

## Human Nondisjunction and Mouse Models in Down Syndrome

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Chromosomal aneuploidy is the leading cause of fetal death in our species. Around 50% of spontaneous abortions until 15 weeks of gestational age are chromosomally aneuploid, with trisomies accounting for 50% of the abnormal abortions. Most of our knowledge about chromosomal nondisjunction in man comes from studies in trisomy 21, the most frequent of the autosomal trisomies in liveborns. The condition is usually the result of malsegregation (nondisjunction) of chromosome 21 in meiosis in either oogenesis or spermatogenesis. The clinical entity, that we know as Down syndrome (DS) is caused by trisomy 21 and is the most common single cause of mental retardation.

With an incidence of 1-2:1,000 in human populations, DS is the most common single cause of mental retardation [1]. It is now known, that about 95% of individuals with DS have an extra chromosome 21 as a result of meiotic nondisjunction. About 4% of cases are due to Robertsonian translocations and 1% is due to mosaicism with a normal cell line. A recent large study in the US obtained an estimate of the birth prevalence of DS based on data obtained from 11 birth surveillance systems [2]. The birth prevalence was estimated to be 13.65 per 10,000 or 1/732. Some differences in maternal age adjusted prevalence rates among different ethnic groups were observed, and these were attributed to differences in technical issues, completeness of ascertainment, socioeconomic class, environmental exposures, and genetic risk factors [2,3]. Obviously, termination of pregnancy after prenatal diagnosis is a strong socio-cultural variable.

The alternative modes of cell division in mitosis and meiosis play different roles of particular interest in the life cycle of diploid organisms, such as animals and humans. While the chromosome number is kept strictly constant by mitosis in the diploid body cells, as well as in the mitotic germ line, it is reduced to half by meiosis in the generation of male or female haploid germ cells.

During mitosis, each chromosome consists of two sister chromatids, which stem from the preceding round of replication and are identical throughout their length. The regular segregation of chromosomes in mitosis, as well as bivalents in meiosis I, critically depends on their bipolar spindle attachment. If any chromosome should be connected to one pole only, cells have a limited capacity to rectify this potentially hazardous situation, as mediated by the spindle attachment checkpoint system. During meiosis, in particular, monopolar spindle attachment can accidentally arise from various causes.

In humans, the ovulation cycle is connected to a decline in functional oocytes, not only due to those being ovulated, but also by additional ones becoming atretic. As women age, the decline in the size of the total oocyte pool is accompanied by a decline in the number of antral follicles that mature during each menstrual cycle. Mechanisms related to nondisjunction could, in theory, operate at any time between the formation of the oocyte pool – when the woman herself is *in utero* and meiosis I begins – and the completion of meiosis I at ovulation [4]. There appears to be a link between the incidence of trisomy and the speed of oocyte depletion.

About 5% of cases of trisomy 21 are probably due to mitotic (postzygotic) nondisjunction of a chromosome 21 in the early embryo, as determined by pericentromeric DNA markers and the lack of

observed recombination along the entire long arm of chromosome 21 [5]. The mitotic errors are not associated with advanced maternal age and show no preference in the parental origin of the duplicated chromosome 21 [5]. Mosaicism with a normal cell line occurs in about 2%-4% of DS newborns [1]. DNA polymorphism analysis in mosaic trisomy 21 probands showed that the majority of cases resulted from a trisomic zygote with mitotic loss of one chromosome [6].

Efforts to create mice with three copies of a defined chromosomal segment using chromosome engineering [7] are being pursued in a number of laboratories and they have provided refined genetic models for assessment of hypotheses concerning critical genes versus destabilising effects of trisomy.

A basic assumption of using animal models to study DS is that although the phenotypes will still vary in ways that reflect species differences, the genetic processes disrupted by gene-dosage imbalance will frequently be conserved. Chromosome 21 gene order and content are highly conserved in mouse, facilitating development of genetic models. The gene-dosage effects hypothesis lends itself to direct testing by transgenesis, and a large number of genetically modified mice have been reported [8].

Evaluating the effects of single genes in mouse models is complicated by not knowing what phenotypic consequences of gene-dosage imbalance can occur in trisomic mice. The creation of the “Ts65Dn” mouse [9] that has segmental trisomy for the distal end of mouse chromosome 16 provides a system to address this problem. The Ts65Dn model is a Robertsonian translocation resulting from experimental exposure to radiation [9]. The distal chromosome 16 segment in Ts65Dn mice corresponds to a portion of the chromosome 21 gene catalogue [10]. Thus, the genetic insult in these mice corresponds closely to that of segmental trisomy in humans [11]. These mice display a variety of phenotypic abnormalities, including early developmental delay evidenced by reduced birth weight, muscular trembling, male sterility and abnormal facies. Other characteristics include changes in behavior, alterations in the structure of dendritic spines in the cortex and hippocampus, and failed long-term potentiation in the hippocampus and fascia dentate. Ts65Dn mice do not display some DS-associated phenotypes such as cardiac and skeletal anomalies or leukemia. Moreover, evaluation of the performance of the Ts65Dn mice in a variety of behavioural tests demonstrates that segmental trisomy 16 results in spontaneous locomotor hyperactivity and impaired performance on a complex visual spatial learning and memory task.

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A second segmental trisomy 16 model, Ts1Cje, arose as a fortuitous translocation of chromosome 16 in a transgenic mouse line [12]. These mice are at dosage imbalance for a subset of the segment triplicated in Ts65Dn, corresponding to a human chromosome 21 region.

Other mouse models, including Ts16, Ts1Cje and Ms1Cje, Ts1Rhr and MTs1Rhr, Ts1Yah and Ms2Yah, and Dp(10)1Yey/+; Dp(16)1Yey/+; Dp(17)1Yey/+ models have been previously recruited for DS [13].

“Phenotype maps” have been used to correlate expression of specific genes with specific aspects of DS. These are developed from the assessment of persons with segmental trisomy involving only a portion of human chromosome 21 (HSA21). The smallest chromosomal region in common among individuals who share a given feature is referred to as a “Down’s syndrome critical region” (DSCR). The best defined DSCR extends ~5.4 Mb on HSA21q22 [14]. The critical region concept predicts that genes in a specific region are sufficient to produce DS phenotypes. However, a recent detailed study of segmental trisomy 21 in DS subjects argues against a single DSCR [15]. The point of these efforts is not to prove whether “critical regions” exist, but rather to understand which dosage-sensitive genes contribute to specific DS phenotypes. Given small numbers of subjects with partial trisomy 21 and a high degree of phenotypic variability even among those with full trisomy 21, this concept is difficult to be investigated in human beings.

Molecular quantitative analyses indicated that trisomy is inducing an overexpression for a large part of the triplicated genes and deregulates also pathways involving non HSA21 genes. Together with the physiological description of murine models overexpressing orthologous genes, these data have allowed to elaborate hypotheses on the cause of cognitive impairment. From these hypotheses and using murine models it is now possible to assess the efficiency of various therapeutic strategies. A recent paper [16] reviewed these new perspectives starting from the strategies targeting the level of HSA21 RNAs or HSA21 proteins; then it described methods targeting activities either of proteins involved in cell cycle pathways or of proteins controlling the synaptic plasticity. It is promising that strategies targeting specific genes or specific pathways are already giving positive results.

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