

Editorial

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Down syndrome is the most common genetic cause of intellectual disability. In North America, it occurs in about one of every 800 to 1,000 live-births. John Langdon Down was the first to formally describe this condition in 1866, when he distinguished it from cretinism (which now is known to be caused by a severe deficiency of iodine), although the characteristic physical features of Down syndrome have been depicted for centuries in classical art.

It was not until 1959 that the actual cause of Down syndrome was discovered. Prior to 1956, we did not know the exact number of chromosomes in the typical human cell. Due to improvements in techniques, the correct number was determined to be 46, and not 48 as had been previously believed. Following this discovery, further technological advances allowed for the identification of individual chromosomes and of the specific chromosomes associated with specific genetic disorders. In 1959, groups headed by Dr. Patricia Jacobs in the U.S. and Dr. Jerome Lejeune in France both reported the presence of one extra chromosome, identified as chromosome 21, in the cells of people with Down syndrome. We now know that there are three different types of Down syndrome, all involving the 21st chromosome. Approximately 95% of people with Down syndrome have trisomy 21 (three copies of chromosome 21 instead of the usual two in all cells). This happens because either an ovum of a mother, or a sperm of a father, carries two chromosome 21's instead of the usual one, as the result of a process called non-disjunction. Another 4% have translocation Down syndrome, in which an extra chromosome 21 has become attached to another chromosome in the cell. The other 1% have mosaicism for chromosome 21, meaning that only some of their cells exhibit trisomy 21. In a very small percentage of cases, only a small portion of one chromosome 21 is duplicated.

The risk of having a baby with trisomy 21 increases dramatically with advancing maternal age once this maternal age is more than 35 years. An increased risk is also associated with advancing paternal age, particularly when the maternal age is more than 40 years. Nevertheless, because fertility is greater in younger people, about 80% of babies with Down syndrome are born to mothers under the age of 35 years. Down syndrome is often detected during pregnancy on the basis of fetal ultrasound analysis or a maternal

serum-screening test. If a more accurate diagnosis is desired during a pregnancy, then fetal chromosomes can be studied in cells from amniotic fluid or from a chorionic villus biopsy. Down syndrome can also be diagnosed by studying chromosomes shortly after birth.

In opposition to commonly held beliefs, individuals with Down syndrome vary considerably in their appearance. Like children without Down syndrome, children with Down syndrome are more likely to resemble their parents than they are to resemble other children with Down syndrome. There are, however, a number of physical features that are common to people with Down syndrome. These include almond shaped eyes with an epicanthal fold, small features, and a single palmar crease, and are called the Down syndrome phenotype.

The extra genetic material related to having an extra 21st chromosome, expresses itself differently for different people with Down syndrome. While most people with Down syndrome have mild to moderate intellectual disability, some may present with more severe intellectual impairments. People with Down syndrome do tend to have more health problems than do people who do not have Down syndrome. For example, congenital heart defects affect up to 50% of babies with Down syndrome. Gastro-intestinal blockages are similarly more prevalent. With appropriate medical care, however, these disorders are surgically correctable. Certain types of leukemia and immune disorders such as autoimmune thyroiditis, diabetes, celiac disease and arthritis are unusually common. There is a higher frequency of vision and hearing problems, and of chronic upper respiratory infections. Dementia of the Alzheimer type affects many, though not all, people with Down syndrome 20 to 30 years earlier than those without Down syndrome, manifesting most commonly over the age of 45 or 50 years. It has been known for more than 70 years that the brains of nearly all individuals with Down syndrome who die after the age of 40 years show features that are characteristic of Alzheimer disease – namely, senile plaques and neurofibrillary tangles. The link between Down syndrome and Alzheimer disease was first recognized in North America in 1948 by George A. Jervis. He described three individuals with Down syndrome, aged 37, 42 and 47 years, each of whom had shown a profound emotional and intellectual deterioration in the last few years of life. At autopsy, all were found to have the hallmark lesions of Alzheimer disease. However, Jervis's findings were not generally appreciated for more than 10 years when interest in the association between Down syndrome and Alzheimer disease was revived by neuropathologists.

Despite the myriad of potential complications from having Down syndrome, no one can predict what a person with Down syndrome is capable of achieving. Example after example demonstrates that people with Down syndrome can (and do) grow up to lead fulfilling lives. Many live independently, or in supported independent living arrangements. They enjoy relationships – social, familial, and marital. Many hold paid jobs or actively volunteer in their communities.

Early intervention programs and quality education are crucially important in helping people with Down syndrome to achieve their full potential. Strong, supportive parents, who are able to not only love, value and nurture their child who has Down syndrome, but also to advocate for them, can make a tremendous difference. However, parents and families of children with Down syndrome, like the larger society, hold a range of attitudes and beliefs about disability and are often not prepared for the birth of a child with a disability. Appropriate and sufficient family support is also critical. In addition, health professionals must become familiar with the medical needs of individuals with Down syndrome. With early identification and treatment of medical issues, there is the potential for successful treatment and/or correction, for fewer complications, for reduced impacts upon learning and development, and for living longer and better. The hope for the future lies, at least in part, in the emergence of new interventions as we learn more and more about Down syndrome and the causes of both its non-medical and medical complications. Before antibiotic use and heart surgery, the average life expectancy for a person with Down syndrome was only about 9 years. With better medical care, many people with Down syndrome now live well into their 50s or beyond.

It has only been within the last five years, however, that substantive research has focussed on chromosome 21. This is because, in May 2000, the sequence of chromosome 21 was determined as the result of the Human Genome Project. Human chromosome 21 now is known to carry 225 genes; another 329 are thought to exist. Studies of this small set of genes will not have any immediate benefits for people with Down syndrome, but they are expected to help us understand mechanisms in the brain that are important to memory and intelligence and the physical characteristics associated with Down syndrome. Surprisingly, much of the DNA in chromosome 21 does not code for genes, but, rather, for RNA molecules whose functions are yet unknown.

These advances in research are already improving our knowledge of Down syndrome. At one time, it was thought that the Down syndrome phenotype was due only to a few chromosome 21 genes that were overexpressed. It is

now clear that this is not the case. Furthermore, the gene products that are overexpressed in Down syndrome are not the same for everyone because many chromosome 21 genes come in different forms, called allelic variants. Such variation may explain why some people with Down syndrome, but not others, are born with congenital heart disease or gastrointestinal abnormalities, develop autoimmune thyroiditis, or present with Alzheimer like dementia at a very early age. How the overexpressed gene products of the three chromosome 21s in Down syndrome interact with normally expressed gene products on other chromosomes is another key issue under intensive investigation.

Much research about Down syndrome is being conducted with mouse models of Down syndrome. These mice carry various extra regions of mouse chromosome 16, which is the homologue of human chromosome 21, and have different types of abnormalities of brain and behaviour. Further, it is now possible through genetic engineering to produce mice that lack these particular chromosome 16 genes, or that have human chromosome 21 genes in one or more copies. From such mouse models, it will be possible to identify functions of the genes on human chromosome 21 that are important to cognition and behaviour, to immunity, or that predispose to or protect against certain cancers. It will also be possible to identify the functions of chromosome 21 RNA that does not get translated into protein, as well as understand how chromosome 21 genes 'talk' to one another and to genes on other chromosomes. In addition, we will be able to understand the causes of the non-disjunction that result in trisomy 21. Along with such information, such mouse models will aid enormously in the identification of genes and molecular processes affecting the development of dementia of the Alzheimer type. This will facilitate the testing of new drugs and medicines for treatment of dementia and other conditions resulting from, or affected by, changes in chromosome 21 genes.

Importantly, a number of large clinical trials, designed to improve the health and quality of life for people with Down syndrome on the basis of published research data, are now being conducted to more objectively determine treatment outcomes. One project, *Vitamins and Minerals for Children With Down Syndrome*, is currently analyzing antioxidants and folic acid in babies. Another study, for which participants are being recruited, involves an examination of the ability of high doses of vitamin E to slow down deterioration of neurocognitive and neurobehavioural function in aging persons with Down syndrome (*Vitamin E in Aging Persons With Down syndrome*).

The basic and clinical advances underway will provide information that should help people with Down syndrome to have a better quality of life. In particular, new strategies may be developed that will continue to improve the quality of life for people with Down syndrome over all stages of the life span. Such strategies may decrease the level of intellectual disability and various aspects of the Down syndrome phenotype in children, increase longevity, and even possibly prevent development of the Alzheimer type in older persons with Down syndrome. The research articles dealing with Down syndrome in Part A of this volume of the *Journal on Developmental Disability* capture some of the intriguing neurocognitive and neurobehavioural characteristics of this disorder. The review article about medical health issues in the Supplement to this volume provides a wealth of important information and insights for anyone involved in the care of older people with Down syndrome.

There is, however, another side to the story. A better future for people with Down syndrome lies not only in the important medical and clinical advances outlined in this issue. The social, political, economic, and attitudinal barriers still faced by people with all types of disability continue to impede their progress. Discrimination and devaluation, regrettably, continue to be realities in the lives of many (if not all) people with Down syndrome. The two book reviews and commentary included in this issue address some of these concerns. The first book review considers the ramifications of tenacious stereotypical narrative representations of Down syndrome. The second highlights the lived experience of having Down syndrome. The personal commentary offers poignant insight into a parent's dilemma when she learns that an unborn child has Down syndrome and is faced with negative attitudes in the medical community to the diagnosis and to her decision to continue with her pregnancy.

Resources

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