# 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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<table>
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<th>Hearing Loss</th>
<th>Cystic Fibrosis</th>
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| - 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 | - Characteristic features include: chronic sinopulmonary disease, gastro intestinal 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 wheelchair 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%)
## Sickle Cell Anemia

- Multisystem disease associated with chronic hemolytic anemia, episodes of acute illness, and progressive organ damage
- Missense mutation in \( F_5 \) 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 nearly exclusively in those of African or African admixed ancestry. In African Americans, the \( H_b S \) carrier frequency is about 8%, and the \( H_b S S \) incidence is approximately 0.3%

## Trinucleotide Repeat Disorders

### Prader-Willi
- 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 \( \text{SCA6} \) to 200+ in \( \text{FRAXE} \). In Fragile X syndrome, the \( \text{FRAXA} \) gene 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: Huntington Disease (HD); Spinocerebellar ataxia type 1 (SCA1); Spinobulbar muscular atrophy (SBMA); Spinal and bulbar muscular atrophy (SBMA); 6 are non-polyglutamine disorders: Friedreich ataxia (FRDA); Friedreich ataxia (FRDA); Friedreich ataxia (FRDA)
- Polyglutamine disorders: Huntington Disease (HD); Spinocerebellar ataxia type 1 (SCA1); Spinobulbar muscular atrophy (SBMA); Spinal and bulbar muscular atrophy (SBMA); 6 are non-polyglutamine disorders: Friedreich ataxia (FRDA); Friedreich ataxia (FRDA); Friedreich ataxia (FRDA)
- 9% of cases (recurrence risk <1%)

### Angelman
- 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 excitability.
- Methylation testing for \( T_{15} \) on chromosomes 15q11.2-q13 detects 80% of affected patients and 10% of patients have an unknown genetic etiology
- Mechanisms: Maternal deletion (15q11.2-q13) in 65-75% of cases (recurrence risk <1%)

### Trinucleotide Repeats
- Found in nearly all ancestral groups, with highest population frequency in Caucasians (~5%)

## Factor V

- Leiden-related thrombophilia
- Missense mutation in \( F_5 \) gene, \( p.R560Q \), with risk of mild symptoms
- Associated with \( H_b S \) disease, which is compound heterozygous for both the \( H_b S \) and \( H_b C \) mutations. \( H_b C \) disease is typically milder than \( H_b S \) 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 \( H_b S \) carrier frequency is about 8%, and the \( H_b S S \) incidence is approximately 0.3%