How Does Down Syndrome Occur?

Recent genetic research has opened many new avenues of exploration for scientists to understand the structures and processes that create Down syndrome. Although the DNA sequence of chromosome 21 was completed in 2000, no single gene or gene cluster, to date, has been found to be responsible for all DS phenotypes. In fact, DS may result from a variety of gene combinations, with chromosome 21 varying in its impact and expression. There are some basic principles and patterns that can be described, however.

A number of unpredictable events or mistakes can occur during meiosis. Some of these aberrations can lead to Down syndrome. In Nondisjunction Trisomy 21, the most typical type of Down syndrome, there is a failure of the chromosome 21 pair to disjoin from each other or divide properly in the egg or sperm cells, leaving an extra number-21 chromosome in each cell. Trisomy 21 accounts for 95% of Down syndrome cases. This type is related to maternal age, although the actual number of individuals born with Down syndrome is a function of birthrates for each age group. Similarly, according to Morris, Mutton, and Alberman (2005), there is an additive risk for mothers who have had a pregnancy with Trisomy 21. This additive risk of occurrence is actually less for mothers whose first DS diagnosis occurred after the age of 30 compared with those whose pregnancy occurred prior to age 30. The additive risk overall is less than 1% and ranges from .04% if the first child was born to a 40-year old mother, to .6% if the first child was born to a 20-year-old mother.

A second kind of Down syndrome, mosaicism, occurs when nondisjunction of the 21st chromosome takes place in one of the initial cell divisions after fertilization. This leaves the child with a mixture of two types of cells, some containing the normal 46 chromosomes and some containing 47. Mosaicism is the least common form and is responsible for only one to two percent of cases with Down syndrome.

Translocation, the third form, occurs in only three to four percent of people with Down syndrome. In translocation, a piece of chromosome or a whole chromosome breaks off during meiosis and attaches itself to another chromosome. The presence of an extra part of the number 21 chromosome causes the features of Down syndrome. Although most cases are the result of random events, the risk of recurrence may be greater for translocation since parents have been identified as carriers in about 1/3 of these cases. These “balanced carriers” actually have a full set of chromosomes, but two of the carrier’s chromosomes are stuck together. Thus, a carrier’s total chromosome count is 45 instead of 46, but she or he is unaffected because there is no loss or excess of genetic material. Since this is the only type that is heritable, the risk of recurrence is greater for births from balanced carriers than for parents with 46 chromosomes.

In summary, most cases of Down syndrome are not inherited. They occur because of random events during reproductive cell formation. Heritability factors are high only in Translocation, and then the predictability ratio is not known.

Morris, J.K., Mutton, D.E., & Alberman, E. (2005). Recurrences of free trisomy 21: Analysis of data from the National Down Syndrome Cytogenetic Register. *Prenatal Diagnosis, 25,* 1120-1128.

Funding and support for Brighter Tomorrows was provided by the U.S. Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, through a cooperative agreement with the Association of University Centers on Disabilities (Grant No: AUCD RTOI 2007-03-01).