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SPECIAL ARTICLE

The Possible Primary Causes of Human Aneuploidy

Saifon Chawanpaiboon MD,
Vitaya Titapant MD.

Department of Obstetrics&Gynaecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, 10700.

The main chromosomal abnormalities group is human aneuploidy which leads to spontaneous miscarriage in the first trimester of pregnancy. It also associated with the main cause of human mental retardation.[1] Aneuploidy is defined by the abnormal number of chromosomes which involves an extra or lack of chromosome as they are called trisomy and monosomy, respectively.[2] The one or more extra whole sets of chromosomes are called polyploidy.[3]

Specifically clinical syndromes are correlated with abnormal number of chromosomes which differs from the normal number of 46. Down syndrome is caused from the presence of three copies of chromosome 21 (trisomy 21),[4] Turner syndrome from the presence of only one copy of the X chromosome (monosomy X),[5] Klinefelter syndrome from XXY sex chromosome trisomy,[6] Edwards syndrome from trisomy 18[7] and Patau syndrome from trisomy 13.[8]

Trisomy is the most common cause of the human chromosomal abnormalities. The presence of an extra autosome is associated with severe mental and physical retardation, miscarriage and death during neonatal period; while the presence of an extra sex chromosome is associated with physical, behavioral and intellectual impairments which is more pleasant than the former.[1]

Nondisjunction is the main cause of single chromosome aneuploidy, and can involve the total set of chromosomes. Nondisjunction can be described by the failure of synapsed homologous chromosomes to separate at anaphase of meiosis II, or failure of the mitotic spindle to form and function normally. The presence of nondisjunction after the first clevage division causes a mosaic, which comprises two more cell lines derived from an only one zygote in an individual.[3]

After the first chromosome abnormality was first reported by Lejeune,[4] extensive studies have been proceeded. Cytogenetic study leads to the understanding of the causes, mechanism, incidence and origin of genesis of human aneuploidy. Many essential studies including those of the incidence of aneuploidy in oocytes and sperm, the determination of meiotic stage preimplantation embryos, parental origin and meiotic recombination in trisomic neonate and abortuses, are offered the more detailed and understanding of the primary causes of aneuploidy.

THE INCIDENCE OF HUMAN ANEUPLOIDY

a.) The Incidence of Aneuploidy in Livebirths

Most aneuploidy and other chromosome abnormalities fetuses tend to have a spontaneous miscarriage at the first trimester of pregnancy and a high perinatal mortality rate at livebirth. These are the very interesting natural process which can get rid of the most cases of aneuploidy and many other chromosomal abnormalities, lead to the lower incidence of aneuploidy in livebirth. The overall incidence of aneuploidy in livebirth humans is 0.3%;[9] while those in stillbirth is 4.3% and spontaneous abortions is 34.7%.

The incidence of trisomy 21, 18 and 13 are of 0.13%, 0.01% and 0.05% respectively; all are the most common autosomal trisomies in livebirths.[9] Due to its high incidence, the characteristic of syndromes are demonstrated[4,7,8] and mental retardation is the main feature of these syndromes.[9] The incidence of trisomy 21 in livebirth is more than those of trisomy 18 and 13, which can be explained by a higher initial incidence of nondisjunction in chromosome 21 than chromosome 18 and 13 or a relatively greater spontaneous miscarriage in trisomy 18 and 13. However; the latter seems to be the better explanation since the incidence of miscarriage in trisomies 21, 18 and 13 are 76.2%, 94.6% and 97.2% respectively.[10] Trisomy 1, an autosomal monosomy is lethal and no report indicated the presence in livebirths.[1,9]

The severity of the morphological appearance of sex chromosome aneuploidy is better than autosomal aneuploidy. The sex chromosome aneuploidy; such as XXX, XXY, XYY have the incidence of livebirths as 0.05%, 0.05% and 0.005% respectively.[9] Monosomy X fetuses tend to have a spontaneous miscarriage in the first trimester with a high incidence of 99.7% and this aspect can define the low incidence in livebirth of monosomy X comparing to other sex chromosome aneuploidy. The livebirth of monosomy X has a phenotypic appearance as Turner syndrome;[11] and 47, XXX, 47, XXY and 47, XYY also have a high chance to survive.

The 47, XXX (triple-X) correlates with amenorrhoeic women, the 47, XXY is associated with Klinefelter syndrome;[12] and the 47, XYY is likely to be normal without symptom. The rare cause of other sex chromosome aneuploidy including 48, XXXX, 48,XXXY and 48, XXYY have been found. The incidence of livebirth in some of very rare chromosome aneuploidy are underestimated because there is no symptom except for infertility.

b.) The Incidence of Aneuploidy in Stillbirths

The incidence of aneuploidy in stillbirth is 4.3%. Trisomy 21,18 and 13 are demonstrated in stillbirths with the perinatal mortality incidence of 76.2%, 94.6% and 97.2% respectively. Sex chromosome aneuploidy is also found in stillbirths. The highest death rate during perinatal period is found in monosomy X, with the incidence of 99.7%.[9]

c.) The incidence of Aneuploidy in Spontaneous Abortions

The main aetiology of spontaneous miscarriage in humans is aneuploidy with the overall incidence of 34.7%;[9] and its incidence is inversely associate with the gestational age.[13] The incidence of chromosome abnormalities in spontaneous miscarriage is 50% during 8 to 12 weeks of gestation, and 27% during 13 to 24 weeks of gestation without the obvious report during 3 to 7 weeks of gestation;[10] therefore, it is assumed that the spontaneous miscarriage trends to occur after a few weeks of implantation.

Trisomies of all chromosomes, except chromosome 1, have been demonstrated in spontaneous miscarriages with the highest detection rate in trisomy 16 (about 1/3 cases). The second and third most common causes of spontaneous miscarriage are trisomy 22 and 21; while trisomies 22, 21 and 16 give rise to 50% of all trisomies in spontaneous miscarriage. Monosomy X is the main single aneuploidy which is detected in spontaneous miscarriage[9] and only 0.3% of pregnancy with monosomy X are continued until delivery; although its clinical phenotype is nearly asymptomatic. The overall incidence of aneuploidy in spontaneous miscarriage is 10 times greater than that in stillbirths and 100 times that in livebirths with the proportion of 34.7%: 4.3%: 0.305%.

d.) The Incidence of Aneuploidy in Preimplantation Embryos

The modern techonology of in vitro fertilisation (IVF) is very useful to detect the incidence of aneuploidy during preimplantation embryos;[14] although the effect of hyperstimulated ovarian conditions on the aneuploidy incidence is still undetermined.

The overall incidence of aneuploidy in preimplantation embryos from IVF is 20% by using basic cytogenetic method. Trisomy 16 and acrocentric

chromosome contribute the most proportion of aneuploidy in this group.[15,16] However; the analysis of chromosomal abnormality is karyotyping but this method is not helpful to detect individual chromosome because minimal number of metaphase spreading of the embryonic chromosomes lead to poor result.[17,18]

Fluorescent in situ hybridisation (FISH) has been used to genetically diagnose the preimplantation embryos because almost embryonic cells are in interphase; while the basic cytogenetic method can only detect at metaphase.[17-19] The limitation of the number of the coloured fluorochromes in the visible spectrum decreases the advantage of FISH method in detecting preimplantation embryos because only a few chromosomes can be analysed at one time. However; the detection of chromosomes 21, 18, 13, X and Y are available in many centers now.

The reciprocal events at meiosis give rise to monosomies and trisomies which are found to be common in preimplantation embryos and all autosomal monosomies end up in spontaneous miscarriages prior to the clinical detection.[20] The incidence of aneuploidy is found to be rising in the advanced maternal age. Moreover; the poor quality embryos or developmentally arrested embryos give rise to the presence of chromosome abnormalities.[19]

The incidence of chromosomal abnormalities was found to be 46% by using FISH with two autosome probes,[17] while using multicolour FISH with five probes can give rise to the detection of incidence of chromosome abnormalities and mosaicism in abnormally developing embryos as high as 70%. Trisomy 1, which has never been reported in spontaneous miscarriages, stillbirths or livebirths; has also been reported in an 8-cell stage human embryo.[21] The patterns of chromosome detection in preimplantation embryos can be demonstrated as normal, abnormal (non-mosaic), mosaic and chaotic (uncontrolled division and genetic misunderstanding) which may be the results of mosaic and chaotic presence.[22]

e.) The Incidence of Aneuploidy in Human gamates

The Incidence of aneuploidy in Oocytes

The incidence of aneuploidy in human oocytes is of 13.2%; which is a double greater than that of the hyperhaploidy due to the similar appearance of the actual hypohaploidy and artefactal chromosome loss. Its incidence is much more obvious than that detected in sperm.[23,24]

The Incidence of Aneuploidy in Sperms

The cross-species fertilisation of golden hamster oocytes with human was a first cytogenetic method to study of aneuploidy in human sperm. It was also called human-hamster fusion technique;[25] and give rise to a detection of aneuploidy rate of 1.4%,[23] which is about 1/10 of that in oocytes obtaining from the different conditions of gametogenesis or poor preparation methods. Chromosomes 1, 9, 16, 21 and sex chromosomes trend to have a high incidence of nondisjunction by using this technique. However; its disadvantages are labour-intensive, well-trained need, and the poor preparation quality which is resulted from the resistance to chromosome banding and the difficulty in specific chromosomes.

FISH offers a better method for human sperm studying;[26] but one-colour FISH limits the differentiation between disomy and diploidy. Moreover; it can differentiate the sex chromosome between meiosis I and meiosis II nondisjunction errors, besides those between disomy and diploidy.[27] The incidence of sex chromosome disomy is greater than those of disomy 16 and disomy 18, with the proportion of 0.18%: 0.13%: 0.08%; while the incidence of aneuploidy in human sperm is about 2% by using FISH and human-hamster method.[9]

THE GENESIS OF HUMAN ANEUPLOIDY

The origins of chromosome abnormalities can appear at any stages of gametogenesis, fertilisation and embryogenesis.[19] The gametogenesis mistake usually happens during meiosis in the oogenesis or spermiogenesis. The fertilisation error is always resulted from polyspermic fertilisation which give rise to triploidy and the presence of their haploid chromosome sets, with the incidence of 1% of in vivo

conceptions. Nearly 100% of triploidy cases end up in spontaneous abortion and the rest of the fertilisation errors are monosomy X.[19]

Chromosomal mosaicism results from post-zygotic meiotic errors during embryogenesis with the incidence of 30% in normally fertilised and normally developing, clevage-stage embryos.[22] Most mosaic embryos arise from a normal diploidy during chromosome segregation or duplication of early cleavage mitotic division; and then lead to chromo somally abnormal cell line. A large number of abnormal cells in the trophectoderm and inner cell mass give rise to the poor prognosis.The genesis of restricted placental mosaicism can be described by the presence of the abnormal cells in the trophectoderm; and can be detected by chorionic villous sampling for prenatal diagnosis. Chaotic is the name of the embryo which posses a large abnormal chromosome component; and is does not implant.[22] A study of preimplantation embryos has used the spare embryos from therapeutic IVF; therefore the abnormality detection may be secondary from the patients, whom always had recurrent IVF failure or very early miscarriage.

The cytogenetic polymorphism techniques; such as satellites on the acrocentric chromosomes, restriction fragment length polymorphism studies and highly polymorphic microsatellite markers[9] have been used to detected parental origin of aneuploidy. The most common cause of autosomal trisomies [2, 4, 7, 10, 13-16, 21-22] and the 47, XXY and 47, XXX conditions is maternal nondisjunction[28] where the extra chromosomes (88%) are obtained from the mothers; while the 47, XYY condition is from the fathers.

The mechanism of chromosome nondisjunction are moderately variant;[29,30] such as the chance of paternal nondisjunction varies among the different trisomies. For example ; 80% of monosomy X , 50% of 47, XXY condition, 10-15% of other trisomies , and 0% of trisomy 16 come from paternal nondisjunction. DNA markers are very helpful to detect the parental origin of trisomy during meiotic or mitotic stage of the extrachromosomal origin. The assessment of centromeric or pericentromeric polymorphisms leads to differentiate between meiosis I and meiosis II errors; while the assessment of noncentromeric loci leads to differentiate between meiosis II and mitotic errors.[29] The main causes of trisomy are maternal meiosis I and mitotic errors; while those of chromosome 18 are predominantly the meiosis II errors which are double of the meiosis I errors; and those of chromosome 16 (the most common human trisomy) are meiosis I nondisjunction.

THE POSSIBLE PRIMARY CAUSES OF ANEUPLOIDY

a.) Effect of Maternal Age

Penrose[31] reported the association between the high incidence of Down's syndrome and the advanced maternal age, prior to the understanding of the chromosome defects in Down's syndrome. Trisomy 16 is exclusively associated with the marternal age, while other trisomies are relevant to other aspects which can be demonstrated by the linear pattern and exponential pattern of the association between age and the incidence of trisomy 16 and the other chromosomes respectively.[28] The maternal age effect can be demonstrated to limit to meiosis I error in sex chromosome trisomy.[32] whereas it effects both meiosis I and II in trisomies 21[33] and 18.[34]

1. Production-Line Hypothesis

Production-line hypothesis is the most plausible hypothesis to describe the maternal age effect. It explains that the increased nondisjunction is related to the decreased chiasmata frequency in older mouse oocytes which in turn leading to the increased univalent formation in the older.[35] The chiasmata formation is demonstrated to occur during prenatal period in female. However; a difference is noted in the fetal ovary that the oocytes experiencing meiosis first will ovulate first (several years later), while those experiencing meiosis last (with fewer chiasmata) will ovulate last (some decades later), and trend to have

nondisjunction.[36-39] The association between chiasma frequency, univalent formation and aneuploidy are still not demonstratable.[40]

2. Limited Pool Hypothesis

The limit pool hypothesis defines that maternal age effect is associated with oocytic depletion (without maternal choronological age) because older woman who has a decreasing number of anthral stage follicles per cycle usually has post-mature oocytes which is more likely to have nondisjunction.[9] The increased levels of aneuploidy in unilateral ovulectomised mice[41] and Turner syndrome mosaicism[42] supported this hypothesis.

3. Local Factors Hypothesis

Many studies were performed to hypotheses that proper meiosis decreases with maternal age which involves the hormonal alteration,cause of reduce bivalent separation, the age-related decreasing in spindle-forming ability[43] and age-related prolonged meiotic cell cycle length.[44] The correlation between low intracellular pH, spindle-forming ability and aneuploidy in aging oocytes has been identified to confirm the local factors hypothesis, which described that the maternal age effect is the cause of the comprised microcirculation surrounding growing follicles leads to hypoxic conditions (low oxygen, high carbondioxide and lower pH) to the oocytes.[45]

4. Relaxed Selection Hypothesis

There is a report that the aging uterus reduced ability to avoid trisomic conceptuses cause.[46] However; it is a false hypothesis due to the confirmed studies that both paternal and mitotic- origined trisomies do not demonstrate a maternal age effect, and in oocytes and preimplantation embryos presents the higher aneuploidy rate with advanced maternal age.[9]

5. Howley's Hypothesis

The two different models were present to demonstrate the age-related mechanism of nondisjunction for different chromosomes by Howley.[47]

5.1. Howley's first Hyporhesis

The first model demonstrated the similarity between maternal meiosis I nondisjunction of human chromosome 21 and the nod DTW mutation in Drosophila based on the study of Sherman.[33] The segregation deterioration of both chiasmate and achiasmate bivalents in nod DTW leads to the failure to stabilise the chromosomes ability to support contact among themselves and with the meiotic spindle. Therefore, the postulation is that the capability to form spindle decreases with maternal age; and a chiasmate and distal chiasmate bivalents are more likely to be nondisjunction due to suboptimal function of spindle fiber.

5.2. Hawley's second Hypothesis

The second model of Hawley et al., to demonstrate the age-related increase of X chromosome nondisjunction was introduced by the basic study meiosis I nondisjunction and its relationship with recombination of the human X chromosome.[32] The hypothesis is that transposon-induced breaks, not the effect of chiasmata, and the transposon-mediated events lead to some of the meiotic exchanges demonstrated in X chromosomes, trend to occur frequently with the longer meiotic prophase. The arrest of human oocytes occur at prophase of meiosis I, start from their entering meiosis during prenatal period until ovulation. Therefore, the prolonged staying in the prophase of the later ovulated oocytes trend to have nondisjunction.

6. Delayed Fertilisation

German[48] reported that delayed fertilisation because of the decreasing coitus frequency of ageing women was a cause of nondisjunction but later reported data rejected this hypothesis.[10]

b.) Effect of Paternal Age

Among the obvious data supported the maternal age effect on aneuploidy, general epidemio-

logical and molecular studies have been proceeded to obtain the importance of paternal effect; although the answer is unsatisfied.

1. Epidemiological Studies

Many epidemiological studies supported that there was no paternal age effect for Down's syndrome;[30,49,50] while some studies confirmed the presence of paternal age effect.[51,52] No definite summary has been obtained. However; the 47, XYY condition has some association with a little paternal age effect.

2. Molecular Studies

The study of the association between paternal age and paternal origin trisomies can obtained by DNA polymorphism. Many controversial reports were found; such as a little increasing in paternal age in meiosis I paternal origin trisomies,[53] a definitely increasing in paternal age in paternal origin XXY trisomies and the absence of paternal age effect in the paternal origin 47, XXY and 47, XXX conditions.[32] Therefore, the definite conclusion can not be obtained from those studying.

3. Sperm Studies

The comparison between the nondisjunction rate in the sperms of the older men with those of the younger has been studied to obtain the paternal age effect. The human-hamster fusion method is the early cytogenetic sperm study which provided very few aneuploidy metaphase with unsatisfactory result; while the mesoderm FISH-sperm assay provides more satisfactory result. The incidence of disomy for the sex chromosome increases in ageing men, but not for chromosome 18.[54] The sex chromosome trisomy progendy of a 50 years old man are double geater than those of a 20 years old woman.[54] No demonstration of the paternal age effect in trisomy 18; therefore the conclusion can not be obtained. There is also a report that a post-zygotic mitotic nondisjunction errors give rise to all paternal origin trisomy 18.[34]

c.) Aberrant Genetic Recombination

The correlation between meiotic recombination errors and nondisjunction in female Drosophila and yeast were obtained by the presence of DNA polymorphism method. There are reports that homologous chromosomes with meiosis I nondisjunction do not have chiasmata in paternal origin XXY trisomies;[55] and a general reduction was detected in recombination in trisomy 21.[56] A lot of recent studies demonstrate that chiasmate bivalents lead to nondisjunction; hence, a reduced deviation levels of recombination cause nondisjunction in trisomies of chromosome 21, 16 and X. However; the recombination in the terminal portion of the chromosome is obviously increased, those in nondisjunction bivalents is also reduced from a study in trisomy 21 livebirths.[33] This supports the Hawley's first hypothesis that nondisjunction usually causes from the achiasmate and distal chiasmate bivalents, particularly in aging mothers; greater than those with bichiasmata and proximal chiasmata.[28] The recombination of maternal origin XXY and XXX conditions are reported to reduced;[32] while those of around the centromere are increased. Due to no recombination of the centromere, this hypothesis is unacceptable. Howley[47] suggested their second hypothesis that the mature chiasmata does not give rise to these recombination. There is a study supported that in trisomy16 spontaneous miscarriage, the recombination in nondisjunction bivalents is decreased, which is dense around pericentromic area.[57]

d.) Environmental Factors

Many environmental factors; such as iridiation, oral contraceptives, spermicides, fertility drugs, smoking and alcohol have been studied to obtain the directly association between these factors and the incidence of aneuploidy; however; no study supports these association because the limitation in epidemiological study design.[9] The meiotic products and nondisjunction gametes have been studies by the useful technique of FISH-sperm assay.[58] The nondisjunction rates increase in the men who smoke

heavily and/or received chemotherapy.[58]

e.) Genetic Factors

There is no evidence supported the association between the incidence of aneuploidy and the intrinsic factors; such as consanguineous mating, rare alpha-1-antitripsin haplotypes, thyroid antibodies and chromosome polymorphisms. The important technique to study the genetic factors effect on nondisjunction is the FISH-sperm assay.[9]

1. The Correlation with Centromere Size

Many studies are arised to obtain the effect of the variation in chromosome structures on the nondisjunction rate of the same chromosome. Abruzzo,et al[59] made a hypothesis that the size of the (-satellite; which is a functional part of the centromere associates with a chromosome segregation by using centromere to be an observation marker. They postulated that the smaller centromeres may be rarely to segregate a chromosome. The Y chromosome was selected to study due to its smallest (-sattelite array where there were two different array size group in individual men and its characterised sequence-specific haplotypes. Moreover; the differentiation of meiosis I from meiosis II errors in this chromosome can be detected by FISH method. The first result presented no such effect in the sperm from the 14 men. The second result presented the slightly higher nondisjunction rate in men whom were 40 years old or lesser with the larger centromeres, which was opposite to their hypothesis. They finally summarised that the centromere haplotype (not its size) affects the nondisjunction rate. The study on chromosome variation, its effect on the nondisjunction rate and the investigation for the genetic components correlated with this matter can be continued based on the FISH method.

2. Subfertile Males

Males with oligo-astheno-teratozoospermia trend to have a high nondisjunction rate by FISH-sperm method investigation; with the disomy rates ten times greater than those in normal males.[60] The knowledge about aneuploidy can be obtained by the understanding the mechanism of this phenomenon.

f.) Sex Ratios in Trisomy

The proportion of male to female at birth and in trisomy 21 are 1.06:1 and 1.2:1 respectively. However; the females have more livebirths than male in trisomy 18.[61] A meiosis errors in the testis may give rise to the excess males in Down's syndrome with the ratio of 3.5:1 because this was detected in paternal origin trisomy 21.[53] The recent study in disomy 21 sperm also identified the excess of Y-bearing sperm. No sex ratio difference was demonstrated on the disomy 18 investigation. In trisomy 18, there was a marked excess of females cases which is probably resulted from the impossibility of male conceptuses, particularly all paternal origin trisomy 18 are derived from post-zygotic miotic errors.[9]

Conclusion

The most likely primary cause of human aneuploidy and some opinion for the understanding of aneuploidy have been discussed. The incidence and the genesis of aneuploidy can lead to the finding of the primary cause. Some serious sequalaes relevant to aneuploidy are mental retardation and multiple organs malformations. Many advance techniques including molecular cytogenetic and reproductive biology are very helpful to identify the cause. All chromosomes should be studied to explain how certain chromosome characterises shows marked difference. Although, many update techniques are very helpful to identify the cause of human aneuploidy, the natural ovulated oocytes should be determined to carry on the study in order to receive the real datas. The FISH-sperm assay is also important to study the intrinsic and extrinsic factors related to aneuploidy; however, a plenty of limitations have been defined such as a few number of oocytes received, the superovulation effected from drugs and hormones and underlying condition of infertile women.

The cause of aneuploidy is nondisjunction in

meiosis I in most chromosomes, except trisomy 18 which occurs during meiosis II. Moreover, maternal nondisjunction cause the main of autosomal trisomies (88%), while paternal and maternal errors give rise equally to the 47, XXY condition, and paternal meiosis cause 80% of monosomy X. The influence of maternal age is also mentioned in many theories. The possible primary cause of maternal age related aneuploidy are supported by precoccious separation theory of the centromere, production-line hypothesis, limited pool theory, Howley's first and second theories, local factors hypotheses of the age-related hormonal changes, reduced spindle forming ability, prolonged cell cycle length and compromised microcirculation. The paternal age effects in sex chromosomes, except chromosome 18. The reduction combination is also the essential cause of aneuploidy and needed more studies to confirm the conclusion of every chromosome. Chemotherapy and heavily smoking are also confirmed to be the primary causes of aneuploidy while other intrinsic and extrinsic causes are still controversy. Many studies are needed to describe the effect of chromosome structures on the genesis of aneuploidy that why different chromosomes give rise to particular features.

Finally, the understanding of all primary causes of human aneuploidy will be obtained soon by the combination of excellent researches and update molecular technology and will get more advantages in the detection, prevention and management for the aneuploidy in the near future.

References

1. Hassold TJ, Jacobs PA. Trisomy in man. Ann Rev Genet 1984; 18: 69-97.
2. Tackholm G. 1992. Zytologische Studien uber die Gattung Rosa. acta hort. Berg 7, 97-381. Cited in Bond DJ, Chandley AC. Aneuploidy. In: Fraser Roberts JA, Carter CO, Motulsky AG, eds. Oxford monographs on medical genetics. No. 11 Oxford: Oxford University Press. 1983:1-198.
3. McConkey EH. Human genetics: the molecular revolution. Boston: Jones and Bartlett Publishers. 1993: 152-5.
4. Lejeune J, Gautier M, turpin R. 1959. Etude de chromosomes somatiques de neuf enfants mongoliens. C. R. hebd. Seanc Acad Sci., Paris 248: 1721-1722. Cited in abruzzo MA, Hassold TJ. Etiology of nondisjunction in humans. Environ Mol Mutagen 1995; 25 (Suppl. 26): 38-47.
5. Ford CE, jones KW, Polani PE, de Almeida JC, Briggs JH. A sex chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). Lancet 1959; 1: 771-3.
6. Jacobs PA, strong JA. A case of human intersexuality having a possible XXY sex-determining mechanism. Nature 1959; 183: 302-3.
7. Edwards JH, Harnden DG, Cameron AH, Crosse VM, Wolf OH. A new trisomic syndrome. Lancet 1960; 1: 787-9.
8. Patau KA, Smith DW, Therman EM, Inhorn SL, Wagner HP. Multiple congenital anomaly caused by an extra autosome. Lancet 1960; 1: 790-3.
9. Griffin DK. The incidence, origin and etiology of aneuploidy. In: Jeon KW, ed. Internal review of cytology. San Diego: Academic Press, 1996; 167: 263-6.
10. Bond DJ, Chandley AC. Aneuploidy. In: Fraser Roberts JA, Carter CO, Motulsky AG, eds. Oxford monographs on medical genetics. No. 11. Oxford: Oxford University Press. 1983: 1-198.
11. Turner HH. A syndrome of infantilism, congenital webb neck and cubitus valgus. Endocrinol 1938; 23: 566-74.
12. Klinefelter HF Jr, Reifenstein EC Jr, albright F. Syndrome characterized by gynaecomastia aspermatogenesis with a-Leydignism, and increased excretion of follicle stimulating hormone. J Clin Endocr 1942; 2: 615-27.
13. Creasy MR, Crolla JA, Alberman ED. A cytogenetic study of human spontaneous abortions using banding techniques. Hum Genet 1976; 31: 177-96.
14. Handyside AH, Pattinson JK, Penketh RJA, Delhanty JDA, Winston RML, Tuddenham EGD. Biopsy of human preimplantation embryos and sexing by DNA amplification. Lancet 1989; 1: 347-9.
15. Jamieson ME, Coutts JRT, Connor JM. The chromosome constitution of human preimplantation embryos fertilized in-vitro. Hum Repro 1994; 9: 709-15.
16. Angell RR, Templeton AA, Aitken RJ. Chromosome studies in human in-vitro fertilisation. Hum Genet 1986; 72: 333-9.
17. Harper JC, Coonen E, Handyside AH, winston RML, Hopman AHN, Delhanty JDA. Mosaicism of autosomes and sex chromosomes in morphologically normal, monospermic preimplantation human embryos. Prenat Diagn 1995a; 15: 41-79.
18. Harper JC, Dawson K, Delhanty JDA, Winston RML. The use of fluorescent in-situ hybridization (FISH) for the analysis of in-vitro fertilization embryos: a diagnostic tool for the infertile couple. Hum Reprod 1995b; 10: 3255-8.
19. Delhanty JDA, Harper JC, Ao A, Handyside AH, Winston RML. Multicolour FISH detects frequent chromosomal mosaicism and chaotic division in normal preimplantation embryos from fertile patients. Hum Genet 1997; 99: 755-60.
20. Munne S, Alikani M, Tomkin G, Grifo J, Cohen J. Embryo morphology, developmental rates and maternal age are correlated with chromosome abnormalities. Fertil Steril 1995; 64: 382-91.
21. Watt JL, Templeton AA, Messinis I, Bell L, Cunningham

P, Duncan RO. Trisomy 1 in an eight cell human pre-embryo. J Med Genet 1987; 24: 60-4.
22. Delhanty JDA, Harper JC, Ao A, Handyside AH, Winston RML. Multicolour FISH detects frequent chromosomal mosaicism and chaotic division in normal preimplantation embryos from fertile patients. Hum Genet 1997; 99: 755-60.
23. Jacobs PA. The chromosome complement of human gametes. Oxford Rev Reprod Biol 1992; 14: 48-72.
24. Zenzes MT, Casper RF. Cytogenetics of human oocytes, zygotes and embryos after in vitro fertilization. Hum Genet 1992; 88: 367-75.
25. Rudak E, Jacobs PA, Yanagimachi R. The chromosome constitution of human spermatozoa: a method of direct chromosome analysis. Nature 1978; 274: 911-3.
26. Wyrobek A, Alhborn T, Balhorn R, Stanker L, Pinkel D. Fluorescence in situ hybridization to Y chromosomes in decondensed human sperm nuclei. Mol Reprod Dev 1990; 27: 200-8.
27. William BJ, Balenger CA, Malter HE, Bishop F, Tucker M, Zwingman TA, Hassold TJ. Non-disjunction in human sperm: results of fluorescence in situ hybridization studies using two and three probes. Hum Mol Genet 1993; 2: 1929-36.
28. Hassold TJ, Sherman S. The origin of non-disjunction in humans. Chromosomes Today. 11: 313-22.
29. Abruzzo MA, Hassold TJ. Etiology of nondisjunction in humans. Enviro Mol Mutagen 1995; 25 (Suppl. 26): 38-47.
30. Chandley AC. On the paternal origin of de novo mutation in man. J Med Genet 1991; 28: 217-23.
31. Penrose LS. 1933. The relative effects of paternal and maternal age in mongolism. J Genet. 27: 219-224. Cited in Griffin DK. The incidence, origin and etiology of aneuploidy. In: Jeon KW, ed. Internal review of cytology. San Diego: Academic Press, Incidence. 1996; 167: 263-96.
32. MacDonald M, Hassold T, Harvey J, Wang LH, morton LH, morton NE, Jacobs PA. The origin of 47, XXY and 47, XXX aneuploidy: heterogenous mechanisms and of aberrant recombination. Hum Mol Genet 1994; 3: 1365-71.
33. Sherman SL, Petersen MB, Freeman SB, Hersey J, Pettay D, Taft L, Frantzen M, Mikkelsen M, Hassold TJ. Non-disjunction of chromosome 21 in maternal meiosis I: evidence for a maternal-age dependent mechanism involving reduced recombination. Hum Mol Genet 1994; 3: 1529-35.
34. Fisher JM, Harvey JF, Morton NE, Jacobs PA. Trisomy 18: studies of the parent and cell division of origin and the effect of aberrant recombination on nondisjunction. Am J Hum Genet 1995; 56: 669-75.
35. Henderson SA, Edwards RG. Chiasma frequency and maternal age in mammals. Nature 1968; 218: 22-8.
36. Polani PE, Jagiello GM. A test of the production line hypothesis of mammalian oogenesis. Hum Genet 1991; 88: 64-70.
37. Sugawara S, Mikamo K. Absence of correlation between univalent formation and meiotic nondisjunction in aged female Chinese hamsters. Cytogenet Cell Genet 1983; 35: 34-40.
38. Luthardt FW. Cytogenetic analysis of human aneuploidy. Am J Hum Genet 1977; 29: 71A.
39. Polani PE, Jagiello GM. Chiasma, meiotic univalents and age in relation to aneuploid imbalance in mice. Cytogenet Cell Genet 1976; 16: 505-29.
40. Speed PE, Chandley AC. Meiosis in the foetal mouse ovary. II. Oocyte development and age-related aneuploidy. Does a production line exists? Chromosoma 1983; 88: 184-9.
41. Brook JD, Gosden RG, Chandley AC. Maternal aging and aneuploidy embryos- evidence from the mouse that biological and not chronological age is the important influence. Hum Genet 1984; 66: 41-5. 28: 217-23.
42. King CR, Magenis E, Bennet S. Pregnancy and the Turner syndrome. Obstet Gynecol 1978; 52: 617-24.
43. Angell RR, Xian J, Keith J, Ledger W, Baird OT. First meiotic division abnormalities in human oocytes: mechanism of trisomy formation. Cytogenet Cell Genet 1994; 65: 194-202.
44. Eichenlaub-Ritter U, Chandley AC, Gosden RG. The CBA mouse as a model for age-related aneuploidy in man: studies of oocyte maturation spindle formation, and chromosome alignment during during meiosis. Chromosoma 1988; 96: 220-6.
45. Gaulden ME. Maternal age effect: the engima of Down syndrome and other trisomic conditions. Mutat Res 1992; 296: 69-88.
46. Ayme S, Lippman-Hand A. Maternal-age effect in aneuploidy: Does altered embryonic selection play a role? Am J Hum Genet 1982; 34: 558-65.
47. Hawley RS, Frazier JA, Rosooly R. Separation anxiety: the etiology of nondisjunction in flies and people. Hum Mol Genet 1994; 3: 1521-8.
48. German J. Mongolism, delayed fertilization and human sexual behavior. Nature 1968; 217: 516-8.
49. Cross PK, Hook EB. An analysis of paternal age and 47, +21 in 35000 new prenatal cytogenetic diagnosis data from the New York State Chromosome Registry: no significant effect. Hum Genet 1987; 77: 307-13.
50. Erickson JD. Down syndrome, paternal age, maternal age and birth order. Ann Hum Genet 1978; 41: 289-98.
51. Steve J, Fischer G, Stene E, Mikkelsen M, Petersen E. Paternal age effect in Down's syndrome. Am J Hum Genet 1977; 40: 299-306.
52. Steve J, Stene E. Paternal age and Down's syndrome. Hum Genet1981; 59: 119-24.
53. Petersen MB, Antonarakis SE, Hassold TJ, Freeman SB, Sherman SL, Avramopoulos D, Mikkelsen M. Paternal nondisjunction in trisomy 21: excess of male patients. Hum Mol Genet 1993; 10: 1691-5.
54. Griffin DK, Abruzzo MA, Millie EA, Sheean LA, Feingold E, Sherman SL, Hassold TJ. Non-disjunction in human sperm: evidence for an effect of increasing age. Hum Mol Genet 1995; 4: 2227-32.
55. Hassold TJ, Sherman SL, Pettay D, Page DC, Jacobs PA. X-Y chromosome nondisjunction in man is associated with diminished recombination in the pseudoautosomal region. Am J Hum Genet 1991; 49: 253-60.

56. Warren AC, Chakravarti A, Wong C, Slaugenhaupt SA, Halloran SL, Watkins PC, Metaxotau C. Evidence for reduced recombination on the nondisjoined chromosomes 21 in down syndrome. Science 1987; 237: 652-4.
57. Hassold TJ, Abruzzo M, Adkins K, Griffin D, Merril M, Millie E, Saker D, Shen J, Zaragaza M. Human aneuploidy. Incidence, origin and etiology. Environ Mol Mutagen 1996; 28: 167-75.
58. Wyrobek AJ, Rubes J, Cassel M, Moore D, Perreaultes S, Slott U, Evenson D, Zudova Z, Borkovec L, Selevan S, Lowe X. Smokers produce more aneuploid sperm than non-smokers. Am J Hum Genet 1995; 57: ss737.
59. Abruzzo MA, Griffin DK, Millie EA, Sheean LA, Hassold TJ. The effect of Y-chromosome alpha-satellite array length on the rate of sex chromosome disomy in human sperm. Hum Genet 1996; 97: 819-23.
60. Pang MG, Zackowski JL, Hoegerman SF, Friedman E, Moon SY, Cutticia AJ, Acosta AA, Kearns WG. Detection by fluorescence in situ hybridisation of chromosome 4, 6, 7, 8, 9, 10, 11, 12, 13, 17, 18, 21, X and Y aneuploidy in sperm from oligo-asthenoterato-zoospermic patients of an in-vitro fertilization program. Am J Genet 1995; 57: A121.
61. Baty BJ, Blackburn BL, Carey JC. Natural history of trisomy 18 and trisomy 13: I. Growth, physical assessment, medical histories, survival and recurrence risk. Am J Med Genet. 49: 175-88.