



Related Disorders; A Presentation Given at the SOFT Conference, Roanoke, Va, July, 2009

Workshop: Related Disorders

Stephen Braddock has been a professor of clinical Genetics at the University of Virginia School of Medicine since 2006. Dr. Braddock graduated from Notre Dame and earned his medical degree from University of Missouri-Columbia. His internship/residency was at the University of Utah Affiliated Hospitals where he worked with Dr. Carey. His Fellowships in genetics were in California. He taught at the University of Missouri-Columbia School of Medicine and at the Sinclair School of Nursing until 2006. He has published and lectured extensively in his areas of research, which includes syndrome delineation and dysmorphology, teratology, and fetal alcohol syndrome.

Dr. Braddock began his presentation with an overview of chromosomal genetics and moved to information about specific chromosomal syndromes considered in SOFT as related disorders. Chromosomes, first described by Strausberger in 1875, and named chromosomes by Waldeyer in 1888, are in every nucleated cell, therefore not in red blood cells, and are only visualized during cell division. In humans there are 46 chromosomes, including 22 pairs of autosomes and one pair of sex chromosomes, XY for males and XX for females. Homologous chromosomes are those in the same pair, that is, the chromosome from the father and the chromosome from the mother in each pair. Chromosomes are numbered 1-22, and XY by size, morphology and banding patterns, based on an international system of nomenclature. Chromosomes are made of DNA with genes that cannot be seen along the length of each chromosome. We know where some genes are located, for instance, the gene for cystic fibrosis is on chromosome 7. Knowledge about the location of some genes came from studying those with translocations, thus, specific extra or missing parts of identified chromosomes. Chromosomes are stretched when possible to enhance resolution.

Chromosomes that are studied are derived from amniocentesis, from blood and skin, and at autopsy. The structure of a chromosome varies from one chromosome to the next but includes two arms, the short arm, p, for petite, and the long arm q which is the next letter in the alphabet. Between the two arms is a pinched area called the centromere. The ends of the chromosome are the telomere. Throughout the chromosome are bands, made visible by staining. An acrocentric chromosome such as chromosome 13 has only a q arm at the centromere. The number of known or estimated genes varies from one chromosome to another. The largest chromosome, which is 1, has 2,968 genes, the Y chromosome has 231 genes. At this time scientists do not know about all genes and what they do, but it is known that genes do different things at different times.

Nondisjunction, which results in extra or missing genetic material, occurs during meiosis I and II in the sex cells (egg and sperm). Cells divide unevenly and homologous chromosomes, rather than splitting away from each other, travel together to one daughter cell, leaving the other missing that chromosome.

The only viable condition with a missing chromosome is Turner syndrome in which one copy of the X chromosome is missing (XO). That eggs have more difficulty with division with advanced maternal age has been known for some time, but more recently it has been determined that advanced paternal age (after age 32) is also a risk factor. The presence of a third chromosome was first discovered by LeJeune fifty years ago to explain the cluster of symptoms described in 1866 by Langdon Down. A year later Edwards discovered the three chromosomes of trisomy 18 and Patau the three chromosomes of trisomy 13. With the advance of karyotypes and more advanced chromosomal tests and with more routine testing, other rarer chromosomal syndromes of nondisjunction have been identified.

There are also structural abnormalities of chromosomes which are more rare than nondisjunction. There is an endless variety of pieces of chromosomes attached to other chromosome or missing. This gives rise to the related disorders of partial trisomies and monosomies. Some occur de novo, or first in the affected individual. Others come from a parent with a balanced translocation. In this case the parent has a reciprocal translocation with genetic material missing from one chromosome but present attached to another. No DNA has been lost or duplicated. Also, the break has not been between genes that must be contiguous in order to work. It is the presence of the genetic material from each chromosome that is important for the healthy functioning of the individual, not the structure of the person's actual chromosomes. What can happen is that at disjunction the chromosome with the extra material and the chromosome missing that same genetic material are separated, one going to one daughter cell and the other to the other daughter cell. For instance, chromosome 5 with an attached piece of chromosome 13 and perhaps a missing piece of 5 travels with a full chromosome 13, resulting in two copies of part of chromosome 13 and missing genetic material on 5. The other cell has a chromosome 13 which is missing genetic material and may contain an extra part of 5. At fertilization a full set of chromosomes from the other parent is added resulting in a zygote with too much or too little DNA. The resulting unbalanced translocation or partial trisomy or monosomy is no one's fault, although the parent or grandparent with the balanced translocation may express guilt and accept blame. With the birth of a child with a translocation, there is the need for genetic testing of the siblings of the parent with the balanced translocation, since it may not be de novo in that child or parent. Genetic testing would inform those of child-bearing age whether they are at risk for having a child with a similar genetic disorder. Cousins could subsequently be born with a similar constellation of chromosomes. Several SOFT members have reported familial patterns with balanced translocations going back a generation and then passed intact to several members of the next generation, but passed with extra material to cousins in the third generation. It was mentioned that the suggestion of testing in the family can open doors to metaphoric closets and reveal family skeletons long kept secret. Responsible action is to determine who is at risk and proceed with knowledge.

Another related disorder involves a Robertsonian translocation, which involves an acrocentric chromosome with two chromosomes breaking near the centromere and attaching. A deletion refers to missing material on a chromosome and can be terminal, meaning the end of a chromosome or interstitial, meaning loss of material between breaks somewhere along the length of the chromosome.

The most common trisomies are trisomy 21, Down syndrome, trisomy 18, Edward syndrome and trisomy 13, Patau syndrome, each named after the person who first identified the constellation of physical manifestations that characterize the syndrome. Less common are trisomies of the other chromosomes, which are viable in mosaic or partial form. Mosaic means there are cell lines with the

normal complement of chromosomes and cell lines with a third chromosome. Partial means there is a third copy of part of a chromosome in all cell lines or in a deletion syndrome, genetic material missing from one chromosome in all cell lines. The chromosomal material present results in a syndrome with specific characteristics with each individual having many but not all characteristics, just as is true with full trisomies. It was emphasized that despite the pattern of dysmorphic features and cognitive limitations, determined by the extra or missing genetic material, all the other chromosomes that are present in complete pairs result in a human being with capabilities beyond the disabilities. Dr. Braddock gave examples. Trisomy 6p is characterized by pulmonary abnormalities, low set ears, retarded growth, ptosis (droopy eyes), high nasal bridge, prominent forehead and cognitive delays. Trisomy 8 which is almost always mosaic is characterized by poor coordination, agenesis of the corpus callosum, cardiac, skeletal and renal abnormalities, deep set eyes, deep creases on the soles and palms, bulbous nose, campodactyly (finger contractures) and an increased chance of leukemia because bone marrow is over produced. Trisomy 9, generally mosaic, is characterized by growth retardation, sloping forehead, deep set eyes, micrognathia (small chin), deep set eyes, joint contractures, scoliosis, severe failure to thrive and brain abnormalities. Those with trisomy 9p are characterized by similar cranial-facial features, including low set ears, palpebral fissures of eyes, high forehead, as well as skeletal, cardiac defects and growth and cognitive delays. Depending on the part of the chromosome that is extra, individuals can have different characteristics. Trisomy 16 is the most common trisomy at conception and the most common cause of miscarriage, about 100,000 a year. Partial trisomy 16 occurs rarely and has characteristic heart defects, intrauterine growth retardation and cognitive delays. SOFT members may remember Richard Capp who was at the Pittsburgh conference and subsequently was diagnosed with partial trisomy 16. There is the extremely rare distal trisomy 10q with duplication of certain bands from the long arm. Triple X occurs in 1 in 1000 females with increased height, possibly some mild developmental delays and normal fertility. Most have no clue they have this condition and the next generation is genetically fine with the extra X not being passed on.

Triploidy which means three sets of all chromosome occurs in 2% of conceptions, 20% of all miscarriages and is associated with maternal toxemia. The condition is usually paternally derived with two sperm fertilizing a single egg. Sixty percent are XXY and 40% are XXX. There is no association with advanced maternal age. Most live born infants with triploidy survive less than five months.

Research is on-going with partial trisomies with an approach of working backward to match location on chromosome with characteristics to determine the link between specific characteristics and triplicated regions. Finally, Dr. Braddock emphasized the importance of support groups to those with children with chromosomal disorders, in order for parents to be educated and to find others facing the same challenges. A helpful website is www.rarechromosomes.org.