The ultrasound detection of chromosomal anomalies[1]

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A review of the genetic concepts and terminology

A chromosome is a linear structure with a short arm called "p", a centromere that is the attachment of the short arm and long arm, and a long arm which is called "q" which is the next letter after P in the alphabet.

Figure 1: A chromosome is a linear structure with a short arm called "p" (for petit-short- in French (on top), a centromere that is the attachment of the short arm and long arm, and a long arm which is called "q" which is the next letter after "p" in the alphabet.

A cell that contains the normal number of sets of chromosomes is called euploid. In the gamete, (the ovum or sperm), which contain 23 chromosomes, therefore one set chromosomes, the cell is call haploid. In other cells of the body that contains two sets of chromosome the cells are called diploid

Chromosome are displayed in a karyotype in order or decreasing size, with the small arm "p" on top and the longer arm "q" at the bottom. The last pair of chromosome represented in a karyotype is the sex chromosomes. The other 22 pairs of chromosomes are called autosomes.

FISH is an acronym for "fluorescence in-situ hybridization". This is a technique by which chromosomes are recognized by being labeled with fluorescent probes. This technique allows very rapids results, usually hours, instead of days for amniocentesis. But it does not provide information about all the chromosomes; just selected portion of chromosomes.

Mitosis

One of the important cell division forms is the mitosis, which is normal cell division form that results in two daughter cells identical to the parent cell. Originally the cell contains DNA which organizes before the division into chromatids. Each cell contains one chromosome from the mother and one chromosome from the father, and these are called homologue chromosomes. In human cells there are 23 pairs of chromosomes resulting in 46 chromosomes. In the early stage of cell division the chromatids replicate into identical copies called sister chromatids. Then the sister chromatids separate from each other and migrate into each daughter cell. At the end two cells identical to the parents cell are produced.

Meiosis is the other form of cell division, which occurs in the germ cells and results in two daughter cells containing half of the genetic material of the parents' cell. The difference between the meiosis and the mitosis is that during the first phase of the meiosis, the gametocytes which is either the oocyte or the spermatocyte, divide into secondary gametocytes that contain undivided chromosomes. During the first

phase of the meiosis, the homologue chromosomes pair and exchange segments during two events called synapsis and recombination, so that segments of one chromosome will end up being transferred onto the homologue chromosome. Then in contrast with what happened in mitosis, during the first phase of meiosis, the sister chromatid do not separate but migrate each towards one of the daughter cell, so that the daughter cell receive one chromosome each and each chromosome is a double chromatid chromosome. Then in the second phase of meiosis, the two secondary gametocytes that were just produced divide and each daughter cell receive one of the chromatid of the parents' cell. So that ultimately at the end of the second division of meiosis, four cells are produced which will be for instance four spermatids, which would all be equal in size, or one mature ovum and three polar bodies.

Anomalies of the chromosome

Aneuploidy

A cell that contains an uneven number of sets of chromosome is called aneuploid. A common example is to contain an extra chromosome: a condition referred to as "trisomy". Another condition is missing a chromosome: a condition referred to as "monosomy". Monosomy is less common than trisomy because the absence of a chromosome is more lethal than the presence of an extra chromosome unless the missing chromosome it is a sexual chromosome.

When a cell contains 3 sets of chromosomes it is called "triploid". The most common form of triploidy results from the fertilization of a normal egg by two normal sperm, a condition called dispermy. Less frequently an abnormal sperm that contains 2 set of chromosomes can fertilize a normal egg, or a normal sperm fertilize an egg that contains 2 sets of chromosomes. A cell that contains four sets of chromosomes is called "tetraploid".

Inversion

An **inversion** result from a double break in an arm, with the segment between the two breaks being reinserted upside-down. This is usually fairly benign. For instance INV(11)(q13-q22), would represent an inversion of the segment between band 13 and band 22 of the long arm of chromosomes 11.

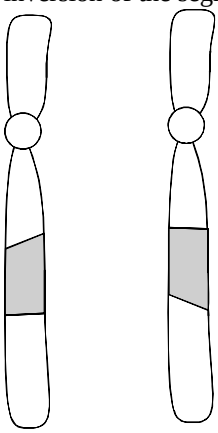

Figure 2: A segment of the chromosome has been inverted, but no material deleted.

Isochromosomes

An **Isochromosomes** results from an aberrant equatorial division of the sister chromatid, instead of a longitudinal division. One chromosomes gets both the short arms the "p" arms at one chromosomes gets both the long arms, the "q" arms.

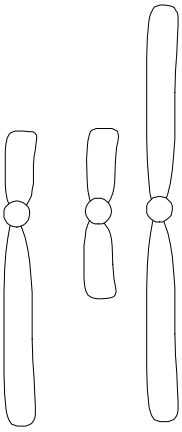

Figure 3: The division of the left chromosome has resulted in one chromosomes that gets both the short arms (the second chromosome), the "p" arms, at one chromosomes gets both the long arms, the "q" arms.

Uniparental disomy

Uniparental disomy is one of the conditions that result from gametocytes that have abnormal number of chromosomes. The association of a normal gamete with a disomic gamete will produce a trisomic embryo and all the cells of that embryo will be trisomic. The union of a normal gamete with a nullisomic gamete will produce a monosomy. The union of 2 nullisomic gametes would produce an embryo with a double monosomy, and those are not expected to survive. Finally the association of a disomic gamete with a nullisomic gamete, or more commonly the rescue of a trisomic gamete by loss of a chromosome may produce a gamete that has 2 chromosomes, the normal number, but both homologue chromosomes of a certain pair come from one single parent instead of each homologue coming from different parents. This is a condition called uniparental disomy.

Deletions

There are two forms of deletions. The terminal deletions result from loss of terminal material in the chromosome, while an interstitial deletion result from loss of the middle material.

Duplications

Duplication results from an unequal transfer between sister chromatid during the synapsis and recombination so that one arm gets more material than it has given, and this leads to partial trisomy or monosomy of the affected segments.

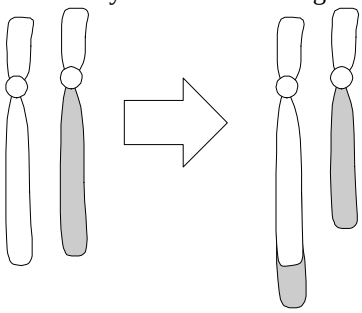

Figure 4: Duplication results from an unequal transfer between sister chromatid during the synapsis and recombination so that one arm gets more material than it has given, and this leads to partial trisomy or monosomy of the affected segments.

A ring chromosome

A ring chromosome is a chromosome that is produced by the fusion, usually with loss of the distal material, of the small arm with the long arm.

Reciprocal translocation

A reciprocal translocation results from exchange of material between two non-homologous chromosomes, so instead of these two chromosomes being part of a pair they are part of different pairs (one and nine for instance). If a reciprocal translocation of the distal end of chromosome 1 and chromosome nine has occurred, the patient can then transfer a set of perfectly normal chromosome to his children, or a balanced set in which the right amount of material is transmitted on the wrong set of chromosome, or an imbalanced set with duplication of one portion of a chromosome and deletion of the equivalent portion of the other chromosome.

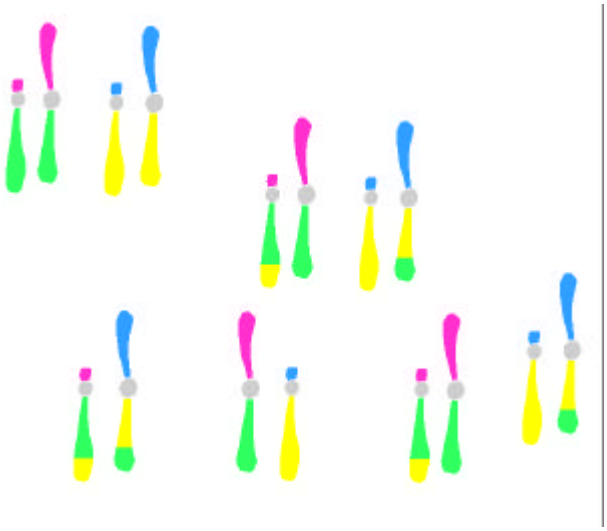

Figure 5: The 2 pairs of chromosomes on the first row, divided and resulted in a balanced translocation (middle row). The patient can then transfer to his children a balanced set in which the right amount of material is transmitted on the wrong set of chromosome (last row first set), a set of perfectly normal chromosome (last row second set), or, or an imbalanced set with duplication of one portion of a chromosome and deletion of the equivalent portion of the other chromosome (last 2 sets).

Robertsonian translocation

The fusion of two acrocentric chromosomes which are chromosomes with very short *short* arms, results in a composite chromosome in which the long arm of both original chromosomes are retained. This has been called a “Robertsonian translocation” to honor the entomologist which at the beginning of the century described the phenomenon in insects. It occurs with the acrocentric chromosomes, which are chromosomes 13, 14, 15, 21 and 22.

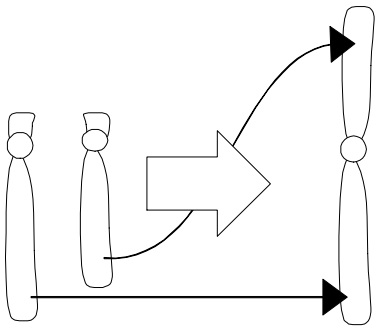

Figure 6: The fusion of two acrocentric chromosomes that are chromosomes with very short short *arms, results in a composite chromosome in which the long arm of both original chromosomes are retained.*

Dominant and recessive alleles

We have seen previously that for each pair of chromosome one is inherited from the mother at one from the father, and these are called homologue chromosomes. Similar genes exist on homologue chromosomes and they are called alleles. When both alleles are identical the individual is called homozygous. While when both alleles are different the individual is referred to as heterozygous.

When both alleles are different and the altered or "mutant" allele is expressed than that disorder is said to be dominant. When both alleles are different and the function of the normal allele masks the expression of the altered or "mutant" allele then the disorder is said to be recessive. Both alleles of a recessive disorder must be altered or "mutant" for the disorder to be manifest.

Autosomal dominant

The knowledge of the transmission of autosomal dominant and recessive disorder is an important topic for us who do prenatal diagnoses by ultrasound. Autosomal dominant disorders are usually manifested in the heterozygous form. They affect males and females equally. They have variable degree of expression, and may have an age-dependent expression. Autosomal dominant disorders are usually due to the production of a defective protein or developmental morphogens. One allele codes for the correct protein while the mutant allele codes for the defective protein.

The graph illustrates what would happen in an autosomal dominant disorder. As an illustration let us assume that the father is carrier of the gene, and the since this is an autosomal dominant disorder the father is affected. Half of his children will have the abnormal gene and half of his children will have the normal gene. The mother transmits normal genes to all of her children. Therefore 50 percent of the children will have the abnormal gene and be affected and half of the children will be normal.

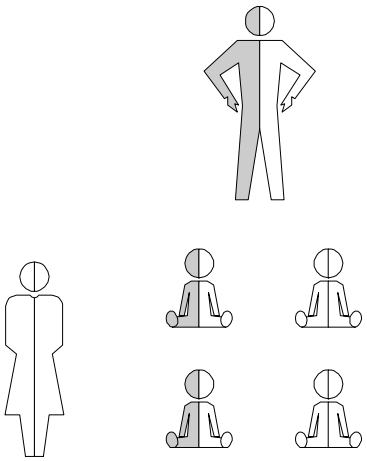

Figure : In an autosomal dominant disorder in which

have the abnormal gene and half of his children will have the normal gene. The mother transmits normal

children will have the abnormal gene and be affected and half of the children will be normal.

In a less common scenario, both parents are affected of the autosomal dominant disorder, and an example of that would be the union of two parents with achondroplasia. Here again, the father transmits the abnormal gene to half of its children and so will the mother. Half of the children therefore will be affected. A quarter of the children will receive the abnormal gene from both the mother and the father and therefore will be homozygous for the abnormal gene and this is often a lethal condition. In particular in cases of parents with achondroplasia, this will result in a fetus that has a condition similar to achondrogenesis. Finally a quarter of the children will receive the normal gene both from the father and from the mother and will be perfectly normal

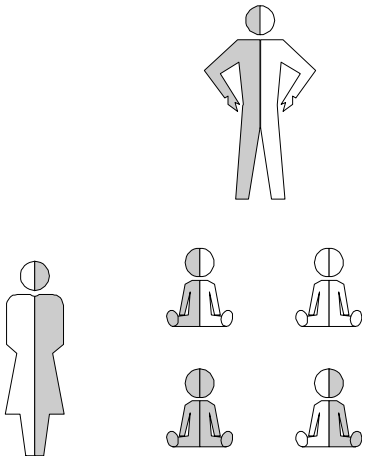

Figure 8: When both parents are affected of an autosomal dominant disorder, both parents transmit the abnormal gene to half of their children. Half of the children therefore will be affected. A quarter of the children will receive the abnormal gene from both the mother and the father and therefore will be homozygous for the abnormal gene and this is often a lethal condition. Finally a quarter of the children will receive the normal gene both from the father and from the mother and will be perfectly normal.

Autosomal recessive

An autosomal recessive disorder is usually manifested only in the homozygous form, therefore in babies that have the abnormal gene both from the mother and from the father. The mother and the father usually are not affected by disorder. It affects males and females equally. Usually autosomal recessive disorders are due to the omission of an enzyme, factor or receptor. If only one parent has the abnormal gene it will transmit it to half of his children which will not be affected, but have the same carrier status of the father. The same graph as the autosomal dominant graph can be used, but instead of “gray” representing affected, it would represent carrier.

If both parents carry the recessive gene, half of the children will have the abnormal gene either from the father or the mother, and will simply be carrier. A quarter will have the normal gene of both parents, thus be normal and no longer be carrier. Finally, a quarter of the children are homozygous, they carry the abnormal gene both from the father and mother, and are the only one that will express the disorder. This is the similar condition as the graph for both parents with an autosomal dominant disorder except that again the “gray” would represent carrier and the child with both abnormal alleles would be the only one to express the disorder completely.

X-link transmission

Up to now we have dealt with anomalies of the autosomes. Now if we look at the sexual chromosomes, in particular the X-linked disorders, there are a few peculiarities that are worth mentioning. X-linked disorders can be dominant or recessive in heterozygous females, and are usually manifested in males that are called

hemizygous because they have only one chromosome. In X-linked dominant disorders, if the mother is

of his daughters will be affected, but none of his sons will be affected. Let us start first with an X-linked dominant disorders in which the mother is affected. As the father does not have the abnormal gene he will

her children. There is nothing unusual here aside from the fact that the X-chromosome is affected. The situation is a little bit more unusual if the father carries the abnormal gene and therefore since this is a

daughters but will not transmit the X-chromosome to his sons (he only passes Y chromosome to his sons). Therefore all the daughters of the affected father will be affected, but none of the sons will be affected.

their carrier mother. If the mother is affected, half of the sons will be affected, and half of the daughter will be carrier. If the father is affected, all the sons will be normal, and all the daughters will be carriers. Finally,

disorders. Since the father has only one X, the father will be affected, while the mother is only a carrier. 50% of the daughters are affected, 50% of the daughters are carrier, and half of the sons are affected.

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