

## Molecular in My Pocket...

### Inherited Conditions

Prepared by the Association for Molecular Pathology Training and Education Committee

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#### 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 wheel-chair-dependent in young adulthood.
- Cardiomyopathy is a common feature even in female carriers
- Incidence ~1 in 3,500 newborns
- 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, 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**

#### Prothrombin-related Thrombophilia

- Thrombophilia related to prothrombin (factor II)
- 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 any symptoms, therefore population screening is inappropriate.
- Found in nearly all ancestral groups, with highest population frequency in Caucasians (~2%)

#### 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 non-syndromic hearing loss and majority (80%) are autosomal recessive conditions. May be also transmitted as autosomal dominant, X-linked, or through mitochondrial inheritance
- ~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, 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
- 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 most common, pan-ethnic 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

Factor V Leiden	Sickle Cell Anemia	
<p>Factor V related thrombophilia</p> <ul style="list-style-type: none"> <li>Missense mutation in <i>F5</i> gene: p.R560Q</li> <li>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.</li> <li>Hormone replacement therapy is discouraged in homozygous women</li> <li>Low penetrance: Most heterozygotes do not experience any symptoms, therefore population screening is inappropriate.</li> <li>Found in nearly all ancestral groups, with highest population frequency in Caucasians (~5%)</li> </ul>	<p>Multisystem disease associated with chronic hemolytic anemia, episodes of acute illness, infection, and systemic vaso-occlusive disease which can result in organ infarct/ischemia</p> <ul style="list-style-type: none"> <li>Missense mutation in <i>HBB</i> gene: p.E6V. Homozygous state causes classic sickle cell disease (HbSS). Heterozygous carriers have sickle cell trait (HbS), with 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.</li> <li>Results in hemoglobin polymerization causing erythrocyte sickling which results in vaso-occlusive crises</li> <li>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%</li> </ul>	<p>Angelman</p>
<p>Trinucleotide Repeat Disorders</p> <ul style="list-style-type: none"> <li>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</li> <li>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.</li> <li>There are currently 15 known trinucleotide repeat disorders. 9 are polyglutamine disorders and 6 are non-polyglutamine disorders.</li> <li>Polyglutamine disorders: Huntington Disease (HD); Spinobulbar Muscular Atrophy (SBMA); Spinocerebellar Ataxias (SCA-1, 2, 3, 6, 7, and 17); Dentatorubro-Pallidolusian Atrophy (DRPLA)</li> <li>Non-polyglutamine disorders: Fragile X Syndrome; Fragile XE Mental Retardation (FRAXE); Friedreich Ataxia (FRDA); myotonic Dystrophy (DM); Spinocerebellar Ataxias (SCA-8 and 12)</li> </ul>	<p>Prader-Willi</p> <ul style="list-style-type: none"> <li>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</li> <li>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 (see below) and recurrence risk</li> </ul> <p>Mechanisms:</p> <ul style="list-style-type: none"> <li>Paternal Deletion (15q11.2-q13) in 65-75% of cases (recurrence risk &lt;1%)</li> <li>Maternal UPD: 20-30% (recurrence risk &lt;1%)</li> <li>Imprinting defect 5% (recurrence risk up to 50%)</li> <li>Chromosomal rearrangement: &lt;1% (recurrence risk up to 25%)</li> </ul>	<p>Angelman</p> <ul style="list-style-type: none"> <li>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.</li> <li>Methylation testing (15q11.2-q13) detects 80% of affected patients and <i>UBE3A</i> testing (11%), 10% of patients have an unknown genetic etiology</li> </ul> <p>Mechanisms:</p> <ul style="list-style-type: none"> <li>Maternal deletion (15q11.2-q13) in 65-75% of cases (recurrence risk &lt;1%)</li> <li>Paternal UPD: 5% (recurrence risk &lt;1%)</li> <li>Imprinting defect: 5% (recurrence risk up to 50%)</li> <li><i>UBE3A</i> gene mutations: 10% (recurrence risk up to 50%)</li> <li>Chromosomal rearrangement: 10-15% (recurrence risk up to 25%)</li> </ul>