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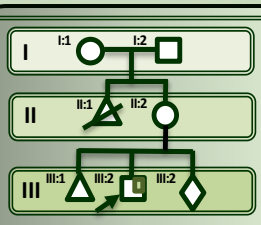
Pulmogenetics-XIII/ Syndromes associated with Bronchiectasis / Hyper-IgE syndrome with recurrent infections (HIES) including *STAT3*-HIES

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.



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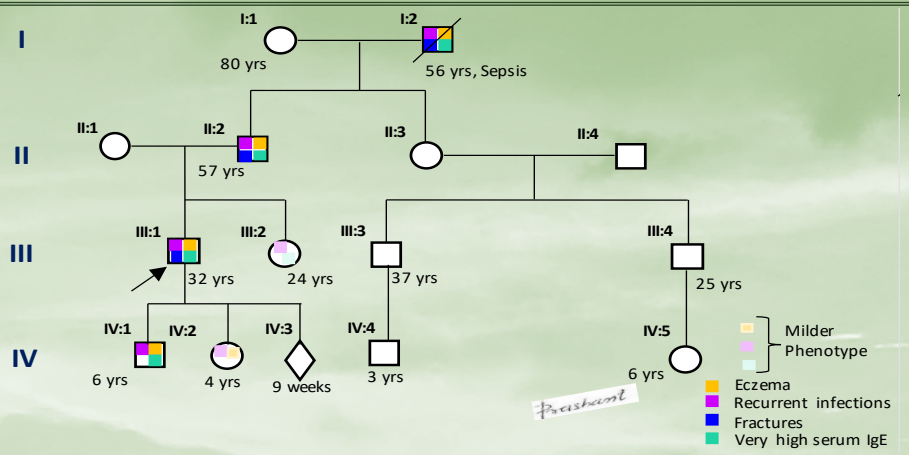

NGS data analysis initial step: BCL file (raw data) to Fastq file

bcl2fastq conversion steps for Window based system

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

https://learn.microsoft.com/en-us/windows/wsl/install

Download and install
bcl2fastq Conversion Software
dual role **demultiplexes data and conversion**

https://anaconda.org/dranew/bcl2fastq
https://sapac.support.illumina.com/sequencing/sequencing_software/bcl2fastq-conversion-software.html
https://support.parsebiosciences.com/hc/en-us/articles/360058912372-Generating-fastq-files-with-bcl2fastq
https://sapac.support.illumina.com/sequencing/sequencing_software/**bcl-convert.html**

Command for Run the converiosn command with SampleSheet.csv input (demultiplexes)

```
bcl2fastq --runfolder-dir <path/to/illumina/run/folder>
--output-dir <path/to/output/folder> --sample-sheet <path/to/SampleSheet.csv>
```

Online alternatives to bcl2fastq
Illumina BaseSpace Sequence Hub
10x Genomics Cloud Analysis

https://sapac.illumina.com/products/by-type/informatics-products/basespace-sequence-hub.html
https://www.10xgenomics.com/products/cloud-analysis

Insight:

1. How does the bcl2file convert to the fastq?
2. What is the phenotypic spectrum of "Autoimmune disease, multisystem, infantile-onset,1" (ADMIO1)?
3. How would you approach a case with eosinophilic pustular folliculitis (EPF)?
4. What are the specific points of ponder for doing antenatal genetic testing counselling for **Case IV: 3**?
5. What are the key characteristic features of different types of "hyper-IgE recurrent infection syndromes" (HIES)?

Plausible tenets:

Gene: STAT3 (Signal Transducer and Activator of Transcription 3) 17q21.2, genomic coordinates (GRCh38): 17:42,313,324-42,388,442 (from NCBI)

- A member from a family of seven STAT proteins (1 to 6, with 5A/5B) related to cytokine signaling . All STAT proteins have conserved six domains. They are basically transcription factors in active state, and activate the targeted genomic sites in the nucleus.
- **Activation Process:** Activated receptors after binding of cytokines or growth factors → Activated Janus kinases (JAKs) leads to phosphorylation of STAT→ STAT dimerization and nuclear translocation→ altered targated genes transcription directly or indirectly [such as recruits coactivators (NCOA1 or MED1)]→ Inactivation by nuclear phosphatases dephosphorylate and cytoplasmic transportation.
- Inflamation regulation by regulating differentiation of naive CD4(+) T-cells into regulatory T-cells (Treg) or T-helper indirectly by promoter acetylation. Cell cycle regulation by controlling expression of cell cycle key genes like as CCND.
- Gene : 75,245 bases, 215 orthologues, 6 paralogues, and 14 splice variants.
- Transcript: 24 exons & 23 coding exons; 21 domains and features; transcript length 5,047 bps.
- Protein: 770 AA with 88068 Da molecular mass.
- **Gene tree (a pedigree of gene)** ENSGT01050000244905, ***Number of*** genes - 928, speciation nodes - 798, duplication -80, ambiguous - 42, gene split events - 7
  https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000168610;r=17:42313324-42388568

- **Genotypes and phenotypes correlation**: **Dominant Negative Loss Of Function(DNLOS)** mutations lead to HIES, while **gain of function(GOF)** persistently activate the immune response, known as Autoimmune disease, multisystem, infantile-onset,1 **(ADMIO1)**

Phenotype: AD mode of inheritance (**MOI**), with recurrent infections (**Job syndrome**)-

- **Confirmatory diagnosis by molecular testing**, a clincial scoring sysem can be used for suspected cases of HIES[PMID: 10441580].
- Additional head to toe exmination findings with STAT3 related HIES: delay shedding of primary teeth, **Infantile EPF**; various collagenopathy like features as joint hyperlaxity, coronary artery and cerebral aneurysms, bone fragility (osteoporosis); **coarse facial features with widene alar width as a charecteristic consistent facial feature**.
- Infections specrum: cold absecess at various sites; recurrent pneumonia, bronchitis, and otitis; nail infections, chronic mucocutaneous candidiasis.
- The **classic triad** of abscesses, pneumonia, and an elevated IgE level in around 80 % of cases [PMID: 10053178].
- Cancer incidence is 8.2%, in which NHL is the most common type in dominant-negative mutations in the STAT3 gene **(STAT3DN)** mutant cases [PMID: 35059947].
- **Management: primary and followup evaluation is mandatory. There is a role of hematopoietic cell transplantation (HSCT) in selected cases for immunological issues. https://www.ncbi.nlm.nih.gov/books/NBK25507/#higes.Management**

Hyper-IgE recurrent infection syndrome (HIES) - PS147060 - 6 Entries with key characteristic features

Phenotype/MIM	Location	Gene/MOI	Gene function	Age of onset	Course facies	Skeletal features	Miscellaneous
HIES1/147060	17q21.2	STAT3/**AD**	Mediates cytokine-induced signal transduction	Early childhood	Present	Fracture, scoliosis, joint hyperlaxity	Classic triad (77%), cancer risk (8.2%), pneumatoceles requiring surgery, retained primary tooth.
HIES2/243700	9p24.3	DOCK8/AR	Regulates immune cell signaling pathways.	6 months to 5 years	Absent	Absent	Autoimmune hemolytic anemia, severe CNS complications, high mortality.
HIES3/618282	20q11.22	ZNF341/AR	Activates STAT1 and STAT3 transcription	Infancy to early childhood	Present (mild)	Joint hyperlaxity, fracture	No viral infection/allergies, intellectual disability common, retained primary tooth.
HIES4A/619752	5q11.2	IL6ST/**AD**	GP130 (IL6ST)- Mediates IL-6 family cytokine signaling.	Early childhood	Present (mild)	Scoliosis, club foot	No chronic mucocutaneous candidiasis, variable severity within families, supernumerary tooth.
HIES4B/618523	5q11.2	IL6ST/AR	Unit of the cytokine receptor complex	Infancy	Absent	Scoliosis, dislocation of hip, contractures in upper limb	Craniosynostosis pathognomonic, severe skeletal anomalies, delayed tooth eruption, developmental delay.
HIES5/ 618944	1q21.3	IL6R/AR	Part of receptor complex of IL6	Neonatal to childhood	Absent	Absent	Absent inflammatory response, no significant viral/fungal infection

Hyper-IgE syndrome with recurrent infections

A primary immune deficiency syndrome has following features:

- Chronic eczema or atopy
- High IgE
- Eosinophilia
- Recurrent infections with paucity of inflammatory signs

Plus

Immunologic abnormalities:

- Defects in T-lymphocyte subgroups
- Abnormal granulocyte chemotaxis
- Compromised antibody production

Eosinophilic pustular folliculitis (EPF)

- Red-itchy sterile papulopustular lesions around hair follicles, look like ring shaped plaques, mostly on head and neck.
- Three subtypes:
  - Classic EPF (Ofuji disease, in middle age person)
  - HIV-associated EPF
  - Infantile EPF
- Pathophysiology: Immune system dysregulation→ Chemokines (IL-4,5 & 13) and prostaglandins D2→ eosinophilic infiltrate → local reaction and microabscesses

Autoimmune disease, multisystem, infantile-onset,1 (ADMIO1)

- **Autoimmune diseases -** GIT-celiac disease; Endocrine-type 1 DM, delayed puberty, hypothyroidism; Haematological- diverse autoimmune disorders; Musculoskeletal- arthritis, Skin-dermatitis, Pulmonology-interstitial lung disease.
- **Additional features:** increase risk for large granular lymphocytic T-cell leukaemia, short stature, eczema, immunodeficiency but normal response to vaccination,
- Phenotypic Series - PS615952, Types 1 to 5, **AR MOI** except type 1

Counsel the family for Case IV: 3 – Molecular study is helpful to predict hypomorphic versus a strong dominant-negative (DN) variant. But **STAT3-HIES shows significant intrafamilial variability** (incomplete penetrance), and the disease is not fatal in all affected family members, so antenatal molecular testing, and clinical analysis of family will not definitely help in predicting the disease severity. It would help them to reach final decision. There is no strong genotype and phenotype relationship for many variants except a few.

Thought Riveting:

- ***What could the most common domain of STAT3 involved with collagen biosynthesis regulation?***
- ***Is prevalence of an inborn error of cytokine signaling (mild spectrum) quite common in society?***
- ***What will be the phenotype of compound heterozygous, LOF with dominant negative mutation of STAT3 gene?***
- ***Can upregulation of STAT3 be used as a disease modifier for cystic fibrosis?***
- ***What can be the broadened uses of Tofacitinib (JAK inhibitors) in autoimmune disorders?***