Trisomy

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Introduction

Human trisomy is a leading cause of fetal wastage, perinatal and infant mortality, congenital malformation and mental retardation. This includes only the impact of trisomy where the individual’s constitutional karyotype is determined during fertilization or the first few cell divisions thereafter. If this restriction were to be relaxed, then a large proportion, if not the majority, of malignancies would also be included as well as an uncertain proportion of disorders associated with aging and/or autoimmune processes. In the material that follows, only human trisomy as a cause of constitutional genetic disease will be addressed.

Incidence

Trisomy is extremely common in humans. Among newborns, 0.3% of live births are trisomic with the most common anomalies being trisomy 21 and sex chromosome polysomies (47,XXX, 47,XYY and 47,XXY). The incidence increases to 4% among stillbirths, with the autosomal trisomies being similar to those observed among newborns. Among clinically recognized spontaneous abortions, 26.1% are trisomic, but unlike stillbirths or live births, different trisomies are found. The most common anomaly is trisomy 16, which constitutes about one-third of all trisomies identified in spontaneous abortions. Using these figures and assuming that 15% of clinically recognized pregnancies spontaneously abort whereas 1% are stillborn and the rest are liveborn, it has been estimated that at least 4.1% of all human conceptions are trisomic. Of course this figure underestimates the real incidence of trisomy in humans because it does not include conceptions that spontaneously abort during the first month of gestation (Hassold and Jacobs, 1984).

Origin

Over the past decade, DNA polymorphisms have been used to track down the parental and the meiotic/mitotic stage of origin of different trisomic conditions. The results from such studies have been reviewed by Hassold and Hunt (2001). They are summarized in Table 1. Although maternal meiosis I (MI) errors predominate, the parent and meiotic stage of origin of the additional chromosome do vary from one trisomic condition to another. For example, paternal errors account for 46% of the 47,XXY condition but only 8% of trisomy 21. They are rarely the cause of trisomy 16 or trisomy 18. Similarly, the importance of MI versus meiosis II (MII) errors varies among chromosomes. For example, among trisomies of maternal origin, all cases of trisomy 16 seem to be due to MI errors but for trisomy 18 about 60% of cases involve MII nondisjunction.

It is important to stress, however, that studies tracking DNA polymorphisms between parents and offspring is an indirect way of looking at meiotic processes. Investigations using fluorescence in situ hybridization (FISH) provide conflicting results regarding both stage and type of segregation errors (Mahmood et al., 2000). Therefore, it is fair to say that we are still ignorant about the mechanisms of origin of constitutional trisomies, comprising the most common type of genetic disease in humans.

Mechanisms

Recently, several studies comparing the frequency and distribution of meiotic exchanges in meioses
generating a trisomy with those observed in normal meioses have shown that a reduction in the number of chromosome exchanges is a feature of all trisomies derived from MI error. This includes trisomies 15, 16, 18, 21, sex chromosome polysomies derived from a maternal error and cases of trisomy 21 derived from a paternal error. The most pronounced reduction is observed in the XXY condition resulting from a paternal error. In this instance, the genetic map of the XY pseudoautosomal pairing region is decreased from 50 cM in normal meioses to 10 cM in meioses generating the polysomy. In some instances, an absence of exchange is responsible for this overall decrease in the map length. For example, about 40% of cases of trisomy 21 derived from a maternal MI error result from an achiasmate bivalent. Similar findings have been observed for trisomy 21 and the 47,XXY condition resulting from a paternal error, as well as trisomies 15, 18 and sex chromosome polysomies resulting from an MI maternal error. In addition, when a single exchange is observed in maternal MI-derived cases of trisomy 21, the exchange is displaced toward the telomere. In contrast, an increase in pericentromeric exchanges is observed in cases of trisomy 21 resulting from an MII maternal error. It has been suggested that these pericentromeric exchanges might produce chromosome entanglement. The subsequent segregation at MII would then result in a disomic gamete having identical centromeres. This would be scored as an MII nondisjunctional event. Although this might be the case for trisomy 21, more recent studies have shown that chromosome 18 and sex chromosomes behave differently (Hassold and Hunt, 2001).

**Etiology**

After many years of study, apart from maternal age no single parental factor, whether environmental or genetic in nature, has been consistently implicated as a determinant of human trisomy. The association between increasing maternal age and Down syndrome was recognized long before the syndrome was known to result from trisomy 21 (Penrose, 1933). A similar effect is also observed for other viable and nonviable trisomies. The rapid increase begins around 35 years of age. For example, among woman aged 20 years, 2% of all clinically recognized pregnancies are trisomic, but among women over 40 years this value approaches 35% (Hassold and Chiu, 1985). Also, studies of double and mosaic trisomies have shown that they are affected by increasing maternal age, the effect being more important in the case of double trisomies. In addition, the relationship is specific to the chromosome involved in the trisomy, that is, the maternal age effect is greatest for trisomies involving the smallest chromosome and absent for most larger chromosomes (Risch et al., 1986). Interestingly, trisomy 16 is a clear outlier in this relationship as its frequency increases linearly and not exponentially with maternal age. Nevertheless, much remains to be learned about the biological basis of the maternal age effect. One model has suggested that abnormal recombination and nondisjunction associated with maternal age are causally related (Lamb et al., 1996). Indeed, this model proposes that at least two hits are required for age-dependent trisomy. The first hit is age independent as it occurs in the fetal ovary and involves the establishment of bivalents liable to nondisjunction. The second hit is age dependent as it occurs at metaphase I in the adult ovary and involves an abnormal processing of these liable bivalents. The abnormal processing might result from a defect in oocyte maturation, a change in the hormonal milieu or a change in the level of proteins that influence proper chromosome segregation.

**Phenotypic Consequences**

From classical studies in plant genetics, it was known that trisomy produced easily recognizable phenotypes (Blakeslee, 1932). Similarly, the adverse effects of trisomy on the phenotype in humans are now well established. Among live births which represent the least affected of all trisomic conceptions, the presence of an additional autosome is often associated with a severe mental and physical handicap and early lethality (Table 2). In contrast, the gain of an additional sex chromosome is relatively well tolerated and is associated with much variation in phenotype (Table 3). In addition, mosaicism including a normal cell line is common and accounts for much variation between individual cases of autosomal trisomies as well as sex chromosome aneuploidy. How the inheritance of three ‘normal’ copies of a gene on the additional chromosome results in disruption of normal development remains unknown (Reeves et al., 2001). The developmental instability hypothesis suggests that the correct balance of gene expression in pathways regulating development is upset by the dosage imbalance of genes on the additional chromosome. This leads to an increased frequency and increased variability of phenoderviant characters among trisomic individuals when compared with euploid individuals. Another hypothesis holds that dosage imbalance of a specific gene or group of genes on the additional chromosome is responsible for specific individual traits. Although the first proposal has been considered as an untestable hypothesis, the second hypothesis has been rather difficult to demonstrate (Korenberg et al., 1994). Presumably, a comprehensive explanation for
the phenotypes observed in trisomic conditions should consider the consequences of trisomy on the embryo’s normal developmental pattern (i.e. its norm of reaction) rather than the direct consequences of the overexpression of the triplicated genes (Vekemans and Trasler, 1986).

See also

Down Syndrome
Karyotype Interpretation
Monosomies
Uniparental Disomy
XYY Syndrome

Table 2  Autosomal trisomy syndromes

| Syndrome   | Incidence | Phenotype                                                                 |
|------------|-----------|---------------------------------------------------------------------------|
| Trisomy 8  | 1:25,000, most often mosaicism | Most often early childhood lethality                                      |
| Trisomy 13 | 1:15,000, early childhood lethality | Mental retardation, forebrain defects                                   |
| Trisomy 18 | 1:8000, early childhood lethality | Mental retardation, hypertonia                                           |
| Trisomy 21 | 1:700     | Mental retardation, hypotonia                                             |

VSD: ventricular septal defect; ASD: atrial septal defect; PDA: patent ductus arteriosus; AV: atrioventricular.
Adapted from Nora JJ and Fraser FC (1994) Medical Genetics Principles and Practice, 4th edn. Philadelphia, PA: Lea & Febiger.

Table 3  Sex chromosome polysomy syndromes

| Syndrome   | Incidence | Phenotype |
|------------|-----------|-----------|
| 47,XXY     | 1:1000 males | Male usually with long arms and legs. Small genitalia. Educational problems frequent. Mostly infertile |
| 47,YYY     | 1:1000 males | Male with tall stature. Normal to reduced intelligence. Behavioral problems. Normal to reduced fertility |
| 47,XXX     | 1:1000 females | Female with tall stature. Educational problems frequent. Normal fertility |

Adapted from Thompson MW, McInnes RR and Willard HF (1991) Thompson and Thompson: Genetics in Medicine, 5th edn. Philadelphia, PA: WB Saunders.

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