Genetic/Genomic Column October – 2015

I would like to say thank-you to the ORN members who completed the Genetics/Genomics Information Survey. I will attach a link at the end of this column for anyone still interested in completing the survey. Due to the interests expressed in the survey thus far, I will be discussing the most commonly used genetics/genomics terms, as well as, different inherited cancer predisposition syndromes in the subsequent newsletter columns.

Genetic/Genomic Terminology:

1. Autosomes: Humans have 23 pairs of chromosomes, totaling 46 chromosomes, in the nucleus of the cell. Chromosome pairs numbered 1-22 are autosomes. They are identical in both sexes. Chromosome pair 23 is the sex determining chromosome, or allosomes, which is designated XX or XY for females and males, respectively.

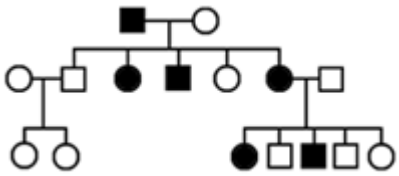
Autosomes are arranged by size: #1 being the largest and #22 the smallest

Telomere
P Arm – small arm - top
Q arm – long arm - bottom
Centromere

23rd chromosome pair is the sex determining chromosomes: XX female XY male.

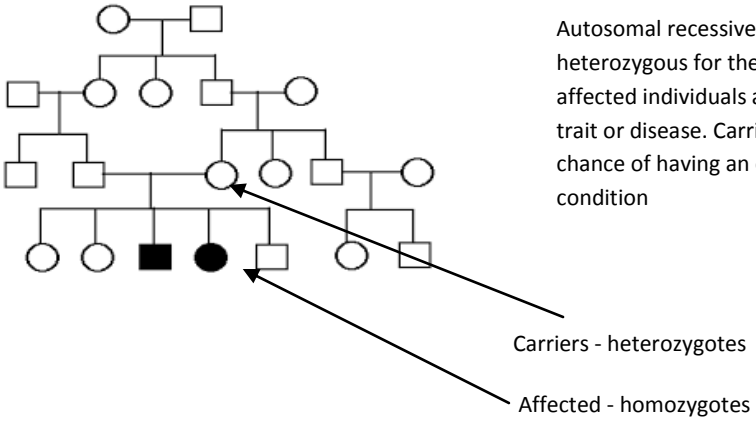
2. Autosomal dominant inheritance: a trait or disease is expressed when one gene of an autosomal chromosome pair (1-22) contains a variant or mutation. This occurrence is termed a *heterozygous* state for that trait. The trait or disease may be present in a parent and, consequently, passed on to the child. Males and females are equally affected by autosomal dominant inheritance. In family genetic pedigrees, this is termed *vertical transmission* of a trait. There is a 50% chance for a person with an autosomal dominant trait to pass it to their offspring.

Autosomal dominant inheritance:
Affected individuals are heterozygous for the trait or disease.



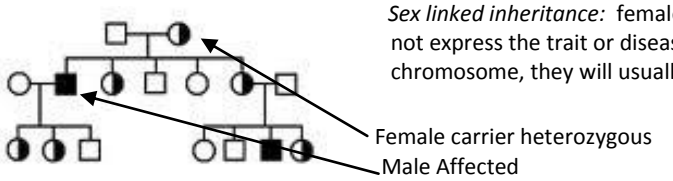
3. Autosomal recessive inheritance: a trait or disease is expressed when both genes of an autosomal chromosome pair (1-22) contain a variant or mutation. This characteristic is termed a *homozygous* state for that trait. In general, the trait or disease is NOT seen in multiple generations in a family. However, multiple family members in the same generation, such as siblings, may express the trait or disease. Parents of affected off spring are carriers and, usually,

do not express the trait or disease. Males and females are equally affected. Autosomal recessive traits or diseases can be seen more commonly in consanguineous, or related, populations.



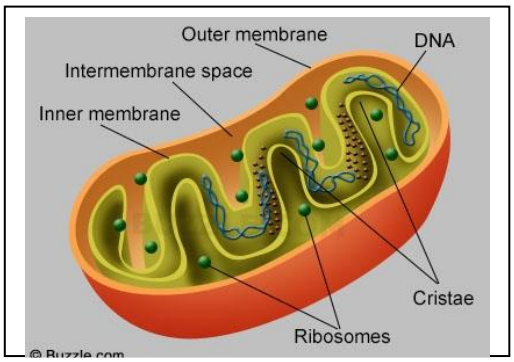
Autosomal recessive inheritance: carriers are heterozygous for the trait or disease and affected individuals are homozygous for the trait or disease. Carrier parents have a 25% chance of having an offspring with the condition

4. <u>X linked inheritance</u>: the genes for X linked inheritance are located on the X chromosome. Since females have two X chromosomes, they permanently inactivate one of the X chromosomes in their somatic cells very early in fetal development. This process of X inactivation is responsible for ensuring that the expression of X linked genes is equal in both sexes. X linked inheritance can be dominant or recessive. In instances where X linked inheritance is dominant, females express the trait or disease while males are often lethally affected early in fetal development. When the X linked inheritance is recessive, males are affected and females are only carriers and do not usually express the gene or trait.



Sex linked inheritance: females are heterozygous for and will usually not express the trait or disease. Since males have only one X chromosome, they will usually express the trait or disease.

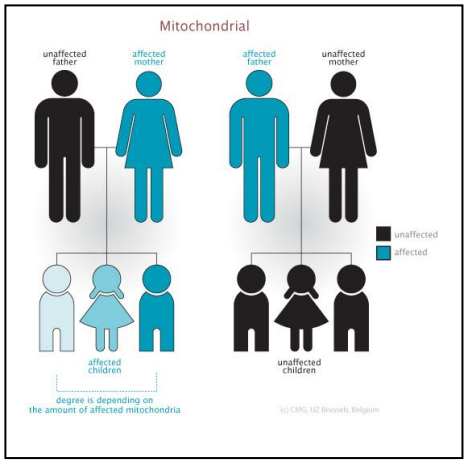
5. <u>Mitochondria</u>:



http://www.buzzle.com/articles/mitochondria-structure-and-functions.html

Mitochondria are intra cellular organelles that contain their own separate DNA (mtDNA) that encodes 37 mitochondrial genes. The mitochondria have been described as "the powerhouse of the cell" because they generate most of the cell's supply of adenosine triphosphate (ATP), used as a source of chemical energy. In addition to supplying cellular energy, mitochondria are involved in many other cellular functions including: cell signaling, cellular differentiation, cell death (apoptosis), and in maintaining control of the cell cycle and cell growth and aging. Mitochondrial DNA abnormalities have been implicated in several human diseases [mitochondrial disorders]. Eukaryotic cells often contain many mitochondria organelles (liver cells have >1000). Mitochondria are entirely inherited from the mother.

6. <u>Mitochondrial inheritance</u>:



The 37 mtDNA genes are maternally inherited through the fertilized ovum at conception. A mixture of wild type (normal mtDNA) and mutated mtDNA in a cell is called heteroplasmy. Because of the unique nature of mtDNA in heritance (there can be multiple copies of mitochondria with either normal or abnormal mtDNA) in different tissues of the body, there can be great variability of disease symptoms in family members with mtDNA diseases – **clinical heterogeneity**.

However, there are many nuclear genes that code for proteins that interact with or directly affect mitochondria and these nuclear genes follow the patterns of Mendelian inheritance. Thus mitochondrial diseases can be inherited maternally through the transmission of mitochondria or in autosomal dominant, autosomal recessive and X linked inheritance patterns.

Cancer predisposition syndromes with Different Modes of Inheritance:

1. Li-Fraumeni Syndrome – autosomal dominant: This condition is caused by mutations in the tumor suppressor TP53 gene located on chromosome 17 and was first described in 1969 by two physicians from the NCI: Dr. Joseph Fraumeni and Dr. Frederick Li. It is inherited in an autosomal dominant pattern and highly penetrant. **Penetrance refers to the percentage of people who have a particular genotype, or gene mutation, and display phenotypical (clinical) symptoms of the disease. For example, if a condition is 100% penetrant, then any person who inherits the mutated gene for the condition will demonstrate some sign or symptom. Expressivity refers to the severity of the symptoms of a genetic disease. Thus, a condition may be 100% penetrant but the symptoms may vary from mild to very severe.**

   Symptoms of Li-Fraumeni syndrome include early age of cancer development—often in childhood or adolescence—and multiple primary cancers. Epidemiology studies show, amongst the people diagnosed with Li-Fraumeni Syndrome, the chances for developing some type of cancer by the age of 50 is 93% for women and 68% for men (**penetrance**). In addition, women tend to develop cancer at an earlier age, with the median age for the first cancer being 29 years, for women and 40 years for men. Li-Fraumeni syndrome is suspected when there is a strong multigenerational family history of cancer.

   There are specific tumor types that raise suspicion for Li-Fraumeni syndrome, including: breast cancer, **soft tissue sarcomas**, **osteosarcomas**, brain tumors, acute leukemia, adrenocortical carcinomas, lung adenocarcinoma, colon cancer, pancreatic cancer, prostate cancer, Wilms tumor, phyllodes tumor (a rare form of breast tumor). Cancer patients with Li-Fraumeni syndrome will often be younger than age 50, have several family members who developed cancer before age 60 and have family members who have had more than one primary cancer or cancers occurring in paired organs (i.e. bilateral breast cancer). Since the Li-Fraumani type tumors are also commonly occurring sporadic tumors, the age of the patient at diagnosis and the family history are important criteria for consideration of Li-Fraumeni syndrome. There are several clinical ongoing clinical trials for patients with Li-Fraumeni syndrome.

2. Bloom syndrome – autosomal recessive: The gene for Bloom syndrome (BLM) is a DNA repair gene located on chromosome 15. This condition is inherited in an autosomal recessive pattern and the carrier parents are not symptomatic. Although Bloom syndrome is rare, it is more common in people of Ashkenazi Jewish ancestry.

   The symptoms of Bloom syndrome begin prenatally with the affected infants being smaller than average at birth—often weighing less than 2500 grams. The small stature and decreased body fat continues throughout life, with children and adults affected by Bloom syndrome falling below the 3rd percentile in height and weight. Children with Bloom syndrome can demonstrate feeding problems as infants by suffering from severe problems with reflux. They also have recurrent infections including, pneumonia and otitis media. By 2 years old, people with Bloom syndrome develop a sun sensitive rash across the mid-face, nose cheeks and other sun exposed areas on the arms and back of the hands. This is a chromosome instability syndrome and can be diagnosed by karyotype analysis looking for abnormally dividing chromosomes (abnormal sister chromatid exchange and quadriradial figures).

   Bloom syndrome patients have a very high rate of cancer and can develop bone marrow failure, myelodysplasias, leukemia, lymphoma, breast, colon and other cancers. Cancer usually occurs prematurely compared to the general population, with diagnosis, on average, often before age 30. Leukemia and lymphoma can often occur in childhood or early adolescence. It is not unusual to see cancer occurring multiple times in a person with Bloom syndrome. Due to the basic DNA repair defect responsible for Bloom syndrome, these patients are very sensitive to some DNA damaging chemotherapeutic agents and ionizing radiation that may necessitate modification to standard chemotherapy regimens to prevent potentially fatal complications.

3. Dyskeratosis congenita (DC) – autosomal dominant, autosomal recessive and X linked - is an example of a cancer predisposition syndrome caused by different genes, or **genetic heterogeneity**. There are at least 8 different genes in the telomere maintenance pathway that are known to cause DC: DKC1 (X-linked), TERC and TINF2 (autosomal dominant), TERT (autosomal dominant or autosomal recessive), CTC1, WRAP53, NHP2, and NOP10 (autosomal recessive). These genes are important for the maintenance of telomere length. Telomeres are the "caps" at the ends of chromosomes and are necessary for normal chromosome replication during cell division. Telomeres, normally, shorten over a person's lifetime. However, people with DC have abnormally short telomeres, which cause problems with proper DNA replication at the ends of the chromosomes and, eventually, have the potential to interfere with proper cell division leading to genomic instability.

   Symptoms of DC include: dysplastic nails, observed as ridging, flaking, or poor growth. In some cases there is severe dysplasia with nearly complete loss of the nails. Over time, people with DC will develop a lacy reticular (net like) pigmentation of the upper chest and/or neck the makes the skin appear "dirty". The pigmentation may be subtle or fairly dark. In some cases the pigmentation is both darker, or hyperpigmented, and lighter, or hypopigmented, than the patient's background skin pigmentation. These abnormal pigment changes are not always restricted to the upper chest and neck, but can also be seen on the area of the trunk or extremities. Most people with DC will demonstrate oral leukoplakia (white patches on the oral mucosa of the cheeks, gums and tongue), which can be seen in children. Bone marrow failure is

a common presentation of DC and can be seen as early as the first or second decade. In addition, pulmonary fibrosis is seen in a subset of DC patients and may be the presenting symptom.

Many of the skin and nail symptoms are age dependent. People with DC may only have a few subtle clinical symptoms of the condition until they develop the more serious complications, such as bone marrow failure. Additionally, people with DS have a high risk for developing various cancers, including leukemia, squamous cell carcinoma of the head and neck or anogenital region. The median age of cancer development is around 35 years.

Since there is a great deal of clinical and genetic heterogeneity in DC, this condition should be suspected in patients with bone marrow failure ,where other causes have been ruled out; head and neck cancer before age 50; and pulmonary interstitial fibrosis. A detailed family history may help determine the mode of inheritance of DC in the patient. Also, laboratory testing for telomere length and mutation analysis of DC genes can be done for more accurate diagnosis of DC. Dr. Blanche Alter, a physician in the genetic epidemiology branch of NCI, is actively studying this condition (NCT00027274).

Links:

1. ORN Genomics Survey: https://www.surveymonkey.com/r/GenomicKnowledgeassessment2015
2. Alliance of Genetic Support Groups: links to many genetic disease support groups http://www.geneticalliance.org
3. Fact sheet from NCI on testing for inherited cancer predisposition syndromes: http://www.cancer.gov/about-cancer/causes-prevention/genetics/genetic-testing-fact-sheet
4. Fun YouTube video on mitochondrial function https://www.youtube.com/watch?v=418Ul5YPVAI

Your Genomic Trivia for the Month:

A single evolutionary event appears to explain the short, curved legs that characterize all of today's dachshunds, corgis, basset hounds and at least 16 other breeds of dogs; the work was done by a team led by the National Human Genome Research Institute. In addition to what it reveals about short-legged dogs, the unexpected discovery provides new clues about how physical differences may arise within species and suggests new approaches to understanding a form of human dwarfism. Specifically, the researchers found that in contrast to other dog breeds, all short-legged dog breeds have an extra copy of the gene that codes for a growth-promoting protein called fibroblast growth factor 4 (FGF4). In the case of short-legged dogs, the inserted [gene] results in the overproduction of the FGF4 protein, which researchers hypothesize, may turn on key growth receptors at the wrong times during [dog] fetal development. Veterinary researchers already knew that in certain dog breeds the development of long bones is curtailed due to calcification of growth plates, resulting in short legs with a curved appearance. The trait, called disproportional dwarfism, or chondrodysplasia, is an American Kennel Club standard for more than a dozen domestic dog breeds, including the dachshund, corgi, Pekingese and basset hound. This trait is distinct from the uniformly miniature size of toy breeds, such as the toy poodle. The findings also may have implications for understanding human biology and disease. Researchers note that some people are affected by a similar appearing growth disorder, called hypochondroplasia, which belongs to a group of conditions commonly referred to as dwarfism. While about two-thirds of cases of human hypochondroplasia have been linked to a different gene, the cause of the other one-third remains a mystery. This study points to a new gene that should be investigated for its possible role in human hypochondroplasia. The research was led by NHGRI's Elaine Ostrander, Ph.D.