Molecular in My Pocket…

Inherited Conditions

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Prepared by the Association for Molecular Pathology Training and Education Committee

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AMP Association for Molecular Pathology

Hearing Loss

- Hearing loss can be categorized as syndromic or non-syndromic
- Types of hearing loss—sensorineural, conductive, mixed, or auditory neuropathy
- ~60% genetic and 40% environmental
- 70% of genetic cases are nonsyndromic hearing loss and majority (80%) are autosomal recessive conditions. May be also transmitted as autosomal dominant, X-linked, or matrilineal trait
- ~50% of individuals with autosomal recessive non syndromic sensorineural hearing loss carry *GJB2* mutations (DFNB1 locus)
- Mutation spectrum in *GJB2* includes: missense, nonsense, splicing, frameshift and in-frame deletions
- Carrier frequency is 2-3% Caucasians, 4-5% Ashkenazi Jewish. Most common *GJB2* mutation is c.35delG

Cystic Fibrosis

- Characteristic features include: chronic sinopulmonary disease, gastro intenstinal abnormalities, infertility in males and salt loss syndromes. Autosomal Recessive with biallelic mutations in the *CFTR* gene
- *CFTR* gene : Autosomal recessive
- Incidence: ~1:2000-3000 births
- Two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L)
- Population frequency 1/29 Caucasians and Ashkenazi Jewish
- The American College of Medical Genetics recommended panel includes the 23 pathogenic variants
- Panel has a detection rate of 97% in Ashkenazi Jewish, 88.3% in non-Hispanic whites, 69% in African Americans, and 57% in Hispanic Americans

Duchenne Muscular Dystrophy/Becker Muscular Dystrophy

- Duchenne muscular dystrophy is a progressive muscle disease usually presenting in early childhood with delays in sitting and standing independently, affected children are wheel chair dependent by 13 years.
- Cardiomyopathy is a common feature
- Common X-linked recessive lethal disease with incidence ~1 in 3,500 newborns
- Approximately 1/3 of cases are due to de novo mutations
- BMD: milder phenotype, characterized by later onset skeletal muscle weakness, and dilated cardiomyopathy is a common cause of morbidity.
- *DMD* gene testing: ~65% of mutations are large deletions; 5-10% partial gene duplications, majority are at 5'end of the protein
- Pathogenic variants that do not alter the reading frame (in-frame deletions/duplications) generally correlate with the milder BMD phenotype. Reading frame disruption results in a more severe phenotype

Factor II

- Prothrombin-related thrombophilia
- Mutation in 3' UTR of *F2* gene: c.*97G>A (legacy nomenclature 20210G>A)
- Risk factor for DVT (RR 2-5) and thrombosis (RR 3-4) in heterozygotes; risk is higher in homozygotes. Additional risk factors include pregnancy and oral contraception
- Low penetrance: Most heterozygotes do not experience symptoms. Therefore population screening is inappropriate.
- Found in nearly all ancestral groups, with highest population frequency in Caucasians (~2%)

Factor V

- Factor V Leiden-related thrombophilia
- Missense mutation in *F5* gene: p.R560Q
- Risk factor for DVT and pulmonary embolism; risk is higher in homozygotes compared to heterozygotes. Oral contraceptive use is discouraged in homozygous or heterozygous women; HRT use is discouraged in homozygous women
- Low penetrance: Most heterozygotes do not experience symptoms. Therefore population screening is inappropriate.
- Found in nearly all ancestral groups, with highest population frequency in Caucasians (~5%)

Sickle Cell Anemia

- Multisystem disease associated with chronic hemolytic anemia, episodes of acute illness, and progressive organ damage
- Missense mutation in *HBB* gene: p.E6V. Homozygous state causes classic sickle cell disease (HbSS). Heterozygous carriers have sickle cell trait (HbS), with risk of mild symptoms
- Also associated with HbSC disease, in which a patient is compound heterozygous for both the HbS and HbC mutations. HbC is an alternative mutation at the same amino acid position(p.E6K). HbSC disease is typically milder than HbSS disease
- Pathophysiology: Hemoglobin polymerization leading to erythrocyte rigidity (sickle cell shape) and vasoocclusive crises
- Found nearly exclusively in those of African or African admixed ancestry. In African Americans, the HbS carrier frequency is about 8%, and the HbSS incidence is approximately 0.3%

Trinucleotide Repeat Disorders

- A type of genetic disorder resulting from expansion of the number of trinucleotide repeats in or near certain genes. Each disorder has a unique number of repeats that constitutes the normal threshold
- The range of pathogenic repeats varies greatly, from 21 in Spinocerebellar ataxia Type 6 to 200+ in Fragile X syndrome. The smaller repeats can be sized by triplet repeat-primed PCR and capillary electrophoresis, whereas the larger repeats may require Southern blot.
- There are currently 15 known trinucleotide repeat disorders. 9 are polyglutamine disorders and 6 are non-polyglutamine disorders.
- Polyglutamine disorders: Huntington Disease (HD); Spinobulbar Muscular Atrophy (SBMA); Spinocerebellar Ataxias (SCA-1, 2, 3, 6, 7, and 17); Dentatorubro-Pallidoluysian Atrophy (DRPLA)
- Non-polyglutamine disorders: Fragile X Syndrome; Fragile XE Mental Retardation (FRAXE); Friedreich Ataxia (FRDA); myotonic Dystrophy (DM); Spinocerebellar Ataxias (SCA-8 and 12)

Prader-Willi

- An imprinting disorder characterized by severe hypotonia and feeding difficulties in early infancy, followed by delayed language and motor development, hyperphagia, obesity, distinct behavioral phenotype and hypogonadism
- Primary diagnostic assay: Methylation testing to detect abnormal imprinting in the PWCR critical region on 15q. Detects more than 99% affected individuals. If positive, additional testing is recommended to determine mechanism and recurrence risk

Mechanisms:

- Paternal Deletion (15q11.2-q13) in 65-75% of cases (recurrence risk <1%)
- Maternal UPD: 20-30% (recurrence risk <1%)
- Imprinting defect 5% (recurrence risk up to 50 %)
- Chromosomal rearrangement: <1% (recurrence risk up to 25%)

Angelman

- An imprinting disorder characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and, behavioral phenotype including inappropriate happy demeanor, and excitability.
- Methylation testing (15q11.2-q13) detects 80% of affected patients and *UBE3A* testing (11%), 10% of patients have an unknown genetic etiology

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- *UBE3A* gene mutations: 10% (recurrence risk up to 50 %)
- Chromosomal rearrangement: 10-15% (recurrence risk up to 25%)