafficking
- **Infectious manifestations:** recurrent bacterial infections, chronic sinusitis, otitis media, pneumonia, skin and soft tissue infections, **bronchiectasis**.
- **Hematological abnormalities:** neutropenia, lymphopenia, monocytopenia, leukopenia, hypercellular bone marrow.
- **WHIM does not have severe T and B cell defects, nor bone marrow failure disorders (congenital neutropenia or maturation arrest) so may not be consider as SCID or SCN.**
- **Management:** Symptomatic, personalized, and preventive management: Granulocyte colony-stimulating factor (G-CSF), immunoglobulin replacement therapy (IVIG/SCIG), antibiotic prophylaxis and prompt treatment, HPV surveillance and treatment, and Mavorixafor. Hematopoietic stem cell transplantation (HSCT) is curative but rarely required.

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Mavorixafor (XOLREMDI)- Approved for WHIM in April 2024 by the FDA- ≥12 years, Oral, OD

- A second-generation, monocyclam-based CXCR4 antagonist that blocks excessive CXCR4–CXCL12 signalling**. Originally developed as an anti-HIV drug.**
- Investigational/**Clinical trial indications:** clear cell renal cell carcinoma (ccRCC), melanoma, and other tumours with promoting the CXCR4–CXCL12 axis.

OMIM Entries with search tool- ("Myelokathexis ")

Myelokathexis: abnormal retention, acceleration of death, and accumulation of mature neutrophils within the bone marrow, so a hypercellular bone marrow existing simultaneously with a severe peripheral cytopenia.

Attribute	Severe Congenital Neutropenia-13 (SCN13) / WHIM Syndrome 2	SCN4/ Dursun syndrome included	SCN5
OMIM Phenotype #	#619407	#612541	#615285
Associated Gene	CXCR2	G6PC3	VPS45
Gene OMIM *	*146928	*611045	*610035
MOI	Autosomal Recessive	Autosomal Recessive	Autosomal Recessive
Type of mutations	**Loss-of-function**	**Loss-of-function**	**Loss of function**
Pathophysiology & Cellular Mechanism (Enhanced)	Directly blocks neutrophil chemotaxis, mimicking CXCR4 overactivation dynamics by causing **prolonged bone marrow retention and apoptosis.**	Endoplasmic reticulum (ER) stress, and impaired inner mitochondrial membrane stability, lead to **apoptosis in CD34+ and early myeloid lineages.**	Disruption of endosomal vesicle trafficking results in intracellular transport defects, that trigger cellular collapse, severe bone marrow hyper-retention, and early myeloblast/promyelocyte apoptosis.
Key Clinical Characteristics	**Classic myelokathexis** morphology. Extra-hematologic features like warts and hypogammaglobulinemia are characteristically **absent**.	**Myelokathexis-like degenerative changes,** prominent superficial veins, congenital structural heart defects, urogenital anomalies, and inflammatory bowel disease (IBD).	Secondary **myelokathexis changes** include progressive primary myelofibrosis, nephromegaly, severe recurrent bacterial/fungal infections, and global developmental delays.
Management & Therapy	**Long-term G-CSF therapy**, antimicrobial prophylaxis, and allogeneic Hematopoietic Stem Cell Transplantation **(HSCT)** for refractory cases.	**Continuous G-CSF administration**, broad-spectrum antibiotic regimens for febrile episodes, surgical correction of structural defects, and multidisciplinary immunology/GI care.	**Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)** can cure the condition; **G-CSF support** frequently yields poor or only partial clinical responsiveness; aggressive antifungal/antibacterial prophylaxis.

Neutropenia, severe congenital (SCN)- PS202700 – has 15 entries; only SCN4, and SCN5, and SCN13 have been reported to have myelokathexis morphology. Dursun syndrome additionally has multiple congenital anomalies besides SCN.

Ethical dilemma for Case IV: 3 – whether society should make those treatments accessible. Parents have overall responsibility to take care of the child in spite of social support, and they have to take following into consideration before any final decision.
Financial burden: cost of treatment, travel, accommodation, and loss of income.
Time burden: frequent hospital visits, tests, and lifelong follow-up.
Career impact: parents or caregivers may need to reduce work hours or leave their jobs.
Psychological burden: constant stress, uncertainty, caregiver burnout, and emotional exhaustion.
Social stigma: the child and family may experience discrimination or isolation.
Even if a drug exists, there are many burdens and struggles for the child and family.
Ethically, society should aim not only to provide the medicine but also to support families through affordable healthcare, caregiver assistance, workplace flexibility, and psychological support.
The responsibility should not fall on the family alone. Even if a drug exists, lifelong dependence on expensive treatment can place a major emotional, social, and economic burden on the child and family. Ethically, society should aim not only to provide the medicine but also to support families through affordable healthcare, caregiver assistance, workplace flexibility, and psychological support. The responsibility should not fall on the family alone.

Why should society take responsibility if parents can terminate the affected child? Which ethical principle should take priority: parental responsibility for foreseeable outcomes, or society's commitment to care for all children once they are born, regardless of the circumstances of their birth? There is no universal consensus, and different countries and cultures weigh these principles differently.

Thought Riveting:

- *What is the molecular basis of cardiac defects in CXCR4-associated WHIM syndrome?*
- *Can a CXCR4 agonist be used to promote hematopoietic stem cell engraftment in transplantation?*
- *What could be clinical utilities of Motixafortide, Balixafortide, and LY2510924 (next-generation peptide-based CXCR4 antagonists)?*
- *How do plant-derived phytochemicals inhibit the CXCR4/CXCL12 signaling pathway?*