

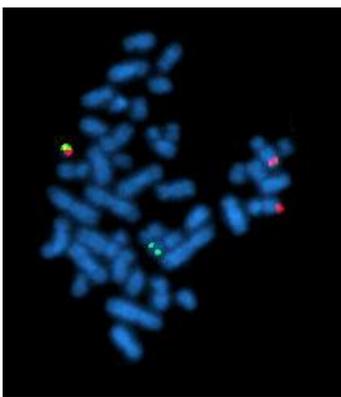
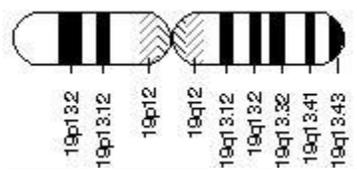
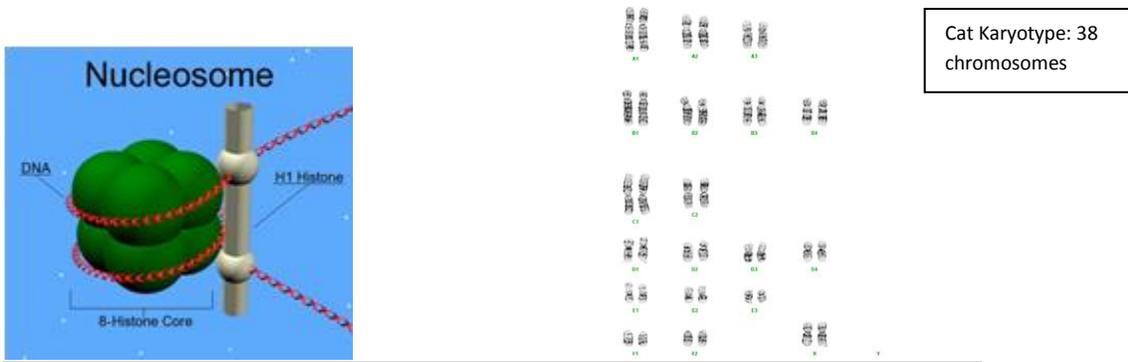
January 2016

Happy New Year! I want to remind everyone that the Genetics/Genomics survey is STILL open, only 8 people have responded so far - so your input is important. This is the link to the survey: ORN Genomics Survey: <https://www.surveymonkey.com/r/Genomicknowledgeassessment2015>. Your feedback helps guide the content of this newsletter.

In this column, I am going to continue the topics from the October Newsletter and discuss several genetic/genomic terms and some inherited cancer predisposition syndromes.

Genetic/Genomic Terminology:

CHROMOSOME (continued): There are approximately 6 feet of DNA in each cell arranged in segments – chromosomes. A chromosome is a structure containing DNA wrapped around proteins known as nucleosomes. The nucleosomes are made up of histones. This combination of DNA and proteins is known as chromatin. Chromosomes are only visible under light microscopy during the metaphase of cell division. A karyotype refers to the complete number and appearance of chromosomes in an organism; the common karyotype picture is of the chromosomes during metaphase.



Chromosomes can be stained in the laboratory to show structures not clearly visible under the microscope. The cat karyotype above is G (Giemsa) banded, one of the most common banding techniques. Various types of stains can illustrate different areas of the chromosomes; the light and dark areas of the chromosomes are called bands and each chromosome has a unique banding pattern. The picture above is of chromosome 19. The bands on the chromosome are numbered i.e. 19p13.2. The band numbers provide an 'address' on the chromosome that help identify chromosome abnormalities or placement of genes. The chromosomes on the left are stained with fluorescent stains – the bright red and green 'dots' (FISH). This type of chromosome stain can detect very small structural changes in chromosomes or can assist in identifying gene placement.

GENE: A gene is a specific segment of DNA on a chromosome that codes for a protein; it is the basic unit of heredity. Parents pass their genes on to offspring via the genes in the DNA of the egg and sperm. A newer broader concept of a gene is it is any discrete section of DNA which affects an organism's traits by being expressed as a functional protein or by exerting an influence on other genes. Such as, the product of one gene may either 'turn on' or 'turn off' another gene.

ALLELE: An allele is one of a number of alternative forms of the same gene. Sometimes, different alleles can result in different heritable traits, such as hair color. But, many genetic variations result in little or no observable variation.

An analogy is the concept of the 'car gene'. Typical 'car gene' characteristics are: has wheels, doors, and an engine and is a method of transportation. However there are many different models of cars – but all fit the stated characteristics. The 'gene' is car and the different models of cars represent alleles of the 'car gene'.



Another gene/allele analogy is petal color for daisies. The gene codes for a protein that affects the color of the flower petals. There are 3 gene alleles for flower petal color: allele 1 codes for red, allele 2 codes for pink, allele 3 codes for white. The petals function normally, but are different colors depending on the inherited allele.

Cancer/tumor predisposition syndromes:

1. MULTIPLE ENDOCRINE NEOPLASIA TYPE I – (Wermer's syndrome) is an autosomal dominant disorder that results in mostly non-cancerous tumors in endocrine glands and other body tissues. It is caused by mutations in the MEN1 gene located on chromosome 11q13.1. and occurs in approximately 1 in 30,000 people. The first symptoms are associated with development of hyperparathyroidism including elevated levels of serum calcium that can result in kidney stones and low bone mineral density. Most patients will have elevated parathyroid levels by age 20. However, some patients may be asymptomatic until age 50 years. There is significant variability of symptoms between patients even in the same family. To manage the hyperparathyroidism, most patients will have most of the parathyroid gland removed. People with MEN 1 also have an approximately 20 to 60% chance of developing gastrinomas. These are small gastrin producing tumors in the pancreas, duodenum, and lymph glands of the abdomen. The excess gastrin results in aggressive ulcer formation that can lead to gastric or intestinal rupture. Often the gastrinomas are too small and numerous to remove and patients

with gastrinomas are placed on a treatment of proton pump inhibitors that block stomach acid release. In addition people with MEN I can develop other pancreas tumors including: insulinomas, glucagon producing tumors, and VIP (vasoactive intestinal peptide) tumors. Pituitary and adrenal tumors also occur more often in people with MEN1 and can result in infertility and cortisol excess. Most of these tumors are benign, but a certain percentage of MEN I people will develop a malignant pancreatic or carcinoid tumor (often in the thymus). Other tumors include skin tumors (lipomas, angiofibromas, and collagenomas). Treatment consists of treating the over functioning endocrine glands (medically or through surgical tumor removal) and monitoring for the development of additional endocrine tumors. With early treatment and close monitoring for symptoms of tumor development (imaging, laboratory assessments) most people with MEN1 will live well into adulthood.

2. MULTIPLE ENDOCRINE NEOPLASIA TYPE II: (Sipple's syndrome) is an autosomal dominant disorder characterized by early onset of cancer of the thyroid and other tumors primarily in the parathyroid and adrenal glands and occurs in approximately 1 in 30 to 50,000 people. It is caused by mutations in the RET gene on chromosome 10q11.21. MEN II is classified into several subtypes depending on the affected organs and appearance of the patient.

MULTIPLE ENDOCRINE NEOPLASIA TYPE IIA: Is characterized by the early development of medullary thyroid cancer (MTC) in almost all affected individuals. In addition, almost half of people with MEN IIA develop a pheochromocytoma. In addition about 5-10% of patients will also develop a parathyroid adenoma (benign tumor) or hyperplasia (increased size) of the parathyroid gland. People with MEN IIA do not have any distinctive external physical findings. Treatment involves thyroidectomy and monitoring for the development of hyperparathyroidism and pheochromocytoma.

MULTIPLE ENDOCRINE NEOPLASIA TYPE IIB: Is seen in approximately 5% of people with MEN and is also characterized by the early development of MTC – the tumor can be seen as early as infancy. They also develop pheochromocytomas at a very high rate. A distinct finding in people with MEN IIB is the growth of mucosal neuromas on the surface of the tongue, palate, or pharynx and development of an unusual appearing face over time. The lips can appear prominent (or 'blubbery') and patients can develop nodules in the mucosa of the lips and along the vermilion border. The patients often develop neuromas of the eyelids causing thickening and eversion of the upper eyelid margins. In addition, almost 40% of people with MEN IIB will develop ganglioneuromatosis in the gastrointestinal tract. This many cause chronic abdominal distension constipation and/or diarrhea that can progress to megacolon. People with MEN IIB appear thin with disproportionally long arms and legs (marfanoid habitus). They can have joint laxity including an increased risk for kyphoscoliosis. In addition some people will also complain of muscle wasting and weakness especially in the proximal muscles of the arms and legs. MEN IIB can limit life span.

FAMILIAL THYROID MEDULLARY CARCINOMA (FMTC): Is now believed to be a variant of MEN IIA, where the only symptom is MTC. People with FMTC, will have a family history of several family members developing MTC and may develop the cancer at a later age than typical patients with MEN IIA. It is important to fully assess patients suspected of having FMTC for a pheochromocytoma prior to determining FMTC as the correct diagnosis.

All three of the MEN II subtypes are caused by mutations in the RET gene. The RET gene can harbor many kinds of mutations and it is the specific kind of mutation in the RET gene, that determines the type of MEN II. This is termed a phenotype/genotype correlation. The term phenotype – refers to appearance or observable traits (this can be physical appearance, disease appearance or a laboratory value “appearance”); the term genotype refers to the genetic make-up. A person with MEN II inherits 2 RET alleles (one from each parent); since MEN II is an autosomal dominant disease, one of the alleles will be normal (WILD TYPE) and one will contain a mutation, causing it not to code for a properly functioning protein. The type of mutation in that mutated allele determines the type of MEN II.

LINKS:

<https://www.youtube.com/user/GenomeTV> - a wealth of videos on genetics from NHGRI

<https://www.youtube.com/watch?v=ofjyw7ARP1c> - nice video on the cell cycle and mitosis

<http://www.amensupport.org/> - patient support group for MEN

See next page for genetic trivia

GENETICS TRIVIA: Interesting article on bacterial genetics and how genetic mutations in bacteria changed the way bubonic plague was transmitted.

Plague bacteria (*Yersinia pestis*) were recently discovered in Bronze Age skeletons, pushing back the recorded origin of plague by about 3,000 years. The new found ancient strains are genetically distinct from modern-day strains. An international team reported its findings last week (October 22) in *Cell*. Researchers led by Eske Willerslev of the University of Copenhagen were searching for the cause of Bronze Age human migrations in Europe and Asia, circa 3,000 BC to 1,000 BC, suspecting that disease might have been a driving factor. So the team sequenced 89 billion DNA sequences from 101 Bronze Age specimens obtained from museums and excavations. Seven of the specimens contained *Y. pestis* DNA. Most of the ancient bacterial genomes lacked a gene known to protect the pathogen while it's inside the flea gut, suggesting that the plague was not spread easily by fleas. The ancient *Y. pestis* bacteria also lacked a mutation that helps present-day strains avoid detection by the host's immune system. The authors suggest that *Y. pestis* did not evolve into its destructive flea-borne form until the beginning of 1,000 BC. "It's really cool that they can pinpoint the acquisition of key genes that allow the movement of this bacteria into fleas," evolutionary geneticist Hendrik Poinar of McMaster University in Canada, who was not involved with the study, told *Science*. "At that time we have a kind of intermediate plague," study coauthor Simon Rasmussen from the Technical University of Denmark told *Smithsonian*. "These Bronze Age strains couldn't cause bubonic plague, but they caused septicemic plague in the blood and pneumonic plague in the lungs, which you can transmit through the air whenever you sneeze or cough."