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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-XV/ Syndromes associated with Bronchiectasis / Respiratory infections, recurrent, and failure to thrive with or without diarrhea (**RIFTD**)

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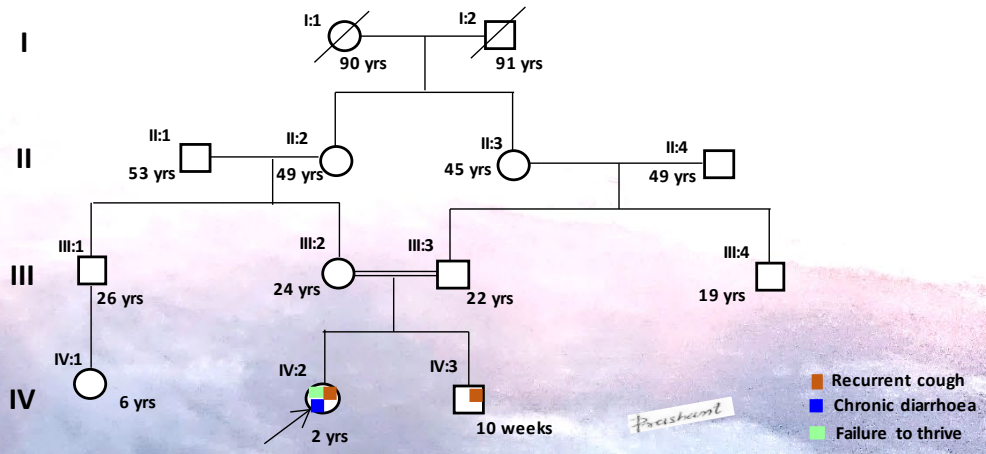
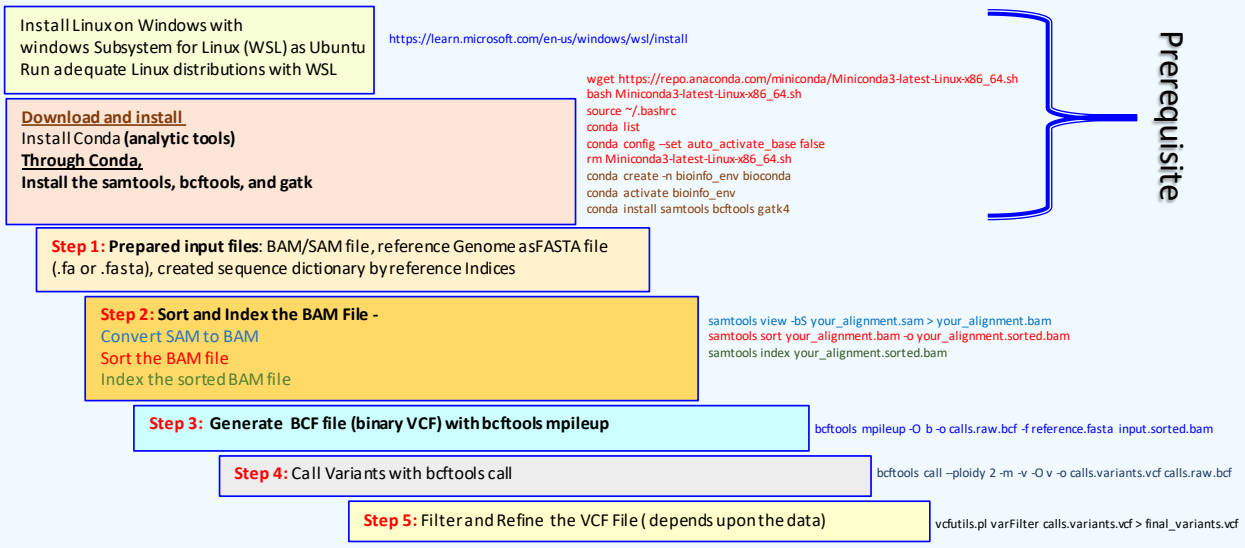


Insight:

1. What are the clinical presentations of RIFTD?
2. What is the Suppression Subtractive Hybridization (SSH)?
3. What are the possible phenotypes of ERCC related disorders?
4. How can BAM/SAM files be converted to VCF files in a Window-based system?
5. What is the differential diagnosis for a case with recurrent respiratory infections and diarrhea, with failure to thrive?
6. Case III:4 wants premarital genetic counseling (**PGC**), what are the steps for **PGC**?

BAM/SAM file to VCF file conversion steps for Window-based systems

Multi-step variant calling in Window based system from BAM/SAM file to VCF file



Plausible tenets:

Gene: AGR2 (Anterior Gradient 2, Protein Disulphide Isomerase Family Member) 7p21.1, genomic coordinates (GRCh38): 7:16,791,811-16,804,999

- Discovered using the technique of **Suppression Subtractive Hybridization (SSH)** in **1998 by Devon A**.
- A member of the protein Disulfide Isomerase (PDI) family. AGR2 functions in a monomer-dimer equilibrium. The monomer, a secreted form, acts as a pro-inflammatory chemokine, and the dimer form (in ER) acts in cellular homeostasis.
- It localizes inside the endoplasmic reticulum (ER), and it helps in folding, trafficking, and assembling the proteins by catalyzing secondary changes of proteins such as folding, quality control, and disulfide bond formation, especially cysteine-rich proteins (MUC2). It indirectly works like chaperone, cell migration, and cellular transformations.
- It acts like a p53 inhibitor, and behaves like a proto-oncogene. It might have a role in inflammatory bowel disease and cancer.
- Dystroglycan (specifically the β-subunit) binds AGR2 protein. AGR2 protein impacts cytoskeleton and cell adhesion by regulating dystroglycan stability (upregulates post-transcriptionally) and localization. This role has been studied in cancer and fetal development.
- The AGR2 protein also binds the Epidermal Growth Factor Receptor (EGFR), and functions as a key regulator of EGFR.
- Gene: 42,047 bases, 211 orthologues, 2 paralogues and 12 splice variants.
- Transcript: 8 exons and 8 coding exons; 15 domains and features; transcript length 1,697 bps.
- Protein: 175 AA with a molecular mass of 19,979 Da.
- Expressed in the majority of tissues, and overexpressed in the gut, respiratory tract and prostate.

Phenotype: Respiratory infections, recurrent, and failure to thrive with or without diarrhea (RIFTD), autosomal recessive MOI.

Clinical phenotype spectrum:

- **Respiratory:** recurrent wheezing, particularly infection triggered, recurrent pneumonitis, bronchiectasis, interstitial lung disease.
- **Gut:** unexplained chronic diarrhea, infantile-onset inflammatory bowel disease (IBD) and recurrent vomiting.
- **Other systems:** (**mostly secondary**) pulmonary hypertension and organomegaly, recurrent otitis media, failure to thrive, and motor delay.
- Significantly high **ceramide-26 isomers** in dried blood spot study.

Suppression Subtractive Hybridization (SSH)

- **PCR based technique, that** helps to differentiate different expression in two related samples (two different cell lines as case and control)
- **Steps:** mRNA to cDNA → cDNA adapter ligation → hybridization with driver cDNA (the reference sample) → Suppression PCR subtractive hybridization (or representational difference analysis, RDA) → subtraction of common hybridized fragments, and retaining differentially expressed cDNA → library construction
- **Utilities**: new gene discoveries, understanding host-pathogen interactions and identifying differentially expressed genes in different situations

Differences between RIFTD and CF

No.	Feature	Cystic Fibrosis (CF)	RIFTD
1.	**Genetic basis**	**CFTR gene** (7q31.2) >2000 mutations documented	**AGR2 gene** (7p21.1) limited mutation spectrum
2.	**Sweat chloride test**	**Elevated** (>60 mmol/L diagnostic)	**Normal** (<30 mmol/L);
3.	**Pancreatic function**	**Pancreatic insufficiency** in ~85%	**Normal pancreatic elastase**
4.	**Meconium ileus**	**Common** (~15-20% of CF neonates)	**Absent** - not reported
5.	**Cilia morphology**	**Normal ciliary structure** and function	**Ciliary abnormalities** (34% in family 8):
6.	**Liver involvement**	**Cirrhosis & portal hypertension** in 3-5%;	**Hepatosplenomegaly** in 31%
7.	**Cardiovascular complications**	**Cor pulmonale** from chronic hypoxia and lung disease; not primary pathology	**Mitral valve insufficiency and right heart failure with severe pulmonary hypertension** (15%)
8.	**Blood/metabolic markers**	**Immunoreactive trypsin (IRT)** elevated in newborns (screening marker)	**Elevated ceramides** (specifically ceramide-26 isomers significantly elevated compared to CF and controls)
9.	**Male infertility**	**Congenital bilateral absence of vas deferens (CBAVD)** in >95% of males; major fertility issue	**Not documented**
10.	**Systemic multi-organ dysfunction**	**Multisystem disease**: pancreas, liver, reproductive tract, sweat glands, intestines	**Primarily respiratory-gastrointestinal**

OMIM Entries with search tool- (("**RECURRENT RESPIRATORY INFECTIONS**" AND **DIARRHOEA** AND **FAILURE TO THRIVE**))

No.	Disorder Name/ OMIM ID	Gene	Distinguishing Features
1	**Respiratory Infections, Recurrent, and Failure to Thrive with or without Diarrhea (RIFTD) /620233**	**AGR2**	Elevated **ceramide-26 isomers** on dried blood spots - ciliary abnormalities on electron microscopy (missing central doublets, dynein arm defects) - Normal sweat chloride & pancreatic elastase
2	**Immunodeficiency-22 (IMD22) / 615758**	**LCK**	**Severe CD4 T-cell lymphopenia**, nodular skin lesions with panniculitis, pericarditis, retinal vasculitis
3	**Immunodeficiency-19, Severe Combined (IMD19) / 615617**	**CD3D**	**Absent circulating CD3+ T cells**, CMV hepatitis with multiorgan viral infections, thymic involution
4	**Immunodeficiency-7 (IMD7)/ 615387**	**TRAC**	**TCR-gamma-delta+ / TCR-alpha-beta- T cells** (reversed normal ratio), vitiligo, eczema, alopecia areata, EBV-positive B-cell lymphomas
5	**Common Variable Immunodeficiency-8 with Autoimmunity (CVID8) / 614700**	**LRBA**	**Marked reduction in CD4+ regulatory T cells (Treg)**, ITP, hemolytic anemia, autoimmune thyroiditis, Granulomatous infiltration
6	**Severe Combined Immunodeficiency due to Adenosine Deaminase Deficiency (SCID-ADA)/ 102700**	**ADA**	**Markedly elevated red cell dATP/dAXP**, lymphopenia with absent CD3+ T cells & impaired T-cell proliferation - Skeletal abnormalities
7	**Congenital Disorder of Glycosylation Type III (CDG2J)/ 613489**	**COG4**	**Profound developmental delay, microcephaly, cerebral atrophy**, liver cirrhosis with coagulopathy
8	**Immunodeficiency-58 (IMD58)/ 618131**	**CARMIL2**	**Chronic mucocutaneous candidiasis**, severe eczema, psoriasis-like lesions, ichthyosis, **disseminated EBV-related smooth muscle tumors**
9	**Agammaglobulinemia- 1, Autosomal Recessive (AGM1) / 601495**	**IGHM**	**Absent B cells with hypogammaglobulinemia**, enteroviral encephalitis with chronic infections
10	**Congenital Disorder of Glycosylation Type 1EE (CDG1EE)/ 621140**	**MAN2B2**	**Severe developmental delay,** dysmorphism- strabismus, beaked nose, lymphopenia with low naive CD4/CD8 T cells & **undetectable TRECs**
11	**Immunodeficiency-85 and Autoimmunity (IMD85)/ 619510**	**TOM1**	**Extreme failure to thrive** (−4 to −5 SD) from infancy - Severe respiratory insufficiency(pneumonitis), Duodenal villous atrophy, aphthous changes in ileum, neutrophilic cryptitis
12	**Pigmentary Disorder, Reticulate, X-linked (PDR)/ 301220**	**POLA1**	**Distinctive reticulate/lacy hyperpigmentation**, **Corneal inflammation & scarring**, Ulcerative colitis with enterocolitis
13	**Immunodeficiency-31 C / Chronic Mucocutaneous Candidiasis, Familial-7 (IMD31C/CANDF7) / 614162**	**STAT1**	**Chronic mucocutaneous candidiasis**, thyroiditis, type 1 diabetes, hemolytic anemia, ITP, autoimmune enteropathy
14	**T-cell Immunodeficiency, Congenital Alopecia, and Nail Dystrophy (TIDAND) / 601705**	**FOXN1**	**Congenital alopecia** (universal hair loss from birth, including eyebrows/eyelashes) - **Congenital nail dystrophy**, Congenital athymia with profound CD4+ T-cell lymphopenia
15	**Immunodeficiency-57 with Autoinflammation (IMD57) / 618108**	**RIPK1**	**Chronic inflammatory bowel disease**, **inflammatory polyarthritis**, Hepatosplenomegaly with mouth ulcers & high burden of atypical organisms (CMV, MAC, Aspergillus)

- **Rest twelve entries consistently did not have the given phenotypes: ICF1 (DNMT3B), CVID11 (IL21), CDG2A (MGAT2), IDAIL (CTLA4), IMD53 (RELB), IMD56 (IL21R), IMD100 (OAS1), IMD112 (MAP3K14), PGBM1 (RBCK1), GLND (GLUL), SGD2 (SMARCD2), and IBDIMDE (TGFB1)**

PGC for Case III: 4 – It empowers couples to understand risk assessment, preventive strategies, and future family planning. It requires two or three rendezvous with a PGC expert. The first meeting includes proper medical clinical evaluation, baseline non-genetic tests, and family records evaluations. Genetic tests are discussed in the second meeting on the basis of data from the first meeting, along with the output of clinical analysis and reports. Final PGC counseling is planned on the basis of the second meeting, and molecular reports; however, it could be conducted in the second session if couples do not want carrier assessment or the availability of their carrier status for genetic diseases.

Thought Riveting:

- *Can Bortezomib and MG132 be used as anticancer drugs in combination therapies especially in estrogen receptor negative breast cancers?*
- *How do different hormones regulate AGR2 levels by epigenetic mechanisms?*
- *Does dysbiosis primarily impact AGR2 expression in the gut, and its somatic mutations can lead to inflammatory bowel disease?*
- *What are the possible autoimmune disorders associated with AGR2 monomer-dimer disequilibrium?*