**DNA Sequencing, Demystified!**

**AGSDUS Conference, September 15th and 16th, 2017**Dr. Deeksha Bali, PhD., FACMG

Professor of Pediatrics

Laboratory Director of the Biochemical Genetics Laboratory

Duke Health, Durham, NC

Dr. McKenna Kyriss, PhD

Human Molecular Geneticist

Specializing in Metabolic Disorders

PreventionGenetics, Marshfield, WI

**ACMG:** American College of Medical Genetics and Genomics

**Allele:** One of alternative versions of a gene; a particular version or copy of a gene.

**(Autosomal) Recessive inheritance:** A genetic disorder in which two disease-causing (pathogenic) sequence variants, one in each copy of the gene, must be inherited for disease to occur. This occurs most often when one variant is inherited from the mother and one from the father. Both males and females can be affected, usually equally.

**Carrier:** Individual with only one copy (heterozygous) for a disease-causing allele.

**Clinical heterogeneity/variability:** The occurrence of variability among people with the same genetic changes.

**Copy number testing:** a technique used to look for larger pieces of DNA that are missing or duplicated. These cannot be detected by some sequencing techniques. (Example: if the sequence ABCDEF is the working copy of a gene, ABF has a deletion and ABCDBCDEF has a duplicated piece).

***De novo* sequence variant:** a sequence variant that is not inherited, but rather occurred as a new variant.

**DNA:** Deoxyribonucleic acid; encodes genes (on the chromosomes in nucleus), double stranded

**(Autosomal) Dominant inheritance:** A genetic disorder in which only one disease-causing sequence variant is required for disease to occur. Dominant disorders may be inherited from a parent (who may also have the disease) or may occur *de novo.* Both males and females can be affected, usually equally.

**Exome sequencing:** A DNA sequencing test that is used to look at all the regions of a person’s genome that are known to code for a protein.

**Gene:** a unit of DNA that codes for a protein.

**Gene panel:** A DNA sequencing test used to analyze more than one gene at the same time.

**Genetic heterogeneity/variability:** The occurrence of similar presentation in patients with different genetic mechanisms.

**Heterozygous:** a sequence variant that only occurs in one copy of the gene (Example: if a gene sequence is ABCDEF, and someone instead has one copy of the sequence ABC**C**EF and one copy of the sequence ABC**D**EF, we would say they are heterozygous for the D>C change).

**Homozygous:** when both copies of a sequence variant or region are the same (Example: if a gene sequence is ABCDEF, and someone instead has two copies of the sequence ABC**C**EF / ABC**C**EF, we would say they are homozygous for the D>C change).

**Human reference genome:** The sequence of the human genome put together by scientists using data from multiple donors. The same reference genome sequences are given specific identifying names and used by many scientists for comparison purposes. DNA sequence variants found in patients are described as a change from a known reference genome sequence.

**RNA:** Ribonucleic acid; single stranded mRNA – carries message to make enzyme/protein

**Whole genome sequencing:** A DNA sequencing test in which a person’s entire genome (all the DNA in a cell) is sequenced at once.

**X-Linked inheritance:** Disease caused by a pathogenic variant found on the X chromosome. In males, this is either inherited from the mom or is a new (*de novo*) variant. Some females can show symptoms.

**ACMG Variant Classification Categories:**

**Pathogenic sequence variant (P):** a DNA sequence variant (change from the reference genome) that has been determined, using evidence-based guidelines, to be causative for a specific disease.

**Likely pathogenic sequence variant (LP):** a DNA sequence variant (change from the reference genome) that has been determined, using evidence-based guidelines, to *probably* be causative for a specific disease, although there is some degree of uncertainty.

**Sequence variant of uncertain significance (VUS):** a DNA sequence variant (change from the reference genome) that has been classified as being of uncertain significance. This is either due to a lack of information about the variant or due to conflicting evidence about its potential to cause disease.

**Likely benign sequence variant (LB):** a DNA sequence variant (change from the reference genome) that has been determined, using evidence-based guidelines, to *probably not* be causative for a specific disease, although there is some degree of uncertainty.

**Benign sequence variant (B):** a DNA sequence variant (change from the reference genome) that has been determined, using evidence-based guidelines, to *not* be causative for a specific disease.