

Trisomy 21: A Possible Molecular Basis

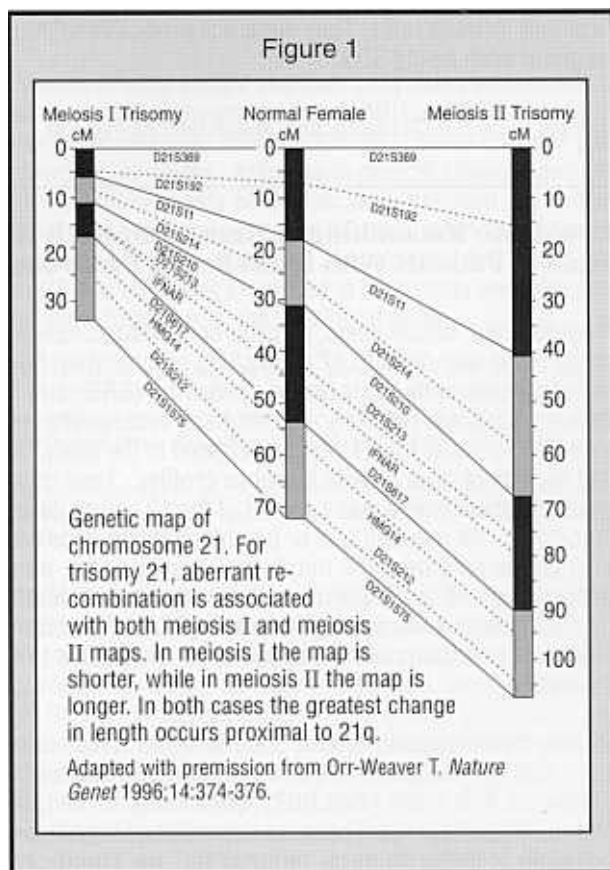
Trisomy 21 accounts for the vast majority of Down syndrome. It is the most common trisomy of newborns and the leading known cause of mental retardation. Trisomy 21 has long been known to result from failure of the 2 homologous chromosome 21s to segregate (nondisjunction) during meiosis, especially during maternal meiosis I. Recently, evidence has emerged that the genetic recombination that normally occurs between homologous chromosomes during meiosis is altered in trisomy 21. Indeed, reduced recombination confined primarily to the proximal region of chromosome 21q was found in cases due to meiosis I errors. Now, abnormal recombination also has been found in cases due to meiosis II errors. In the meiosis II errors, recombination is increased, and accounts for about 20% of trisomy 21.

Lamb et al studied 133 trisomy 21 cases of maternal meiosis II errors using a panel of chromosome 21 DNA markers that allowed them to examine genetic recombination as well as the parental and meiotic origin of the extra chromosome. They found increased recombination restricted mainly to the proximal q arm of the chromosome. Importantly, they detected no difference in the extent of recombination in chromosomes derived from older versus younger women.

The observations prompted speculation from these authors, as well as from Orr-Weaver in an invited editorial, about how decreased and increased recombination might contribute to chromosome segregation errors in meiosis I and meiosis II, respectively. The deviations from "normal" are depicted in the genetic map of chromosome 21, shown in Figure 1, in which the length of chromosome segments corresponds to the extent of recombination. It is suggested that physical attachments that exist between homologous chromosomes during recombination (so-called chiasmata, or sites of crossing over) and between sister chromatids are important for normal chromosome segregation. In the former instance, it is proposed that chiasmata that form near the end of the chromosome are less effective at promoting proper segregation than those formed proximally. Perhaps distal chiasmata are less stable than proximal ones. If so, a reduction in proximal chiasmata, which would be associated with the observed reduced recombination in this region, would predispose to missegregation at meiosis I.

To explain how increased recombination events in the proximal 21q might promote meiosis II errors, the possibility of chromosome entanglement is raised. In this scenario, some of the excessive proximal chiasmata are not resolved during meiosis I. This results in failure of the chromosome 21 homologues to segregate. If the homologues remain entangled after the first segregation, then their chromatids may not segregate properly during meiosis II. This implies that disturbances of meiosis I can adversely affect segregation at meiosis II — a new concept.

Since neither of these explanations addresses why trisomy 21 occurs more frequently in older mothers, a 2-step



process is proposed. In the first step, "susceptible" meiotic chromosome configurations are established prenatally in all female fetuses. In most instances, such configurations are resolved by normal meiotic processes. However, with increasing age, these processes become less effective and unresolved susceptible configurations result in nondisjunction and trisomy. Meiotic-specific proteins, such as spindle or microtubular motor proteins, that degrade with time are mentioned as candidates to explain the age-dependency of the meiotic errors.

Lamb NE, et al. Susceptible chiasmata configurations of chromosome 21 predispose to non-disjunction in both maternal meiosis I and meiosis II. *Nature Genet* 1996;14:400-405.

Orr-Weaver T. Meiotic nondisjunction does the two-step. *Nature Genet* 1996;14:374-376. Editorial.

Editor's comments: History has tended to keep the disciplines of cytogenetics and molecular genetics apart in many institutions. The work described above importantly demonstrates the value of integrating the 2 to address questions that have been around for decades. The results may not explain precisely why trisomy 21 occurs, but they provide hypotheses to test and molecular contexts in which to consider alternative possibilities.

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