Molecular in My Pocket…

Inherited Conditions

Prepared by the Association for Molecular Pathology
Training and Education Committee

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Hearing Loss

- Hearing loss can be categorized as syndromic or non-syndromic
- Types of hearing loss—sensorineural, conductive, mixed, or auditory neuropathy
- ~65% genetic and 35% environmental
- 70% of genetic cases are non-syndromic hearing loss and the majority (80%) are autosomal recessive conditions. It may also be transmitted as autosomal dominant, X-linked, or through mitochondrial inheritance
- ~50% of individuals with autosomal recessive non-syndromic sensorineural hearing loss carry *GJB2* disease causing variants (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. The most common *GJB2* mutation is c.35delG
- Biallelic *STRC* pathogenic variants a common cause of autosomal recessive hearing loss

Cystic Fibrosis

- Cystic fibrosis (CF) is a multisystem disease; features include: chronic sinopulmonary disease, pancreatic insufficiency, meconium ileus, failure to thrive in children, infertility in males, salt loss syndromes, and malnutrition.
- Autosomal Recessive with biallelic mutations in the *CFTR* gene
- CF affects 100,000 individuals worldwide.
- Two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mmol/L)
- Population frequency 1/29 Caucasians and Ashkenazi Jewish
- American College of Medical Genetics recommended panel includes minimum of 100 pan-ethnic CF-causing variants (updated in 2023 from 23 variants)
- Panel has 95% coverage of *CFTR* alleles in the US population.

Duchenne Muscular Dystrophy/Becker Muscular Dystrophy

- Duchenne muscular dystrophy (DMD) is an X-linked progressive muscular dystrophy which presents in the proximal muscles of the lower limbs in young children. Children often have the characteristic Gower's sign when rising to stand. Affected children are wheelchair-dependent in young adulthood.
- Cardiomyopathy is a common feature even in female carriers
- Incidence ~1 in 4,700 live male births
- Approximately 1/3 of cases are due to *de novo* mutations
- Becker muscular dystrophy (BMD) has a 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, and the 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
- Exon-skipping therapy in DMD restores the reading frame

Prothrombin-related Thrombophilia

- Thrombophilia related to prothrombin (factor II): leads to production of too much coagulation factor 2 (F2, also called prothrombin); disease inheritance is autosomal dominant
- 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
- Clinical expression of prothrombin thrombophilia is variable: Most heterozygotes do not experience any symptoms, therefore population screening is inappropriate.
- Found in nearly all ancestral groups, with the highest population frequency in Caucasians (~2-5%)

Revised 10/2023

Factor V Leiden

- Most common inherited form of thrombophilia characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism
- 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.
- Hormone replacement therapy is discouraged in homozygous women
- PTM is inherited in an autosomal dominant pattern with variable penetrance.: Most heterozygotes do not experience any symptoms, therefore population screening is inappropriate.
- Found in nearly all ancestral groups, with the highest population frequency in Caucasians (~5%)

Sickle Cell Anemia

- Multisystem disease associated with chronic hemolytic anemia, episodes of acute illness, infection, and systemic vaso-occlusive disease which can result in organ infarct/ischemia
- Missense mutation in *HBB* gene: p.E6V. The homozygous state causes classic sickle cell disease (HbSS). Heterozygous carriers have sickle cell trait (HbS), with a risk of mild symptoms. HbC is an alternative mutation at the same amino acid position (p.E6K). Patients that are compound heterozygous for both the HbS and HbC mutations have HbSC disease which is typically milder than HbSS disease.
- Results in hemoglobin polymerization causing erythrocyte sickling which results in vaso-occlusive 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%
- Sickle cell anemia occurs often among people from parts of the world where malaria is or at one point was common

Trinucleotide Repeat (TNR) Disorders

- A type of genetic disorder resulting from the expansion of the number of trinucleotide repeats (TNR) 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. TNRs can typically 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)
- TNRs inheritance is dynamic and is termed 'anticipation'. Depending on parent of origin, in subsequent generations, the number of repeats increases
- Age at which the patient presents is inversely related to number of expansions

Prader-Willi Syndrome (PWS)

- 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% of affected individuals. If positive, additional testing is recommended to determine the mechanism (see below) and recurrence risk
- Methylation specific (MS) Multiplex-ligation dependent probe amplification (MLPA) can establish the diagnosis of PWS by identification of maternal-only imprinting and those caused by maternal UPD

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 Syndrome (AS)

- An imprinting disorder characterized by severe developmental delay or intellectual disability, severe speech impairment, gait ataxia and, behavioral phenotype including inappropriate happy demeanor, seizures, and excitability.
- Methylation testing (15q11.2-q13) detects 80% of affected patients and *UBE3A* testing (11%), 10% of patients have an unknown genetic etiology
- MS-MLPA is able to differentiate between AS caused by maternal deletion and those caused by paternal UPD

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