

==== REVIEW ====

THE MOST COMMON HUMAN AUTOSOMAL TRISOMIES

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SUMMARY. Trisomy is a chromosomal abnormality, characterized by the appearance of an extra chromosome in the genetic material. Usually, human autosomal trisomies are not compatible with live birth, but there are some exceptions of live born trisomies. The most common live born trisomies are: Down syndrome, Edwards syndrome and Patau syndrome. All of these trisomies cause growth retardation, mental retardation and several congenital abnormalities. All of them show distinctive features. Autosomal trisomies are caused especially by chromosomal nondisjunction during meiosis. Advanced maternal age is considered to be a main reason for non-disjunction disorder, but understanding the mechanisms of this effect still remains unclear. Influence of paternal age on trisomies is controversial, but it was demonstrated that advanced paternal age together with maternal age has a significant role in occurrence of Down syndrome.

Keywords: Down syndrome, Edwards syndrome, maternal age, Patau syndrome, trisomy.

Introduction

Trisomy is a form of aneuploidy, which means that a karyotype shows the occurrence of one or more extra or missing chromosomes. This abnormality leads to genetic disorders with different effects on embryos and live birth persons. Trisomy, a numerical chromosomal aberration, means that there is one extra chromosome in the affected karyotype instead of normal two.

The most common human autosomal trisomies are those which affect the numerical alterations of chromosomes 21, 18 and 13. Among these, the chromosome trisomy 21, known as Down syndrome (DS) named for John Langdon Down, the physician who first described the condition in 1866, is the most frequent chromosome

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aberration leading to mental retardation. 3-5% of mentally retarded people have DS. Nowadays the birth prevalence is 1/900 for DS. At the time of conception, the zygote frequency with chromosome 21 trisomy is high, but 85% of these abnormal embryos die in uterus leading to spontaneous abortion or late fetal loss (Papp, 1995). But, lately there are real possibilities to decrease the frequency of trisomy born infants by prenatal screening.

The connection between maternal age and human trisomies

During the last few decades different approaches have been used to investigate oocyte chromosomes and to recognize the presence of chromosomal aberrations in human female gametes, which include cytogenetic and different staining methods. The results of these screening methods indicated distinct variability in the occurrence of chromosomal aberrations, which reflect the difficulties of this kind of studies. However, the only unambiguous factor associated with human chromosome numerical variations is the maternal age (Pellestor *et al.*, 2005). At the 16-th week of pregnancy, which is the optimal time for amniocentesis, the frequency of chromosome 21 trisomy at 36 years old women is 1/200, at 39 age is 1/100 and at 42 age is 1/50. These data significantly change according to father's age (Table 1).

Table 1.

Chromosomal non-disjunction trisomy 21 and other chromosome aberrations depending on maternal and paternal age (Papp, 1995)

Paternal age	Maternal age			
	35 – 40		41 - 46	
	trisomy 21	total chromosome aberrations	trisomy 21	total chromosome aberrations
≤ 34	0.4	1.3	1.0	1.7
35 - 40	0.6	1.6	1.2	2.8
41 - 46	1.3	2.1	2.8	5.6
≥ 47	2.0	2.3	4.1	6.5

It has long been known that trisomies appear more frequent with increasing maternal age, but it depends not only of mother, but the father's age also (Table 1). As shown in table 1, at maternal age above 40, the cytogenetic risk is double compared with maternal age under 40, but there are the same data if father's age is above 40 (Papp, 1995; Fisch *et al.*, 2003).

Define reasons of Down syndrome formation

All people with DS have an extra chromosome 21 material. An extra whole chromosome 21 in all cells of an individual with DS is found in 92% of cases.

Beside advanced maternal age (Hassold and Chiu, 1985), altered chromosome recombination (Warren *et al.*, 1987; Sherman *et al.*, 1991) constitutes the major risk to evolve DS when the appearance of an extra chromosome 21 in the oocytes during meiosis is responsible for this genetic condition (Sherman *et al.*, 2007). Studying a population from eastern part of India, Ghosh *et al.* (2009) reported a correlation between meiosis I nondisjunction and recombination in the telomeric 5.1 Mb of chromosome 21. Otherwise, in meiosis II the same authors observed preferential pericentromeric exchanges covering the proximal 5.7 Mb region, with interaction between maternal age and the location of the crossover. Generally, defective recombination independent of maternal age is also obvious in meiosis I cases (Ghosh *et al.*, 2009).

In 3-4% of DS individuals, a Robertsonian translocation happens. It is formed when one chromosome 21 (long arm) attaches to another chromosome, which is usually chromosome 14 (long arm) and forms a new chromosome (Benke *et al.*, 1995). If we analyze the DS carrying children of young mothers, we will find that in some occurrences the cause of appearance of syndrome is not simply the trisomy 21, but other numerical chromosome aberration: number of G group chromosomes (includes chromosomes 21 and 22) are normal four, number of D group chromosomes (includes chromosomes 13, 14 and 15) are only five (one chromosome is missing), and there is one extra C group chromosome (includes chromosomes 6 – 12). It is possible only if the extra chromosome 21 has translocated to D group chromosomes. In such cases one of the parents carries a translocation, but apparently one chromosome 21 is missing, meaning that this parent has only 45 chromosomes without any kind of affection (Szemere, 2001). Another kind of translocation happens within the G group chromosomes. In such cases there are only three G chromosomes, but there are five F group chromosomes (includes chromosomes 19 and 20), so the total number of chromosomes are 46, nevertheless the child has DS. The former translocation is called D/G, the latter is called G/C translocation (Szemere, 2001). Translocations involving chromosome 22 have a lower risk because trisomy 22 has very limited potential to be viable (Scriven *et al.*, 2001).

20% of the children from translocation carrier mother and 5-10% from translocation carrier father have the risk to evolve DS (Szemere, 2001).

Mosaic trisomy 21 is a form of DS when the individual has two populations of cells, the cells with trisomy 21, and a set of normal cell line. This form constitutes 2-4% of the persons with DS (Benke *et al.*, 1995).

Genes involved in Down syndrome development

There are several theories about which genes are required in DS development. One accepted theory affirms that only a small portion of chromosome 21, called DS Critical Region, is needed to be triplicated to get the effect of DS. The 21-st chromosome is the smallest chromosome in the human karyotype (together with chromosome 22) and contains only 200 -250 genes, but only a few of them are involved in producing the phenotype of DS. It is not clearly yet exactly which genes do

what to produce the syndrome (Leshin, 1997). It has been reported (Wiseman *et al.*, 2009) that *DYRK1A* (tyrosine-(Y)-phosphorylation-regulated kinase 1A) and *RCAN1* (regulator of calcineurin 1) genes may have a role on multiple tissues development. Overexpression of *DYRK1A* together with *SIM2* (synaptojanin 1 and single-minded homologue 2) genes and trisomy of neuronal channel proteins, (*GIRK2*), may contribute to learning difficulties in individuals with DS. Trisomy of *APP* (amyloid precursor protein) genes has a great contribution to the high frequency of dementia in persons with DS (Granholm *et al.*, 2000; Seo and Isacson, 2005; Salehi *et al.*, 2006). Trisomy of Hsa21 micro-RNA has-miR-155 may have a role in reduced incidence of hypertension in individuals with DS (Sethupathy *et al.*, 2007). Hsa-miR-155 is supposed to specifically target one allele of type-1 *AGTR1* (angiotensin II receptor) gene, downregulate the expression of gene, which may result in reduced risk of hypertension (Wiseman *et al.*, 2009). Leshin (1997) reported that *SOD1* (superoxide dismutase) gene may cause premature aging and decreased function of the immune system, *COL6A1* (collagen type VI) gene cause heart defects, *ETS2* causes skeletal abnormalities, *CBS* (cystathione beta synthase) disrupt metabolism and DNA repair process, *CRYA* may cause cataract, *IFNAR* affects normal function of the immune system.

Common symptoms of Down syndrome

People with DS show a wide range of symptoms, not everyone with the same symptoms, and they may have encounter different problems at different period of their life cycle.

Physical features of DS comprise: muscular hypotonia, short neck with loose skin on nape of neck, flat nasal bridge and facial profile, small head, ears and mouth, protruding tongue, upward slanting eyes, ring of iris speckles - Brushfield's spots, short broad hands, short little finger, single, deep crease across the palm, a deep groove between the first and second toes (Hassold *et al.*, 1996; O'Nuallain *et al.*, 2007). Beside these physical characteristics, the corporal development of children with DS can take longer compared to children without DS. Because of hypotonia, a child with DS may learn slower to turn over, sit, stand and walk, but these children are able to learn to participate in different physical exercise activities (Carothers *et al.*, 1999).

Intellectual development and learning capacities: frequent cognitive and behavioral problems of people with DS are poor judgment, impulsive behavior and slow learning capacity (Bull *et al.*, 2011; Ulrich *et al.*, 2011). Most of the affected children are able to develop communication skills they need, but usually it takes longer compared with other children (Martin *et al.*, 2009). Määttä *et al.* (2006) described that in a population of 129 persons with DS from Finland, females showed milder forms of intellectual disability, better cognitive abilities and more developed speech compared with males. Attention deficit was observed at children with DS. Young adults showed often depression (Määttä *et al.*, 2006). Depression and Alzheimer disease are common in people with DS (Burt *et al.*, 1992; Määttä *et al.*, 2006).

People with DS has increased risk to develop different affections, including autism, hormones and gland problems, poor immune function (Hummer, 2010), congenital heart defects, hearing and vision difficulties (Baekgaard Laursen *et al.*, 1976; Bull *et al.*, 2011; Sumar, 2011).

Fertility: males with DS usually are sterile; women with DS have lower rates of fertility compared to unaffected women (Pradhan *et al.*, 2006).

Individuals with DS can reach adulthood and even old age regularly and are commonly living till 50-60 or 70 years.

Edwards syndrome

Edwards syndrome (ES) is a chromosome disorder caused by the presence of an extra full, mosaic, or partial chromosome 18 (Goldstein *et al.*, 1988; Embleton *et al.*, 1996; Carey *et al.*, 2010). Full copy of trisomy 18 is the most common. In 95% of cases, Edwards syndrome is represented by trisomy; mosaicism and translocations are very rare. ES is named after John Hilton Edwards, being the first who described the syndrome in 1960 (Edwards *et al.*, 1960). This is the second most common autosomal trisomy after DS, the affected babies usually die in the first half year of life. ES prevalence is around 1/6000 live births, and 80% of affected individuals are female. Many of affected fetuses die before birth (Won *et al.*, 2005; Morris *et al.*, 2008). The occurrence of trisomy 18 increases with advanced maternal age. After a comprehensive study, Savva *et al.*, (2010) suggested that the frequency is constant until age 30, after this age increases exponentially, and becomes constant at age 45.

Symptoms of trisomy 18: prenatal growth retardation is one of the most common sign in trisomy 18 (Yamanaka *et al.*, 2006; Cho *et al.*, 2009; Sepulveda *et al.*, 2010). The low weight and height continues in postnatal period also, and most of the newborn babies have feeding difficulties and may need tube feeding (Cereda and Carey, 2012). Other major physical abnormalities are: clenched hand and overlapping fingers. Gastrointestinal malformations are frequent in patients with Edwards syndrome (Rosa *et al.*, 2013). Congenital structural heart defects are found on a large scale (Carey, 2010), but it is controversial if heart defects affects survey of the patients. Conversely, respiratory problems are one of the most frequent causes of death (Baty *et al.*, 1994; Embleton *et al.*, 1996; Kosho *et al.*, 2006; Carey, 2010). The ears are small with small lobules, the helix is unfolded, simple and sometimes attached to the scalp; intra-abdominal tumors (Wilms tumor) are frequent (Carey, 2010). Beside mentioned physical malformation, individuals with trisomy 18 also suffer from severe mental retardation (Giaccardi *et al.*, 1991; Matthews, 1999).

Reaching adulthood with trisomy 18 is very rare. A few individuals reached their young ages, but they were not able to live independently and needed constant care (Ricki, 2013).

Genes involved in Edwards syndrome development

Several markers are used to detect Edwards syndrome from maternal serum: AFP (alpha-fetoprotein) and hCG (human chorionic gonadotrophin) (Ilnicka *et al.*, 1996; Barkai *et al.*, 1993), PAPP (pregnancy associated plasma protein-A) (de Graaf *et al.*, 1999; Shiefa *et al.*, 2013), APCDD1 (adenomatosis polyposis coli down-regulated 1) and VAPA (vesicle-associated membrane protein) (Tsui *et al.*, 2010). Gene dose effect of *CNDP2* (CNDP dipeptidase 2 metallopeptidase M20 family) gene was demonstrated in a patient with trisomy 18 (Spano *et al.*, 1990). The detection of the presence of unmethylated (U-maspin) and methylated (M-maspin) formes of *MASPIN* (Serpine peptidase inhibitor, clade B (ovalbumin), member 5; SERPINB5) gene may be useful as potential biomarkers for non-invasive detection of fetal trisomy 18 (Lee *et al.*, 2013). Edwards syndrome is also associated with *BCL10* (B-cell CLL/lymphoma 10), *MALT1* (mucosa associated lymphoid tissue lymphoma translocation gene 1) and *XDH* (xanthine dehydrogenase) genes (Nakamura *et al.*, 2007; Go *et al.*, 2011).

Patau syndrome

Patau syndrome (PS), caused by trisomy of chromosome 13, is the third most common autosomal trisomy in newborns (Rasmussen *et al.*, 2003; Duarte *et al.*, 2004) after DS and ES, and has the greatest negative impact on survival of embryos. Rarely, the extra genetic material is attached to another chromosome (Robertsonian translocation), and there can be mosaic variations also. Trisomy 13 was first identified in 1960 by Klaus Patau as a cytogenetic disorder. The risk of PS rises with increasing maternal age but not as strongly as in case of DS and ES (Parker *et al.*, 2003). Many fetuses never survive until term and are stillborn or spontaneously abort. PS frequency is around 1/20000 live births (Brewer *et al.*, 2002). Average time of survival is fewer than three days.

On fetuses who survive to gestation and born alive, many of clinical feature widely vary, but severe mental impairment is a constant feature in infants born with trisomy 13. PS syndrome is recognized at birth by the presence of structural birth deficiency and poor neurologic performance. Other characteristic features include: low birth weight, heart defects, polydactyly and overlapping of fingers over thumb, abnormal palm creases, facial clefting and abnormal genitalia (Plaiasu *et al.*, 2010; Tsukada *et al.*, 2012, Caba *et al.*, 2013; Polli *et al.*, 2014).

Genes involved in Patau syndrome development

Patau syndrome is associated with *AFP* (alpha-fetoprotein) gene (Chen, 2007; Demirhan *et al.*, 2011); *PAPP* (pregnancy associated plasma protein-A) (Bersinger *et al.*, 1994; Shiefa *et al.*, 2013) gene, *EIF2C2* (Protein argonaute-2) gene (Chen *et al.*,

2004), *ZIC2* (zic family member 2) gene (Lim *et al.*, 2008), *SIX3* (SIX homeobox 3) (Sergi *et al.*, 2012), *PTER* (phosphotriesterase related) gene (Tapper *et al.*, 2002) and *ASTML* (acetylserotonin O-methyltransferase-like) gene (Li *et al.*, 2012).

Among all trisomies, DS is the most common (1/900) viable autosomal trisomy in live born infants. Chromosome 21 is the shortest chromosome, and this trisomy is tolerated probably because the number of protein-coding sequences predicted for chromosome 21 is the smallest of any human autosomes. Hence, an extra copy of chromosome 21 would change the normal function of cells less than an extra copy of any other autosome (O'Connor, 2008).

Genome, transcriptome and proteome analysis of trisomies

Gene dosage studies revealed a set of 324 genes with considerable dosage effect from 45 different experiments related to DS. A high number of genes involved in neuro-development, synapsis and neuro-degeneration were identified (Vilardell *et al.*, 2011). Donnelly and Storchova described gene dosage compensation by altering the mRNA levels in aneuploidy cells. Gene dosage changes could be counteracted by up- or downregulation of gene transcription in aneuploids. Aneuploid cells dispose protein level changes, impaired protein folding and protein degradation. Pathways involved in protein degradation have a significant role in interceding the compensation of proteins from additional chromosomes and other key phenotypes of aneuploidy cells (Donnelly and Storchova, 2014).

In a transcriptome analysis study of trisomy 21 and trisomy 13, FitzPatrick suggest the function of a refined primary upregulation of genes on the trisomic chromosome, resulting in a secondary, generalized and more extreme transcriptional misregulation. The level of this misregulation defines the gravity of the phenotype in most aneuploidy (FitzPatrick *et al.*, 2002). Gene expression profiling of 317 differentially expressed genes in the brain of a mouse model for DS revealed that the overexpression of interferon receptor may lead to overstimulation of Jak-Stat signaling pathway which may contribute to the neuropathology DS brain (Ling *et al.*, 2014).

Recent studies demonstrated that aneuploidy inhibits cell proliferation, induces alterations in the transcriptome and proteome and perturbs cellular proteostasis. Aneuploidy impairs induction of the heat shock response, thus activity of the transcription factor heat shock factor 1 (HSF1) is compromised; HSF1 is a critical factor underlying the phenotypes linked to aneuploidy (Donnelly *et al.*, 2014).

Future research should explain the exact influence of aneuploidy on the activity of proteostasis network, and if impaired proteostasis is the basis of reduced cell proliferation and damaged metabolism.

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