Chapter 7

Genetic Mechanisms of Chromosome Nondisjunction in Humans

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Abstract

The human genome is very delicately balanced. Because maintaining a balance in gene dosage and protein activity is essential for maintaining normal cellular functions. One of the most common causes of genetic diseases in humans is chromosomal failure and chromosomal numerical irregularity (Aneuploidy). Missegregation or non-separation of chromosomes in meiosis is common in humans. The most common chromosomal abnormality (CA) in humans is aneuploidy. Aneuploidy is one of the most important causes of reproductive biology and reproductive diseases. It causes major developmental and structural abnormalities and often embryonic death in mammals, especially in early development. Aneuploidy is a condition with abnormal and highly variable DNA and chromosome content found in both hereditary disorders and human malignancy. Chromosome non-separation is associated with advanced maternal age. However, the reason for the dramatic increase in aneuploidy and especially trisomies with age is unknown. There is evidence to suggest that chronological age is less important than biological age for trisomy risk and that some women, regardless of their chronological age, are at higher risk of having a trisomy pregnancy again. It is known that increased aneuploidy in somatic cells is associated with a decrease in telomere length, an increase in replication asynchrony at centromeres and loci, and advanced age. Many people are exposed to environmental genotoxic agents. Genotoxic agents and late marriages are known to cause aneuploidy. In our numerous studies, it has been confirmed that genotoxic substances are associated with chromosome damages (1-14). Cigarettes, mobile phones and harmful rays can cause structural and numerical chromosome damage and potentially increase the level of aneuploidy in the fetus.

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https://doi.org/10.58830/ozgur.pub91.c386

INTRODUCTION

Today, people are heavily exposed to many natural and artificial genotoxic or mutagenic agents, and this situation is increasing rapidly. It is now known that long-term exposure to genotoxic agents not only affects human reproductive health, but also causes cancer and many diseases. Therefore, concerns about possible negative genetic damage in society are increasing. Aneuploidy is known as one or more chromosomes more or less than the diploid number of chromosomes (2n=46). The vast majority of aneuploidies occur spontaneously as a result of sporadic chromosome misalignment in meiosis in the mother or father. The most well-known form of meiotic dissociation is that it increases with increasing maternal age. The mechanisms underlying aneuploidy are still not fully understood. Humans are among mammals with the highest incidence of chromosome mis-separation during meiosis. It is known that 15-20% of all pregnancies result in spontaneous abortion. CAs are responsible for at least 50% of these losses. More than half of these are trisomies (having an extra copy of a chromosome). Trisomic chromosome organization was first described in humans in 1959 (15). Trisomic irregularities are caused by an error in meiosis. It occurs when both chromosomes of a pair of chromosomes or both sister chromatids of a chromosome go together to the same pole. Thus, the gamete has two copies of that chromosome instead of one, and the chromosomes cannot separate correctly. The effect of meiosis on reproduction and genetic disorders of newborns is significant. However, little is known about its etiology. The only known factor associated with the risk of trisomy is advanced maternal age. The risk of trisomy in women under the age of 25 is 2%. This risk increases rapidly with age and approaches 35% in women over 40 years of age (16). Therefore, the relationship between increasing maternal age and trisomy is indisputably the most important etiological factor of genetic diseases (17). The relationship between recombination and chromosomal nondisjunction has been extensively studied along the 21st chromosome. There appears to be a correlation between recombination and inability to separate for the chromosome, both in quantity and location along this chromosome. Altered recombination has been associated with trisomy for other chromosomes. Meiosis is a process that takes place in the germ cells of both males and females. Errors in the meiosis process in female egg cells are responsible for most of the aneuploidy seen in human pregnancies.

Meiosis is the process of halving the number of chromosomes. This process takes place in germ cells during gametogenesis to produce eggs in females and sperm in males. Oogenesis, the process of egg formation, begins

in females early in fetal life. Every female born carries a lifetime of developing oocytes. These oocytes are normally released once a month, starting at puberty. When the level of approximately 1000 oocytes is reached, menopause occurs in women (18). In males, spermatogenesis is the process of forming sperm in the gonads. Beginning at puberty, 100-200 million sperm are produced per ejaculate continuously throughout their lives (19). Meiosis consists of two main cell divisions. Meiosis I (MI), in which the chromosome number is reduced from diploid to haploid (2n=n), and meiosis II (MII), a form of division similar to mitosis. Moreover, each of these divisions is divided into four main stages (prophase, metaphase, anaphase, and telophase). In the synthesis phase, each chromosome doubles itself by replicating its genetic material. Thus, each homologous chromosome consists of two identical sister chromatids held together by proteins called cohesins. Prophase (prophase I) of MI consists of five phases. Since the chromosome number is haploid in MII, the same main stages follow without reduction. During the leptotene stage, the copied chromosomes begin to condense and become visible. The two sister chromatids that make up each chromosome are indistinguishable at this stage. After the homologous chromosomes find each other in zygotene, they pair up with the cohesin protein. Since each pair of homologous chromosomes contains four sister chromatids, they line up with each other longitudinally, forming a bivalent called a tetrad. Cohesin proteins hold sister chromatids together so they don't separate prematurely. Thus, it holds homologous chromosomes together so that recombination can occur before anaphase II. Synapses and the synaptonemal complex (SC), defined as the pairing of homologs during zygotene, are formed. The SC consists of lateral elements located between sister chromatids and a central element connecting these lateral elements. Homologous exchange or recombination takes place throughout this structure. In the pachytene phase, the synapses are completed with pachytene and recombination nodules appear. These nodules are thought to represent regions where recombination has occurred. After completion of recombination, SC begins to fragment and chromatids begin to separate. Chiasmata can be seen in the diplotene stage. The two components of each bivalent begin to repel each other, and each homologous sister chromatids attach to each other at their centromeres. This is the point at which meiosis is stopped/waited until puberty in females. At this point, a single egg completes MI at each ovulation cycle. There is no waiting in meiosis in males. In diakinesis, the chromosomes reach maximum condensation at this point and are clearly visible. In order for homologs to pair and align themselves in the zygotene of the prophase, they must first find each other. Exactly how this happens is unknown. However, two

chromosome regions are thought to play an important role in mediating early mating (telomeres and centered heterochromatin) (20). Aligning these two types of chromosomal domains may be early steps in the mating process. Disruption of telomere-telomere sequences can disrupt synapse and recombination. The formation of a flower bouquet-like structure formed by telomeres that seem to interact with each other in the nucleus of the cells is observed in the cell nucleus. Chromosomes come into contact with each other to determine the level of similarity required to form synapses and recombination. Meiotic bouquet formation is a prominent feature of early prophase in many organisms such as yeast. It has also been reported that it is involved in chromosome pairing in male mouse and human meiosis (21). In addition, it has been reported that telomere movements in tissue sections from human and mouse testicular preparations are associated with the onset of synaptic chromosome pairing. The centromere is a very important element found in all eukaryotic chromosomes. This chromosome region ensures the regular separation of sister chromatids in mitosis and meiosis.

Recombination

Crossing-over is a mutual genetic exchange between homologous chromosomes. It begins with double helix breaks and is the most fundamental step of the meiosis process. It is assumed that chiasmata, which is the physical exchange of homologous chromosome parts, keeps homologous chromosomes together during meiosis. It has been reported that at least one recombination event per chromosome arm is required for segregation to occur in humans (22). Many key proteins involved in recombination, such as RecA, topoisomerases, helicases, and DNA repair molecules, are highly conserved from yeast to humans (23). Performing recombination analyzes in humans is difficult. In men, a testicular biopsy should be performed. This situation is more difficult in females. Recombination takes place in all chromosomes. It has been reported that approximately 50 autosomal recombination foci per nucleus in spermatocytes, and the number of foci in females is much higher (mean=95) (24). In mouse and human studies, distal foci were found to be much more common in males. Recombination has been found in more than 90% of females, and it has been reported that there is more recombination in regions close to telomeres in males (25,25). In contrast to more than 70 recombination foci in oocytes, approximately 50 foci per cell were found in spermatocytes (26). This suggests that longer synaptonemal complex in oocytes may contribute to increased recombination in females. In yeast, the main stages of meiosis may differ slightly from those seen in humans. The study of meiotic mutants in this organism has greatly contributed

to our understanding of the process of meiosis. Homology of yeast genes has been found in Drosophila melanogaster, mouse and human. Meiotic recombination events are uniformly and uniformly distributed throughout the chromosome. The recombination frequency per megabase in humans is extremely low compared to yeast (370 cM/Mb) (28). Crossovers do not happen randomly between chromosomes in any organism. Regions that undergo high levels of recombination in yeast are usually located near promoter regions. These regions correspond to the locations of the double helix break regions (29). Recombination hotspots or regions with high recombination are also present in mammals (30). In humans, hot spots in males and females have been reported (31,32). C. elegans is the only species with the gene that provides the distribution of meiotic recombination events (33). Recombinations are crucial for proper segregation of meiotic chromosomes. It can contribute to the rearrangement of many chromosomes and has been found at higher frequency at the breakpoints of deletions and duplications.

Chromosome Matching and Separation

During the recombination process, the congruence of both sister chromatids and homologous chromosomes is maintained. Then with the timely release of this harmony, the chromosomes (in MI) and chromatids (in MII) separate from each other. Early or late separation of chromatids/chromosomes may cause chromosome failure to separate. There are many structures involved in this complex process regulated by a number of genes and proteins. Cohesins hold sister chromatids together, while chiasmata help keep homologous chromosomes connected. In metaphase I, homologous chromosome pairs line up along the metaphase line and spindle fibers are attached to sister kinetochores. Thus, two sister kinetochores pull the two sister chromatids towards opposite poles of the cell. For this to happen, the kinetochores found in the alpha-satellite sequences of the centromere must be next to each other on sister chromatids. For meiosis to continue, the spindle fibers must maintain a balanced tension in the opposite direction to the two kinetochores. This requires all chromosomes to line up properly on microtubules. In males, an imbalance stops meiosis and drives the cell to death. In women, a chromosomal imbalance may occur without stopping meiosis (34,35). Here, it may occur as a result of the breakdown of cohesion proteins along the chromosome arms, especially in older women. In this case, it can lead to unpaired chromosomes that separate independently from metaphase. The final stage in MI is anaphase I, in which the alignment between the chromosome arms is disrupted and allows the chiasmata to dissolve. The cohesin protein must remain attached to the centromeres. Sister

chromatids must be kept together until anaphase II. The combined homologues then separate and move towards their respective poles. In metaphase II, the chromosomes line up along the metaphase line. Kinetochores attach to microtubules from opposite poles. Later, they move to opposite poles in anaphase II. It is the cohesion protein at the centromere that keeps sister chromosomes intact until anaphase II.

Gender-Specific Differences

Meiosis differs in males and females. One of these differences is timing. In females, meiosis begins in all oocytes in fetal life, while in males it begins during puberty. Males produce sperm every day, while females are born with a certain number of follicles. While meiosis lasts for 40 years in females, the time required for the completion of a spermatogenesis process is approximately 64 days. The second difference is the cessation of meiosis. Meiosis is stopped in females from dicyoten to ovulation and then again from meiosis II to fertilization. In contrast, in males, meiosis is continuous and there is no stopping point. Third, and interestingly, males have checkpoints to monitor division during meiosis. If recombination has not occurred (pachytene checkpoint) the male gametes will be deactivated and die. In humans and mice, these checkpoints have been shown to be less stringent in mammalian oogenesis (36). The fourth difference is recombination. Sex-specific differences in recombination frequency are also found in humans and other organisms. In mammals, recombination shows sex-specific differences, with females generally having higher recombination rates than males (37). The fifth difference is that females have only one fertile oocyte, while males produce four sperm for each diploid cell that initiates meiosis.

Mitosis

Mitosis is a process of cell division in which diploid cells form diploid daughter cells or haploid cells form haploid daughter cells or exact copies of chromosomes are produced. The major difference between mitosis and meiosis is the absence of pairing of homologous chromosomes. In mitosis, there is normally no exchange of genetic material through recombination. Mitosis takes place daily in somatic cells in our body to replace cells that die through apoptosis and to allow growth to occur. Mitosis is required for every developmental stage after fertilization for hair growth, nail growth and embryo formation. Mitosis is also required for the steps leading to meiosis in both males and females. Spermatogenesis in males probably undergoes 20-25 mitotic divisions per year, while in females oogonia originate from primitive germ cells, a process involving 20-30 mitotic divisions. At three

months of intrauterine life, oogonia begin to mature in primary oocytes, which begin to undergo meiosis. Recombination can occur during mitosis. However, it occurs rarely compared to that which occurs in meiosis. It is more difficult to detect and measure. Double helix breaks are required to initiate recombination. However, they are the most harmful form of DNA damage because they are formed by chromosome breaks and rearrangements (38). There are two main ways of repairing double helix breaks. These are the joining of non-homologous ends and homologous recombination (39). Non-homologous splicing repairs broken DNA ends without requiring extensive sequence homology. However, homologous recombination requires an intact homologous chromosome or a sister chromatid to repair the break. During metaphase of mitosis, spindle fibers attach to kinetochores on the centromere of each chromatid. When sister kinetochores separate, each chromatid moves to opposite poles of the cell. For sister chromatids to separate, the cohesin protein that holds them together must be broken down. This is accomplished by a protease called separase, which becomes active in late metaphase (40).

Aneuploidy

Although meiosis has a highly organized control process necessary for sexual reproduction, errors are still common in females. These errors occur as abnormal chromosome separation or failure to separate. Failure to segregate causes gametes to result in a chromosome gain or loss (aneuploidy). This common CA seen in pregnancy is seen in at least 5% of all clinically defined pregnancies. Aneuploidy occurs as trisomy (gain of the entire chromosome) and monosomy (loss of the entire chromosome). It is estimated that these numerical chromosomal irregularities cause miscarriages in 15-20% of all pregnancies. Various chromosomal abnormalities are quite common in humans and can be found in 10-30% of all fertilized eggs. It has been reported that aneuploidy is seen in 20% of female eggs and 2-5% of spermatocytes (41). In other organisms, incorrect segregation of a chromosome is less common. The frequency of aneuploidy in Saccharomyces cerevisiae is as low as 1/10,000 per meiosis. In female Drosophila melanogaster, the inability to separate the X chromosome varies between 1/1.700 and 1/6,000 (42). The overall frequency of aneuploidy in fertilized eggs in mice is 1-2% (43). It is difficult to study the frequency of chromosomal abnormalities in humans because not all developmental stages have been studied. Available date are from studies of clinically recognized pregnancies and gamete studies. More than 35% of all terminated fetuses/embryos were found to be aneuploid (16). Spontaneous abortions with trisomy have been reported

for almost all chromosomes, and the most common is trisomy 16, which constitutes 1/3 of all trisomies (17).

Trisomy

First described in humans in 1959, trisomy is the presence of a third copy of a chromosome in the nucleus. At least 50% of pregnancy losses are chromosomally abnormal, and more than half of them are trisomic. Trisomy 16 is estimated to occur in more than 1% of clinically recognized pregnancies. This makes it the most common trisomy in humans (45). Trisomy 16 normally results in miscarriage in the first trimester of pregnancy. Only 13, 18, 21 and X chromosome trisomies can survive to term. Trisomy 21 is the most common trisomy in approximately 1/700 live births. In general, trisomy mostly originates from chromosomes in meiosis I during oogenesis (42). Early somatic errors can also result in mosaic trisomy and these are less common. Trisomy 16 is almost entirely due to a maternal error of MI. However, most errors for trisomy 18 occur in meiosis II. Approximately 50% of 47,XXY and trisomy 2 originate from the father (46.47). Monosomy X or Turner syndrome is thought to be largely (70-80%) related to producing nullisomic sperm for male sex chromosomes (48). It is not known whether the loss of the other sex chromosome occurs in the sperm or postzygotic, and it is a matter of debate. Therefore, it seems likely that many factors affecting nondisjunction are chromosome-specific. Although the majority of trisomies are lost as early miscarriages, in most mosaic cases they can survive to term. Chromosome mosaicism is the presence of two different cell lines with two different chromosome structures in an individual developing from a single fertilized egg. In prenatal diagnosis, the most common mosaicism is that some cells have normal chromosomes (46,XX or 46,XY) and other cells have trisomic chromosomes. Trisomy mosaicism may occur through a meiotic or somatic mechanism (49). It has been suggested that most mosaicisms begin as trisomic zygotes and subsequently lose an extra chromosome and acquire a normal cell line (50). However, he found that most of the mosaicism was of somatic origin and the origin was linked to the relevant chromosome. The number of mosaic cells in an individual determines the phenotype. In general, the proportion of mosaic cells of meiotic origin is considered to be high, while those of somatic origin are seen at lower levels (51). The abnormal cell line can be found in only one tissue or in multiple tissues. Mosaicism is found in 1-2% of all chorionic villus samples (CVS) (49). Frequently, the trisomy may also be limited to the placenta only. The phenotypic effect of trisomic mosaicism on an individual may be slightly or completely normal for gestational age.

Origin of Mosaicism

If a trisomic embryo begins life and later loses the third chromosome as a result of anaphase delay, this is called trisomic rescue. A trisomic cell can also be caused by a mitotic non-dissociation event. A very early mitotic error can lead to mosaicism, possibly because it will make half of the cells trisomic. If this event occurred at a later embryonic stage, the mosaic cell rate may be less. At the 64-cell stage of an embryo, only 3-5 cells will participate in the formation of the embryo, while the rest will form the extra-embryonic tissue (52). In this case, it seems more likely that the error occurred is of placental origin. It could just be a trisomy that occurs in the germ cell line. This mosaicism in the germline may go unnoticed, leading to new trisomy and recurrent pregnancy loss. This rarely recurring trisomic condition has been shown to occur only in trisomies 18 or 21. Other aneuploidies, when present in female germ cells, may lead to disruption of follicles (53). It is thought that mosaicism in germ cells is responsible for the recurrence of trisomy 21 (54, 55).

Single Ancestral Disomy

Uniparental disomy (UPD) is the presence of a normal chromosome pair with both copies from the same parent. UPD can cause clinical deviations as a result of homozygosity for recessive mutations and abnormal imprinting patterns (56). Isodisomy refers to regions of chromosomes that are derived from identical sister chromatids and heterodisomy from homologous chromosomes. This can occur in several ways. It is usually found as a result of trisomic rescue. If the chromosome lost during rescue in a trisomic embryo of maternal origin is the paternal chromosome, there is maternal UPD for this chromosome. That is, both chromosomes are from the mother or there is no contribution from the father. The distribution of isodisomic and heterodisomic regions depends on the initial stage. If the error occurs in MI, the centromere will also be heterodisomic as the chromosomes are from two different homologs. If the error occurs in MII, the centromere will also be isodisomy since the chromosomes are sister chromatids. However, there may be regions of both isodisomy and heterodisomy along the chromosome as a result of recombination that takes place in gametogenesis (56). Generally, UPD is a benign condition with no adverse phenotypic consequences to the individual (57). However, there are a few chromosomes where UPD has detrimental consequences. These chromosomes contain imprinted genes that are differentially expressed depending on the parent. This means that both mother's and father's input is necessary for proper development to

occur. It is the 15th best-known chromosome containing imprinted genes. Maternal UPD causes Prader-Willi syndrome (PWS). However, paternal UPD causes Angelman syndrome (AS), which is different. This is due to the loss of paternally expressed genes in mat UPD and the loss of a maternally expressed gene in pat UPD (56). Other chromosomes 6, 7, 11 and 14 where UPD is known to cause phenotypic abnormalities due to loss of expression of imprinted genes. More than 40 imprinted genes have been identified throughout the genome in humans (58).

Monosomy

Monosomy is the absence of one copy of a chromosome pair (with a total of 45 chromosomes). Autosomal monosomies cause very early fetal death. Monosomy 21 is an autosomal monosomy seen in dead fetuses. Sex chromosome monosomy (45,X) is the most common disorder seen in spontaneous abortions. The vast majority of embryos with a 45,X karyotype do not survive (99.5%). They account for about 10% of all spontaneous abortions. Even partial monosomies in the form of large deletions are not easily tolerated. Each non-segregation event that produces a gamete that is disomic rather than monosomic for a chromosome contains a complementary gamete that is nullisomic for that chromosome. Evidence from hamster and human sperm analysis has shown that monosomies are as common as trisomies (59). However, trisomies are more common than monosomies in spontaneous abortions and pregnancy losses. This is most likely because monosomies are much less tolerated during embryonic development. Therefore, monosomic embryos can be lost much earlier. Studies of in vitro fertilized human diploid embryos and preimplantation embryos also support this.

Segmental Aneuploidy

Segmental aneuploidy presents as unbalanced translocations. A duplication or deletion (three copies or more of a region) resulting in loss or gain of a chromosome segment leads to segmental trisomy and segmental monosomy. Unequal recombination can cause both deletions and duplications. Chromosomes with repetitive sequences may mismatch during meiosis. A repeating region of such chromatin may pair with a different region of another chromatin. As a result of recombination, an increase in the number of chromatin repeats and a decrease in the other may occur.

Deletions

A loss occurs when a chromosome is broken at two sites and the piece in between is lost. This in turn causes loss of genetic information. Partial monosomy occurs for the chromosome that has lost a piece. Microdeletion syndromes are large deletions that disable multiple genes that make up specific and recognizable phenotypes. PWS, AS and cri-du-chat syndromes are caused by deletions in chromosome 15qll-ql3 (paternal), 15qll-ql3 (maternal), and 5p, respectively. Repetitive sequences/duplicons (large blocks of folded genes of a DNA sequence) and other sequences have been implicated as catalysts for such breaks.

Repeat Sequences

Chromosomes have copies containing repeat sequences. These copied partitions are called end-to-end and tandem copies. The number of repeat sequences in a region can vary as follows. Unbalanced exchanges are the main cause of disrupting repeat sequences (specifically, Alu-like repeats). There is an Alu sequence every 6 kb in the human genome. Whether a phenotype is associated with a replicated region depends on many factors. These; The size of the duplicate region is known as the function of the genes and the location of the new segment. Duplicons have been shown to cause deletions and other rearrangements as well as abnormal recombination (60). Unnecessary genes and sequences can become new genes with similar or related functions.

RISK FACTORS OF TRISOMY

Although the importance of meiotic division in human reproduction and genetic damage in newborns is known, little is known about its etiology. However, the relationship between advanced maternal age and trisomy is well known. Altered recombination has also been shown to be associated with most trisomy. The associations of mitochondrial mutations, replication timing, centromere size, gene mutations, and environmental factors (smoking, diet, and oral contraceptives) with chromosomal failure were investigated. However, until now, a clear situation regarding these factors has not been revealed.

Epidemiology

It has been suggested that there may be a relationship between trisomy occurring before or after spontaneous abortion (SA) and trisomy (61). However, later studies showed no such relationship. Considering all avail-

able data, it was concluded that trisomy did not cause an abnormal SA in subsequent pregnancies. However, some studies have shown that women who have a baby with trisomy 21 at a young age (<30 years) have an increased risk for subsequent pregnancies (62). However, it was thought that this situation may be due to trisomy 21 mosaicism seen in a small number of couples (55). There are many young women with more than one trisomy. It has been suggested that these may have a risk of trisomy in their next pregnancies (63,64). These findings support the hypothesis that some women have a higher risk of chromosomal aberration than their peers when considering all viable trisomies, including trisomy 21.

Aging

The relationship between advanced maternal age and the risk of trisomy is well known. The risk of trisomy increases exponentially with increasing maternal age. Long before it was determined that Down syndrome was caused by trisomy 21, the relationship of this disease with increasing maternal age was known (65). While this risk is 2% in women under the age of 25, this rate rises to 35% in women over the age of 40 (66). This irregularity is not related to the uterine environment, but rather a problem with the egg itself. It is thought that the rate of trisomy specific to the age of the mother is not related to race, geography and socio-economic status. However, it has been shown that the risk of having a DS pregnancy in a mother with a low socio-economic status is increased (67).

Recombination

It is clearly known that maternal age is important for the risk of trisomy. However, whether other factors contribute to maternal age risk has not yet been fully established. The main reason here is a disruption in the meiosis process, which increases the risk of chromosome failure to separate. The effect of maternal age occurs in the process of chromosome failure to separate. While this process is lower in younger mothers, this possible risk increases with age. Meiotic specific proteins can degrade over time. In addition, spindle fibers can become fragmented and mitochondrial mutations can accumulate as well. Thus, altered recombination increases the risk of trisomics in an older woman's oocyte. Recombination or another factor in fetal life may increase the risk of trisomy. Telomere shortening and untimely replication can contribute to premature aging of chromosomes. In normal recombination, a crossover or exchange of genetic material is usually required for separation between homologous chromosomes. For proper segregation of human chromosomes, a change in the chromosome must be minimal (22). There

are many mutations in yeast and flies that reduce or eliminate trade-offs and cause high frequency of erroneous segregation during division (68,69). The association between reduced recombination and human trisomy was first found with reduced levels of recombination across the chromosome in meiosis leading to trisomy 21 (70). Also, sex chromosome aneuploidies, MI-induced trisomies of chromosomes 15, 16 and 18 are all known to be associated with a reduction in recombination (71).

Ovarian Aging

It has been suggested that the woman's proximity to menopause determines the risk of aneuploidy. The risk decreases as the total number of follicles and the number of developing follicles increase. Menopause is predicted when the total number of follicles reaches about 1000. An artificial or naturally occurring follicle reduction will cause premature menopause. It has been shown that there is an increase in aneuploidy rates with increasing age in mice (72). It has been found that the risk of disease is higher in women with a child with Down syndrome who have a single ovary as a result of ovarian surgery or a congenital absence of an ovary (73). These data suggest that with increasing maternal age, the few remaining oocytes and their quality increase the risk of trisomy. Menopause may occur one year earlier in mothers who have children with trisomy.

Chromosome Structure

Chromosomes have two main structural features called centromere and telomere. Each of these has its own specific repeat sequence and specific function in meiosis/mitosis. Normal centromeres and telomeres are indispensable structures for chromosome separation. It has been found that telomere sequences are a measure of aging, and short telomeres are associated with premature aging diseases and infertility, as well as being important for chromosome and chromatid separation (74).

Centromere

The centromere is a special and important region of the chromosome formed by DNA alpha sequences, other repetitive sequences and proteins. The most common DNA element in the human centromere and the □-satellite sequences that make up 3-5% of the chromosome DNA (75). The human centromere consists of repeat monomers rich in AT and 171 bp long, which are recognized by kinetochore proteins and motifs DNA (76). Centromere proteins are attached to these sequences. Since the centromere is

required for proper segregation of chromosomes in MI and chromatid segregation in MII, changes in sequences or size may affect chromosome segregation (77). In particular, a large discrepancy between an abnormally small and a large alpha sequence sizes within a homologous chromosome pair can lead to homologous chromosome mismatching, alignment, impaired recombination, and inability to separate. There are significant differences in alpha DNA sequence length between homologous chromosomes. For example, the size of the alpha sequence of the X chromosome ranges from 1300 to 3700 kb (78). Therefore, a pair of parental chromosomes may differ by 2400 kb in alpha sequence sizes for the X chromosome. In addition, it has been shown that the centromere on chromosome 21 is short with a frequency of 6.9% in DS patients (75). It is possible that cohesion is compromised because the centromeric heterochromatin size is below the minimum threshold, the alpha DNA does not have sufficient mechanical strength to hold the chromatids together, or the small alpha sequences bind less centromere proteins. This can cause the chromosomes to fail to separate. Failure to maintain sister chromatid cohesion causes premature separation of sister chromatids (in MI) (Maratou et al., 2000). If the centromeric repeats are too long, the chromatids may not separate in time, or if they are too small, the chromatids may not hold together. It has been reported that the alpha sequence on one of the chromosome 21 homologues is small (79). The importance of heterochromatic regions in mediating mating and segregation was first demonstrated by studies on chromosome 4 cleavage in Drosophila oocytes (80). Similar to Drosophila, females with centromeres with longer heterochromatin regions are likely to increase inseparability. Although abnormal alpha sequence size may predispose a chromosome to non-disjunction, additional factors are probably required as well. As with recombination, alteration or insufficient size of alpha DNA combined with maternal age may not allow for normal segregation. Therefore, very small or large alpha sequence size may be multifactorial of age-related chromosome segregation in humans. The centromere may also cause loss of replication control in meiosis and mitosis.

Telomeres

Telomeres are specialized structures found at the chromosome ends of eukaryotic organisms and are important for chromosome stability. They consist of a set of repetitive DNA sequences (TTAGGG in man) and associated proteins. Telomeres are believed to be responsible for positioning chromosomes in mitosis, maintaining chromosome integrity, and maintaining DNA sequences. Reduced telomere sequences are known to be associated

with chromosome segregation errors in mitosis. Chromosomes with short telomeres in aged cells tend to form dicentric chromosomes, most likely to protect their ends (81). In yeast, telomere loss in a single chromosome was found to be sufficient to arrest the cell cycle (82). Disruption of telomere-telomere bonds in meiosis may also disrupt synapse and recombination (20). In male germ cells, telomerase enzyme prevents age-related telomere destruction. In contrast, most telemor sequences decrease with age in tissues at a rate of about 50 to 200 bp per cell division (83). While the average telomere length is 20 kb in children younger than 10 years of age, this number drops to 5 kb in people aged 60-70 years (84). In humans, the inverse relationship between telomere length and age is linear. However, there is great variability in telomere length among individuals of all ages (85).

Regular shortening of telomeres has been associated with replicative aging both in vitro and in vivo and has been termed the mitotic clock. It has been reported that individuals with early aging Progeria and Down syndrome have shorter-than-average telomeres (86). Short telomeres have been found to be associated with aneuploidy and chromosome loss in many cancers and somatic tissues (87). In addition, it has been shown that the frequency of aneuploidy in cultured lymphocytes increases with advancing age. It is possible for short telomeres to cause chromosome missegregation and aneuploidy. However, there are a number of possible explanations for short telomeres. These; Mutations in genes involved in telomerase structure or activity can lead to shortened telomeres. Overexpression of the telomere binding protein TRF1 has been shown to cause telomere shortening (88). After it was reported that shortening of telomeres in Dolly the Sheep, the reprogramming of telomere lengths in cloned animals has sparked controversy. They found that fertile women had significantly longer telomeres compared to women of the same age who underwent IYF with weak oocytes (74). It has been suggested that this may be related to less cell division as a result of the decrease in growth hormones. Therefore, an increase in growth hormones can lead to higher cell divisions and therefore shorter telomeres.

Time of Reproduction

Both alleles of a gene normally replicate synchronously in the cell cycle. However, asynchronous replication is seen for genes on the X chromosome. Genes on the inactive X replicate themselves later than those on the active X chromosome. As with imprinted genes, olfactory receptor genes, and other mono-allelically expressing genes. Higher rates of allelic asynchrony and an-

euploidy were found in cells from older mothers who gave birth to a child with Down syndrome.

Gene Mutations

Methylene-tetra-hydro-folate-reductase (MTHFR), Methionine-synthase-reductase (MTRR). In addition to the structural features of chromosomes that affect chromosome separation, there is some limited evidence that gene variants may also play a role in separation. There is evidence that abnormal folate and methyl metabolism can lead to hypomethylation of DNA and abnormal chromosome segregation. Related to this, it has been suggested that some polymorphisms may be frequently increased in the MTHFR and MTRR genes of the mother of a DS child (89). It is known that these two mutations cause a decrease in enzyme activity in heterozygotes and homozygotes and pose a risk for neural tube defects. Maternal polymorphism analysis of other genes involved in the folate pathway found an increase in the MTRR mutant homozygous variant in mothers with DS. In addition, the combined presence of both mutations was found to increase the risk even more. However, some studies could not show the same association for trisomy 21, but no significant increase in MTHFR or MTRR polymorphisms was observed in more than 200 trisomy except trisomy 21 (42).

Apos4 Alleles: Young mothers who give birth to a child with DS have been shown to have a five-fold higher than normal risk of developing Alzheimer's disease (AD) later in life (90). All individuals with DS over the age of 40 also had AD-specific neuropathological changes. Some forms of AD have been reported to result from mutations in the APP (B-amyloid precursor protein) genes on chromosome 21, presenilin-1 (PS-1) on chromosome 14, and presenilin-2 (PS-2) genes on chromosome 1 (91). Presenilin proteins may be important in chromosome segregation because they bind to the kinetochores and centrosomes. However, Apolipoprotein E (apoE) mutations may explain this association. ApoE is a gene located on chromosome 19. Rarely, allele E4 has been reported to be a risk factor for AD in both familial and sporadic cases (92). A higher frequency of the APOE s4 allele was found in young mothers who gave birth to a DS child due to maternal MII errors (93).

Mitochondrial Mutations: Another factor that has been suggested to contribute to chromosome failure is mitochondrial abnormalities. Mitochondrial dysfunction resulting from decreased ATPase6 and Tfam expressions during meiotic maturation of oocytes has also been suggested to cause non-differentiation errors (Lee et al., 2003). Mitochondrial DNA (mtD-

NA) mutations are also known to increase exponentially with increasing age. The curve for the amount of time- or age-related mtDNA mutations is very similar to the age-related trisomy risk. The accumulation of mtDNA errors over time in both the ovary and somatic tissues can lead to energy deficiency and other problems that can complicate chromosome segregation.

Environmental Factors

The possibility that the environment, what we eat, and the harmful factors we are exposed to can affect reproductive success has always aroused interest. Smoking, alcohol, caffeine, and many other factors have been shown to affect the health of the developing fetus. Exposure to these harmful factors can lead to non-segregation of chromosomes in meiosis and increase the risk of trisomy. There are conflicting studies on the relationship between smoking and DS. It has been suggested that high alcohol and caffeinated coffee consumption reduce the risk of having a DS fetus (94). However, it has been reported that oral contraceptive use in smoking mothers increases the risk of DS fetus, but oral contraceptive use alone is not an important risk factor. There are conflicting findings about the effects of radiation on reproduction and pregnancy. It has been suggested that the increased frequency of trisomy 21 in West Berlin is linked to the Chernobyl reactor accident. However, no genetic link to exposure to other types of radiation has been reported. It has been reported that exposure to an insecticide called trichlorfon can cause an increase in DS (95). Environmental risks seem to be important in terms of trisomy risk by affecting the development of oocytes. Bisphenol A (BPA) is an estrogenic compound widely used in the manufacture of polycarbonate plastics and epoxy resins. It can also be found in feeding bottles, water bottles, can liners, and dental sealants. When BPA was widely used, a significant increase in chromosome non-segregation and meiotic chromosome abnormalities was observed. It was concluded that this was due to the strong meiotic aneugenic effect of BPA. Similar studies support that environmental exposures can lead to changes in the body and oocytes, leading to nondisjunction.

Conclusion

Chromosome failure and aneuploidy events are very important in humans. The relationship between increasing maternal age and the risk of trisomy is widely known. However, little is known about the mechanisms, causes, predictability and prevention of chromosomal nondisjunction. It is well known that chromosomal non-separation is associated with advanced maternal age. Telomere length, the timing of replication at the centromere

and other loci are important in this relationship. It is known that decreasing telomere length is associated with increasing age. Telomere length is known to be associated with reproductive health. Depending on the replication timing, chromatin abnormalities are known to cause trisomy in young women. Decreased recombination frequency was associated with non-segregation at meiosis I, while an increase was associated with non-segregation at meiosis II for most chromosomes. It is not fully known whether methylation or other epigenetic modifications in DNA are related to non-dissociation. Methylation and chromatin changes may be related to recombination, telomere length, and possibly replication timing. Chromosome structure, centromere and telomere sizes/stability are probably crucial for proper pairing and segregation of chromosomes in meiosis. This may not necessarily be related to aging. However, there may also be another factor that somehow contributes to the risk. Non-separation causes abnormalities in the number of chromosomes that often lead to pregnancy loss. Some women appear to be predisposed to trisomy. However, environmental harmful factors such as nicotine, mobile phone and harmful rays can cause numerical chromosome damage. Little is known about the cause of non-separation in human reproduction.

Although there are many important studies in this field of inseparability and aneuploidy, definitive proof of a direct cause of inseparability has not yet been fully revealed.

REFERENCES

1. Demirhan O. The Importance of the Aneuploidy Screening in Pregnancy. Austin J Obstet Gynecol. 2017; 4(2): 1074.
2. Demirhan O. Tobacco Use and Its Genotoxic Effects in Pregnancy, Tobacco Addiction: Effect on Human Health, Chapter 5, 2018;1-15.
3. Demirhan O. Results of Smoking in Pregnancy: The Genotoxic Effect of Nicotine or why Cigarette should not be Smoked in Pregnancy? J Addict Med Ther 2017;5(1):1026.
4. Demirhan O, Demir C, Tunç E, Inandiklioglu N, Sütcü E, Sadikoglu N, et al. The genotoxic effect of nicotine on chromosomes of human fetal cells: the first report described as an important study. Inhal Toxicol. 2011; 23: 829-834.
5. Demirhan O. Genotoxic Effects of Radiofrequency-Electromagnetic Fields. Journal of Toxicology and Environmental Sciences. 2021:1;1-4.
6. Uslu N, Demirhan O, Emre M. The genotoxic effects of 900-1800 MHz radiofrequency electromagnetic fields on chromosomes of human fetal cells. Biomedical Research and Clinical Practice. 2019;4:1-6.
7. Çetinel N, Demirhan O, Demirtaş M, Çağlıyan ÇE, Cüreoğlu A, Uslu IN, Sertdemir Y. The Genotoxic Effect Of Interventional Cardiac Radiologic Procedures On Human Chromosomes. Clinical Medical Reviews and Reports. 2020; 3(1):1-10.
8. Korkmaz DT, Demirhan O, Abat D, Demirberk B, Tunç E, Kuleci S. Microchimeric Cells, Sex Chromosome Aneuploidies and Cancer. Pathol Oncol Res. 2015; 21: 1157-1165.
9. Emre M, Boga A, Cetiner S, Tunc E, Demirhan O. The Effects of exposure to 900 MHz Radiofrequency Radiation and Nicotine on Apoptotic Ratio of Human Fetal Cells. SEE J Immunol. 2021;4(1):1-7.
10. Demirhan O, Çetinel N, Çetiner S, Çağlıyan ÇE, Cureoglu A, Uslu IN, Deveci OS, Sertdemir Y, Demirtaş M. Alteration of Peripheral Blood T-cell Subsets in Patients with Cardiovascular Disease; Exposure to Ionizing Radiation (X-rays) and Contrast Medium. Int J Cardiol Res. 2018;5(2):104-108.
11. Boga A, Emre M, Sertdemir Y, Akıllıoglu K, Binokay S, Demirhan O. The Effect of 900 and 1800 MHz GSM-like Radiofrequency Irradiation and Nicotine Sulfate Administration on the Embryonic Development of Xenopus laevis. Ecotoxicology and Environmental Safety. 2015;113:378–390.

12. Boga A, Emre M, Sertdemir Y, Uncu İ, Binokay S, Demirhan O. Effects of GSM-like radiofrequency irradiation during the oogenesis and spermiogenesis of Xenopus laevis. Ecotoxicology and Environmental Safety.129;137-144, 2016.

13. Demirhan O, Akbaba M, Çelik S, Uslu N, Çetinel N, Tunç E, Demirhan ÖF. Chromosomal Aberrations in agricultural farmers exposed to pesticides. Adv Toxicol Toxic Effects. 2019;3(1): 015-022.

14. Daglioglu N, Akcan R, Efeoglu P, Inandiklioglu N, Gulmen MK, Demirhan O. Polychlorinated Biphenyl And Organochlorine Pesticide Levels In Amniotic Fluid; Data From Cukurova, Turkey. Toxicological and Environmental Chemistry. 95(6); 954-961. 2013.

15. Lejeune, J, R Turpin, M Gautier. [Mongolism; a chromosomal disease (trisomy).] Bull Acad Natl Med. 143(11-12):256-265,1959.

16. Hassold, TJ, LC Burrage, ER Chan, L M Judis, S Schwartz, SJ James, PA Jacobs and NS Thomas. Maternal Folate Polymorphisms and the Etiology of Human Nondisjunction. Am J Hum Genet. 69: 434-439, 2001.

17. Hassold, T, S Sherman and P Hunt. Counting cross-overs: characterizing meiotic recombination in mammals. Hum Mol Genet. 9(16):2409-2419, 2000.

18. Faddy, MJ and RG Gosden. A model conforming the decline in follicle numbers to the age of menopause in women. Hum Reprod. 11(&):1484-1486, 1996.

19. Turnpenny, P and S Ellard. Emery's Elements of Medical Genetics. 12th Edition, 2005.

20. Walker, MY and RS Hawley. Hanging on to your homolog: the roles of pairing, synapsis and recombination in the maintenance of homolog adhesion. Chromosoma. 109:3-9, 2000.

21. Scherthan, H, S Weich, H Schwegler, C Heyting, M Harle and T Cremer. Centromere and Telomere Movements during Early Meiotic Prophase of Mouse and Man are Associated with the Onset of Chromosome Pairing. JCB. 134(5): 1996: 1109-1125.

22. Lawrie, NM, C Tease and MA Hulten. Chiasma frequency, distribution and interference maps of mouse autosomes. Chromosoma. 104(4):308-314, 1995.

23. Pittman, DL and JC Schimenti. Recombination in the Mammalian Germ Line. Curr Top Dev Biol. 37:1-35, 1998.

24. Barlow, AL and MA Hulten. Crossing over analysis at pachytene in man. Eur J Hum Genet. 6(4):350-358, 1998.

25. Hubert, R, M MacDonald, J Gusella and N Arnheim. High resolution localization of recombination hot spots using sperm typing. Nature Genetics. 7:420-424, 1994.

26. Robinson, WP The Extent, Mechanism, and Consequences of Genetics Variation, for Recombination Rate Am. J. Hum. Genet. 59:1175-7783, 1996.

27. Tease, C and M A Hulten. Inter-sex variation in synaptonemal complex lengths largely determine the different recombination rates in male and female germ cells. Cytogenet. Genome Res. 107: 208-215, 2004.

28. Symington, LS, A Brown, SG Oliver, P Greenwell and TD Petes. Genetic analysis of a meiotic recombination hotspot on chromosome III of Saccharomyces cerevisiae. Genetics. 128(4):717-727, 1991.

29. Ohta, K, T Shibata and A Nicolas. Changes in chromatin structure at recombination initiation sites during yeast meiosis. EMBO J. 13(23):5754-5763, 1994.

30. Steinmetz, M, K Minard, S Horvath, J McNicholas, J Srelinger, C Wake, E Long, B Mach and L Hood. A molecular map of the immune response region from the major histocompatibility complex of the mouse. Nature. 300(5887):35-42, 1982.

31. Jeffreys, AJ, A Ritchie and R Neumann. High resolution analysis of haplotype diversity and meiotic crossover in the human TAP2 recombination hotspot. Human Molecular Genetics. 9(5): 725-733, 2000.

32. Lercher, MJ and LD Hurst. Imprinted Chromosomal Regions of the Human Genome Have Unusually High Recombination Rates. Genetics. 165:1629-1632, 2003.

33. Zetka M, Rose AM. Mutant rec-1 eliminates the meiotic pattern of crossing over in Caenorhabditis elegans. Genetics. 141:1339-1349, 1995.

34. Angell, R. First-Meiotic-Division Nondisjunction in Human Oocytes. Am J Hum Genet. 61:23-32,1997.

35. Hunt, PA, KE Koehler, M Susiarjo, CA Hodges, A Ilagan, RC Voigt, S Thomas, BF Thomas and TJ Hassold. Bisphenol a exposure causes meiotic aneuploidy in the female mouse. CurrBiol. 13(7):546-53, 2003.

36. Hodges, CA, A Hagan, D Jennings, R Keri, J Nilson and PA Hunt. Experimental evidence that changes in oocyte growth influence meiotic chromosome segregation. Hum Reprod. 17(5):1171-1180, 2002.

37. Dunn, LC and D Bennett. Sex differences in recombination of linked genes in animals. Genet. Res. 9(2):211-220, 1967.

38. Morrison, C and S Takeda. Genetic analysis of homologous DNA recombination in vertebrate somatic cells. Int J Biochem Cell Biol. 32(8):817-831, 2000.

39. Haber, JE. Recombination: a frank view of exchanges and vice versa. Curr. Opin. Cell Biol. 12:286-292, 1999.

40. Revenkova, E, M Eijpe, C Heyting, CA Hodges, PA Hunt, B Liebe, H Scherthan and R Jessberger. ohesin SMCip is required for meiotic chromosome dynamics, sister chromatid cohesion and DNA recombination. Nature Cell Biology. 6(6): 555-562, 2004.

41. Martin, RH, E Spriggs and AW Rademaker. Multicolor Fluorescence In Situ Hybridization Analysis of Aneuploidy and Diploidy Frequencies in 225,846 Sperm from 10 Normal Men. Biology of Reproduction. 54: 394-398, 1996.

42. Hassold, T and P Hunt, To Err (Meiotically) is Human: The Genesis of Human Aneuploidy. Nature. 2: 280-291, 2001.

43. Yamamoto, A Endo and G Watanabe. Maternal age dependence of chromosome anomalies. Nature New Biol 241: 141-142, 1973.

44. Hassold, T, L Judis, ER Chan, S Schwartz, A Seftel and A Lynn. Cytological studies of meiotic recombination in human males. Cytogenet. Genome Res. 107: 249-255, 2004.

45. Hassold, T, M Abruzzo, K Adkins, D Griffin, M Merrill, E Millie, D Saker, J Shen and M Zaragoza. Human Aneuploidy: Incidence, Origin, and Etiology. Env Mol Mut. 28:167-175, 1996.

46. Abruzzo, MA and TJ Hassold. Etiology of Nondisjunction in Humans. Env Mol Mut. 25 (suppl 26):38-47, 1995.

47. Robinson, WP, F Bernasconi, A Lau and DE McFadden. Frequency of Meiotic Trisomy Depends on Involved Chromosome and Mode of Ascertainment. Amer J Med Gen. 84: 34-42, 1999.

48. Hassold, T, D Pettay, A Robinson and I Uchida. Molecular studies of parental origin and mosaicism in 45, X conceptuses. Hum Genet. 89(6):647-652, 1992.

49. Kalousek, DK and M Vekemans. Confined placental mosaicism and genomic imprinting. Bailliere's Clin Ob Gyn. 14(4):723-730, 2000.

50. Hassold, TJ The origin of aneuploidy in humans. In: Vaughn-Dellarco et al. eds. Aneuploidy: etiology and mechanisms. NY: Plenum Press. 1985: 103-116, 1985.

51. Robinson, WP, IJ Barrett, L Bernard, A Telenius, F Bernasconi, RD Wilson, RG Best, PN Howard-Peebles, S Langlois and DK Kalousek. Meiotic origin of trisomy in confined placental mosaicism is correlated with presence of fetal uniparental disomy, high levels trisomy in trophoblast, and increased risk of fetal intrauterine growth restriction. Am J Hum Genet.60(4): 917-927, 1997.

52. Gardner, RL and MF Lyon, X chromosome inactivation studied by injection of a single cell into the mouse blastocyst. Nature. 231: 385-386, 1971.

53. Robinson, WP, DE McFadden, and MD Stephenson. The Origin of Abnormalities in Recurrent Aneuploidy/Polyploidy. Am J Hum Genet. 69(6): 1245-1254, 2001.

54. Pangalos, CC Talbot, JG Lewis, PA Adelsberger, MB Petersen, JL Serre, MO Rethore, MC deBlois, P Parent, AA Schinzel et al. DNA polymorphism analysis in families with recurrence of free trisomy 21. AJHG. 51: 1015-1027, 1992.

55. Bruyere, H, R Rupps, BD Kuchinka, JM Friedman and WP Robinson. Recurrent Trisomy 21 in a Couple With a Child Presenting Trisomy 21 Mosaicism and Maternal Uniparental Disomy for Chromosome 21 in the Euploid Cell Line. Am J Med Genet. 94:2000.

56. Robinson, WP. Mechanisms leading to uniparental disomy and their clinical consequences. BioEssays. 22:452-459, 2000.

57. Kotzot, D. Abnormal phenotypes in uniparental disomy (UPD): fundamental aspects and a critical review with bibliography of UPD other than 15. Am J Med Genet. 82:265-274, 1999.

58. Jorde, LB, JC Carey, MJ Bamshad and RL White. Medical Genetics, 3r d Edition, 2003.

59. Brandriff, B, L Gordon, L Ashworth, G Watchmaker, A Carrano and A Wyrobek. Chromosomal abnormalities in human sperm: Comparisons among four healthy men. Human Genetics. 66: 193-201, 1984.

60. Amos-Landgraf, JM, Y Ji, W Gottlieb, T Depinet, AE Wandstrat, SB Cassidy, DJ Driscoll, PK Rogan, S Schwartz and RD Nicholls. Chromosome Breakage in the Prader-Willi and Angelman Syndromes Involves Recombination between Large, Transcribed Repeats at Proximal and Distal Breakpoints. Am J Hum Genet. 65:370-386, 1999.

61. Alberman, E. The scope of perinatal statistics and the usefulness of international comparisons. Proc. Annu. Symp. Eugen Soc. 17:57-73, 1981.

62. Stene, J, E Stene and M Mikkelsen. Risk for chromosome abnormality at amniocentesis following a child with a non-inherited chromosome aberration. A European Collaborative Study on Prenatal Diagnoses 1981. Prenat. Diagn. 4(SpecNo):81-95, 1984.

63. Warburton, D, L Dallaire, M Thangavelu, L Ross, B Levin and J Kline. Trisomy Recurrence: A Reconsideration Based on North American Data. Am. J Hum Genet. 75:2004.

64. Warburton and Kinney (1996) Chromosomal differences in aneuploidy. Env mol mut 28: 37-247.

65. Penrose, LS. Maternal Age in Familial Mongolism. The British Journal of Psychiatry. 97(409):73 8-747, 1951.

66. Hunt, PA and TJ Hassold. Sex Matters in Meiosis. Science. 296:2181-2183, 2002.

67. Christianson, RE, SL Sherman and CP Torfs. Maternal meiosis II nondisjunction I trisomy 21 is associated with maternal low socioeconomic status. Genet Med. 6(6):487-494, 2004.

68. Jones, M, R Wagner and M Radman. Mismatch repair and recombination in E. Coli. Cell. 50(4):621-626, 1987.

69. Hawley, S Exchange and chromosome segregation in eukaryotes. In Genetic Recombination (eds. R. Kucherlapati and G. Smith) 497-525,1988.

70. Warren, AC, A Chakravarti, C Wong, SA Slaugenhaupt, SL Halloran, PC Watkins, C Metaxotou, SE Antonarakis. Evidence for Reduced Recombination on the Nondisjoined Chromosomes 21 in Down Syndrome. Science 237:652-655, 1987.

71. Thomas, NS, A R Collins, TJ Hassold and PA Hunt. A reinvestigation of non-disjunction resulting in 47,XXY males of paternal origin. Eur. J. Hum. Genet. 8(10):805-808, 2000.

72. Brook, JD, RG Gosden and AC Chandley. Maternal ageing and aneuploid embryos -Evidence from the mouse that biological and not chronological age is the important influence. Hum. Genet. 66:41-45, 1984.

73. Freeman, SB, Q Yang, K Allran, LF Taft and SL Sherman. Women with a Reduced Ovarian Complement May Have an Increased Risk for a Child with Down Syndrome, Am. J. Hum. Genet. 66:1680-1683,2000.

74. Dorland, M, JM van Montfrans, RJ van Koolj, CB Lambalk and ER te Velde. Normal telomere lengths in young mothers of children with Down's syndrome. The Lancet. 352:961-962, 1998.

75. Lo, AWI, GCC Liao, M Rocchi and KHA Choo. Extreme Reduction of ChromosomeSpecific a-Satellite Array is Unusually Common in Human Chromosome 21. Gen. Res. 9:895-908, 1999.

76. Masumoto et al. Properties of CENP-B and its target sequence in a-satellite DNA. In Chromosome Segregation and Aneuploidy (BK. Vig, Ed) 31-43. Spriger-Verlag, Heidelberg, 1993.

77. Abruzzo, MA, DK Griffin, EA Millie, LA Sheean and TJ Hassold. The effect of Y chromosome alpha-satellite array length on the rate of sex chromosome disomy in human sperm. Hum. Genet. 97:819-823, 1996.

78. Mahtani, M M and HF Willard. Pulsed-Field Gel Analysis of a-Satellite DNA at the Human X Chromosome Centromere: High-Frequency Polymorphisms and Array Size Estimate. Genomics. 7:607-613, 1990.

79. Maratou, K, Y Siddique, A M Kessling and GE Davies. Variation in alphoid DNA size and trisomy 21: A possible cause of nondisjunction. Hum. Genet. 106:525-530, 2000.

80. Hawley, RS, H Irick, AE Zitron, DA Haddox, A Lohe, C New, MD Whitley, T Arbel, J Jang, K McKim et al. There are two mechanisms of achiasmate segregation in Drosophila females, one of which requires heterochromatic homology. Dev. Genet. 13: 440-467,1993.

81. DeLange, T. Telomere dynamics and genome instability. In Telomeres, (eds Blackburn, EH and CW Greider) 265-293 (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1995).

82. Sandel, LL and VA Zakian. Loss of a Yeats Telomere: Arrest, Recovery, and Chromosome Loss. Cell. 75:729-739, 1993.

83. Aviv, A, D Levy and M Mangel Growth, telomere dynamics and successful and unsuccessful human aging. Mech. Ageing Dev. 124:829-837, 2003.

84. Schwartz, HS, GA Dahir and MG Butler. Telomere Reduction in Giant Cell Tumor of Bone and with Aging. Cancer Genet. Cytgenet. 71:132-138, 1993.

85. Rufer, N, TH Brummendorf, S Kolvraa, C Bischoff, K Christensen, L Wadsworth, M Schulzer and PM Lansdorp. Telomere Fluorescence Measurements in Granulocytes and T Lymphocyte Subsets Point to a High Turnover of Hematopoietic Stem Cells and Memory T Cells in Early Childhood. J. Exp. Med. 190(2): 157-167, 1999.

86. Vaziri, H, F Schachter, I Uchida, L Wei, X Zhu, R Effros, D Cohen and CB Harley. Loss of Telomeric DNA during Aging of Normal and Trisomy 21 Human Lymphocytes. Am. J. Hum. Genet. 52:661-667, 1993.

87. Butler, MG, J Tilburt, A DeVries, B Muralidhar, G Aue, L Hedges, J Atkinson and H Schwartz. Comparison of chromosome telomere integrity in multiple tissues from subjects at different ages. Cancer Genet. Cytogenet. 105(2):138-144, 1998.

88. vanSteensel, B and T de Lange. Control of telomere length by the human telomeric protein TRF1. Nature. 385(6618):740-743, 1997.

89. James, SJ, M Pogribna, IP Pogribny, S Melnyk, RJ Hine, JB Gibson, P Yi, DL Tafoya, DH Swenson, VL Wilson and DW Gaylor. Abnormal folate metabolism and mutation in the methylenetetrahydrofolate reductase gene may be maternal risk factors for Down syndrome. Am. J. Clin. Nutr. 70:495-501,1999.

90. Potter, H and LN Geller Alzheimer's disease, Down's syndrome, and chromosome segregation. Lancet. 348(9019): 66, 1996.

91. Petersen, MB, G Karadima, M Samaritaki, D Avramopoulos, D Vassilopoulos and M Mikkelsen. Association Between Presenilin-1 Polymorphism

and Maternal Meiosis II Errors in Down Syndrome. American Journal of Medical Genetics 93: 366-372, 2000.

92. Chartier-Harlin, M Parfitt, S Legrain, J Perez-Tur, T Brousseau, A Evans, C Berr, O Vidal, P Roques, V Gourlet et al. Apolipoprotein E, epsilon 4 allele as a major risk factor for sporadic early and late-onset forms of Alzheimer's disease: analysis of the 19ql3.2 chromosomal region. Hum Mol Genet. 3(4):569-74, 1994.
93. Avramopoulos, M Mikkelsen, D Vassilopoulos, M Grigoriadou and MB Petersen. Apolipoprotein E allele distribution in parents of Down's syndrome children. Lancet. 347(9005):862-5, 1996.
94. Torfs, CP and RE Christianson. The effect of maternal smoking and coffee consumption on the risk of having a recognized Down syndrome pregnancy. Am. J. Epidemiol. 152: 1185-1191,2000.
95. Czeizel, AE and E Csaba. Environmental Trichlorfon and Cluster of Congenital Abnormalities. Lancet 341:539-542, 1993.