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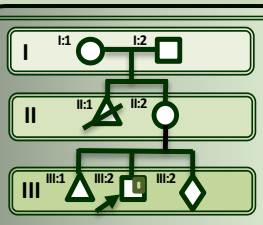
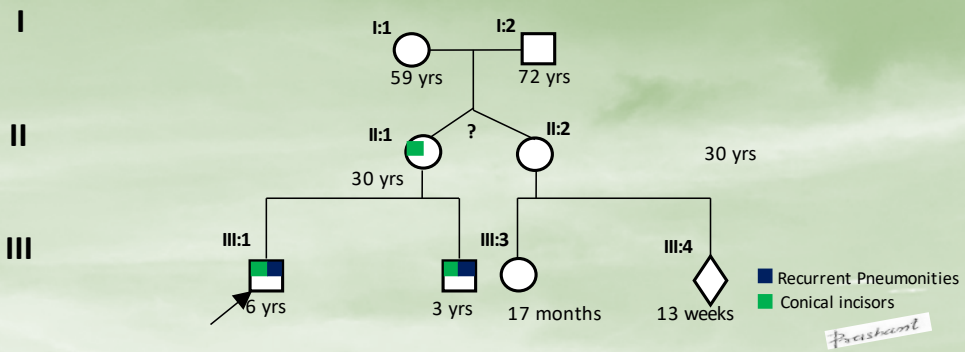
Pulmogenetics-XIII/ Syndromes associated with Bronchiectasis /Ectodermal dysplasia and immunodeficiency type 1(IKBKG related disorders)

From the desk of Editor

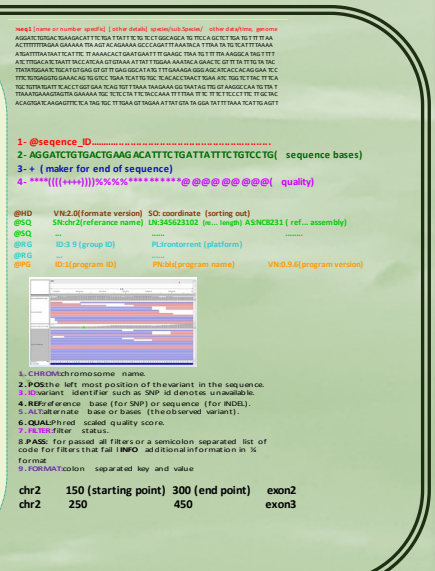
The genetic division of the Pediatric Department publishes a monthly newsletter for all Medical Professionals. The newsletter is related to genealogical parlance and is a deliberate attempt to enhance awareness of genetic disorders with recent updates.





File formats of exome sequencing data

- **FASTA (File, Alignment, Sequence, and Text All)-** a text-based data with two parts: 1. Header line (begins with >) has data information, & 2. Sequence line (max 80 characters/lines, but no limitations for line numbers)
- **FASTQ (quality score)-**four-line data: 1. Begin with @, having read & sequence information, run name, & date, 2. Raw sequence bases - A, T, G, C, & N (unknown), 3. Start with + & serve as a marker indicating the end of the sequence, or repeats first-line information, 4. Indicate quality by special symbols for each base (2nd line data).
- **SAM (Sequence Alignment/Map)** has short/long reads (up to 128 million bp), the header line starts with @HD, while @SQ it functions as a reference sequence dictionary in a BAM/SAM file. @PG lines has program information that used for developing the SMA file. @RG line/s has read group information. It's tab stores the mapped or aligned reference sequence.
- **BAM (Binary Alignment Map)** is a binary compressed form of SAM, and both interchangeable. Need IGV to read the file.
- **VCF (Variant Call Format):** all variant information in compressed text format. It has metadata (header begins with ##) and data lines (tab-delimited text lines). Each line contains nine fixed columns and sample column(s).
- **BED (Browser Extensible Display):** Tab-delimited format for DNA sequences that inform about genes and other features. It has three essential columns & optional columns.



Insight:

1. How will you do counselling for **Case III: 4**?
2. What are the characteristic features of ectodermal dysplasia?
3. What is Ectodermal dysplasia and immunodeficiency type 2?
4. Is there any genotype-phenotype correlation for the IKBKG related phenotypic spectrum?
5. What is the class switch recombination (CSR)?

Plausible tenets:

Gene: IKBKG (Inhibitor Of Nuclear Factor Kappa B Kinase Regulatory Subunit Gamma)/ NEMO(NF-κB Essential Modulator), Xq28, genomic coordinates (GRCh38): X:154,541,238-154,565,046

- A regulatory subunit of the inhibitor of kappaB kinase (IKK) **core complex[**4**(IKBKG)**, 4(CHUK/IKBKA), & 2(IKBKB)**]** that activates NF-kappaB(**NFKB**) by separation and degradation of the inhibitor (**NFKBIA**) from NF-kappa-B complex. Free NFKB stimulates many genomic target sites (genes related to inflammation, cancer, and immunity) in nucleus by bindings at its motifs like 5-prime **H**GGA**R**N**YY**CC 3-prime or 5-prime GGG**R**NN**YY**CC 3-prime(**R** is an A or G purine; **Y** is a C or T pyrimidine; **H** is A, C, or T).
- It has recognizing and binding capacity to 'Lys-63'-linked and linear polyubiquitin. This binding is key for IKK complex activation.
- Protect cytokine toxicity by controlling NF-kappa-B-mediated signallling.
- Many microbes (Hepatitis A, EBV, HTLV-1, coronavirus-2, and Shigella flexneri) escape host innate immunity by inactivating it.
- Gene : 23,848 bases, 1 paralogue, 188 orthologues, and 22 splice variants.
- Transcript: 10 exons & 9 coding exons; 55 domains and features; transcript length 1,973 bps.
- Protein: 419 AA with 48198 Da molecular mass.
- **Gene tree** (**a pedigree of gene**) ENSGT00530000063808, ***Number of*** genes - 400, speciation nodes - 372, duplication -22, ambiguous - 5, gene split events - 0
  https://asia.ensembl.org/Homo_sapiens/Gene/Compara_Tree?db=core;g=ENSG00000269335;r=X:154541199-154565046;t=ENST00000594239

Phenotype: Tissue threshold for protein truncation: nervous system > eye > ectoderm > Immune system

Ectodermal dysplasia and **immunodeficiency** 1(**EDAID1**), XLR inheritance

- Infantile onset of repetitive severe infections by various microbes in various systems, especially recurrent pneumonia.
- **Compromised 'class-switching' of B cells**: deficiency of particular IgG subclasses with or without raised IgA & IgM. Inadequate and variable response to vaccination
- **Other findings:** variable haematological abnormalities, organomegaly, osteopetrosis, lymphadenopathy.
- Females may express mild features of the disease especially the ectodermal dysplasia feature such as conical teeth and mild recurrent infections

Managemet: IV immunoglobulines, prophylactic antibiotics, and BMT

IKBKG related phenotypic spectrum

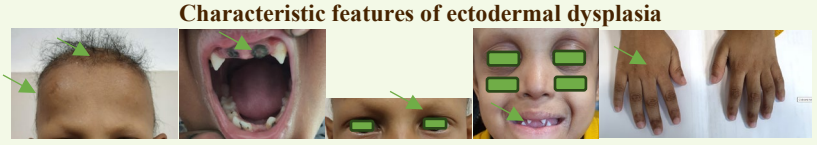
Phenotype	OMIM /MOI	Key features	Variation
Autoinflammatory disease, systemic, X-linked/	301081/ XL	Granulomatous inflammation in many organs, organomegaly, lipodystrophy, panniculitis, and lymphopenia	hypomorphic, NEMOdelEx5 splice isoform
Ectodermal dysplasia and immunodeficiency 1	300291/ XLR	Recurrent infections (low IgG2), ectodermal dysplasia.	Hypomorphic to amorphic allele for zinc finger domain alteration
Immunodeficiency 33	300636 / XLR	Predominantly immunodeficiency, increased risk for mycobacterial disease	Interference of leucine zipper domain, exon 9 variants
Incontinentia pigmenti (After apoptosis of unskewed X cells in early life, leaving the normal cells with sequelae on different body system) (a neuroectodermal dysplasia)	308300 / XLD	**Genodermatosis**, 4 classic cutaneous stages, retinal detachments, dental dysplasia, transient immunodeficiency, CP mimic (molecular sequence-CP)	Amorphic or "null" allele for zinc finger domain alteration, extremely skewed X-inactivation to save another X with a functional gene

Ectodermal dysplasia and immunodeficiency 2

- NFKBIA/ or IKBA (Nuclear Factor Kappa-B Inhibitor, Alpha), 14q13.2, Genomic coordinates (GRCh38): 14:35,401,513-35,404,749

- Normal cellular milieu keeps NFKB silenced [PubMed: 10199915].
- Steroids directly activate the synthesis of this protein, leading to supressed cellular immune reactivity [PubMed: 7569975].
- **Role of probiotics in IBD:** NFKBIA do not degrade in the presence of non-pathogenic bacteria in intestinal epithelium, that reduces the inflammation.
- Less activity of IKBA supresses the apoptosis, and it increases the changes of cell mutagenesis.
- Phenotype has overlapping features with type 1 &, it additionally may lead to neutrophilic leucocytosis and autoinflammatory disease.
- **Genotype-phenotype relationship:** Missense variants with gain of function have a more severe phenotype than non-sense variants.

Characteristic features of ectodermal dysplasia



Sparse, thin fragile hair; hypodontia, conical or pegged-shape incisors; and thin, hypo/anhidrosis dry coarse skin

'Class-switching' of B cells

- Essential molecular process for **switching IgM to other Ig** in activated B lymphocytes by double-stranded DNA break (DSB) & followed by DSB repair with activation-induced cytidine deaminase (AID)- mediated deamination.

Counsel the family for Case III: 4 – First, molecular testing in the proband, later on, testing the same variant in case II:2 to rule out a carrier status [intrafamilial variability has been reported due to unknown modifier gene(s)]. There is no additional risk compared to the control population with a negative report, so no molecular testing is recommended. In case of a positive report for case:II, antenatal testing can be planned.

Thought Riveting:

- ***What are the non-canonical functions of the IKK-signalosome holo-complex?***
- ***Can IKBKG signaling pathway dysfunction lead to immune dysregulation and autoimmune diseases?***
- ***What are the potential endotypes for suppressing the overactivity of IKBKG?***
- ***What are likely hypotheses for unreported human diseases with ubiquitin C & B (UBC & UBB)?***
- ***What are the prerequisites and guidelines to select a protein in drug design as a biological-agents?***