The Chromosomal Basis of Down Syndrome

To understand why Down syndrome occurs, the structure and function of the human chromosome must be understood. The human body is made of cells; all cells contain chromosomes, structures that transmit genetic information. Most cells of the human body contain 23 pairs of chromosomes, half of which are inherited from each parent. Only the human reproductive cells, the sperm cells in males and the ovum in females, have 23 individual chromosomes, not pairs. Scientists identify these chromosome pairs as the XX pair, present in females, and the XY pair, present in males, and number them 1 through 22.

When the reproductive cells, the sperm and ovum, combine at fertilization, the fertilized egg that results contains 23 chromosome pairs. A fertilized egg that will develop into a female contains chromosome pairs 1 through 22, and the XX pair. A fertilized egg that will develop into a male contains chromosome pairs 1 through 22, and the XY pair. When the fertilized egg contains extra material from chromosome number 21, this results in Down syndrome.

The Genetic Variations That Can Cause Down Syndrome

Three genetic variations can cause Down syndrome. In most cases, approximately 92% of the time, Down syndrome is caused by the presence of an extra chromosome 21 in all cells of the individual. In such cases, the extra chromosome originates in the development of either the egg or the sperm. Consequently, when the egg and sperm unite to form the fertilized egg, three–rather than two–chromosomes 21 are present. As the embryo develops, the extra chromosome is repeated in every cell. This condition, in which three copies of chromosome 21 are present in all cells of the individual, is called trisomy 21.

In approximately 2-4% of cases, Down syndrome is due to mosaic

trisomy 21. This situation is similar to simple trisomy 21, but, in this instance, the extra chromosome 21 is present in some, but not all, cells of the individual. For example, the fertilized egg may have the right number of chromosomes, but, due to an error in chromosome division early in embryonic development, some cells acquire an extra chromosome 21. Thus, an individual with Down syndrome due to mosaic trisomy 21 will typically have 46 chromosomes in some cells, but will have 47 chromosomes (including an extra chromosome 21) in others. In this situation, the range of the physical problems may vary, depending on the proportion of cells that carry the additional chromosome 21.

Chromosome 21

In trisomy 21 and mosaic trisomy 21, Down syndrome occurs because some or all of the cells have 47 chromosomes, including three chromosomes 21. However, approximately 3-4% of individuals with Down syndrome have cells containing 46 chromosomes, but still have the features associated with Down syndrome. How can this be? In such cases, material from one chromosome 21 gets stuck or translocated onto another chromosome, either prior to or at conception. In such situations, cells from individuals with Down syndrome have two normal chromosomes 21, but also have additional chromosome 21 material on the translocated chromosome. Thus, there is still too much material from chromosome 21, resulting in the features associated with Down syndrome. In such situations, the individual with Down syndrome is said to have translocation trisomy 21.

The Occurrence of Down Syndrome

Most of the time, the occurrence of Down syndrome is due to a random event that occurred during formation of the reproductive cells, the ovum or sperm. As far as we know, Down syndrome is not attributable to any behavioral activity of the parents or

environmental factors. The probability that another child with Down syndrome will be born in a subsequent pregnancy is about 1 percent, regardless of maternal age.

The incidence of Down syndrome rises with increasing maternal age.

For parents of a child with Down syndrome due to translocation trisomy 21, there may be an increased likelihood of Down syndrome in future pregnancies. This is because one of the two parents may be a balanced carrier of the translocation. The translocation occurs when a piece of chromosome 21 becomes attached to another chromosome, often number 14, during cell division. If the resulting sperm or ovum receives a chromosome 14 (or another chromosome), with a piece of chromosome 21 attached and retains the chromosome 21 that lost a section due to translocation, then the reproductive cells contain the normal or balanced amount of chromosome 21. While there will be no Down syndrome associated characteristics exhibited, the individual who develops from this fertilized egg will be a carrier of Down syndrome. Genetic counseling can be sought to find the origin of the translocation. However, it is important to realize that not all parents of individuals with translocation trisomy 21 are themselves balanced carriers. In such situations, there is no increased risk for Down syndrome in future pregnancies.

Researchers have extensively studied the defects in chromosome 21 that cause Down syndrome. In 88% of cases, the extra copy of chromosome 21 is derived from the mother. In 8% of the cases, the father provided the extra copy of chromosome 21. In the remaining 2% of the cases, Down syndrome is due to mitotic errors, an error in cell division which occurs after fertilization when the sperm and ovum are joined.

Down Syndrome And Maternal Age

Researchers have established that the likelihood that a reproductive cell will contain an extra copy of chromosome 21 increases dramatically as a woman ages. Therefore, an older mother is more likely than a younger mother to have a baby with Down syndrome. However, of the total population, older mothers have fewer babies; about 75% of babies with Down syndrome are born to younger women because more younger women than older women have babies. Only about nine percent of total pregnancies occur in women 35 years or older each year, but about 25% of babies with Down syndrome are born to women in this age group.

The incidence of Down syndrome rises with increasing maternal age. Many specialists recommend that women who become pregnant at age 35 or older undergo prenatal testing for Down syndrome. The likelihood that a woman under 30 who becomes pregnant will have a baby with Down syndrome is less than 1 in 1,000, but the chance of having a baby with Down syndrome increases to 1 in 400 for women who become pregnant at age 35. The likelihood of Down syndrome continues to increase as a woman ages, so that by age 42, the chance is 1 in 60 that a pregnant woman will have a baby with Down syndrome, and by age 49, the chance is 1 in 12. But using maternal age alone will not detect over 75% of pregnancies that will result in Down syndrome.

Relationship Of Down Syndrome Incidence To Mothers' Age

Under 30 Less than 1 in 1,000
30 1 in 900
35 1 in 400
36 1 in 300
37 1 in 230
38 1 in 180
39 1 in 135
40 1 in 105
42 1 in 60
44 1 in 35
46 1 in 20
48 1 in 16
49 1 in 12

Source: Hook, E.G., Lindsjo, A. Down Syndrome in Live Births by Single Year Maternal Age.

Prenatal Screening for Down Syndrome

Prenatal screening for Down syndrome is available. There is a relatively simple, noninvasive screening test that examines a drop of the mother's blood to determine if there is an increased likelihood for Down syndrome. This blood test measures the levels of three markers for Down syndrome: serum alpha feto-protein (MSAFP), chorionic gonadotropin (hCG), and unconjugated estriol (uE3). While these measurements are not a definitive test for Down syndrome, a lower MSAFP value, a lower uE3 level, and an elevated hCG level, on average, suggests an increased likelihood of a Down syndrome fetus, and additional diagnostic testing may be desired.

Diagnostic Testing For Down Syndrome

There are several prenatal diagnostic tests that can be performed to determine the occurrence of Down syndrome. These tests include amniocentesis, chorionic villus sampling (CVS), and percutaneous umbilical blood sampling (PUBS). However, before undergoing any of these diagnostic tests, patients and their families should seek detailed genetic counseling to discuss their family history in relationship to the risks and benefits of performing these diagnostic procedures.

Amniocentesis, the removal and analysis of a small sample of fetal cells from the amniotic fluid, is widely available and involves a lower risk of miscarriage than chorionic villus sampling. However, amniocentesis cannot be done until the 14th to 18th week of pregnancy, and it usually takes additional time to determine whether the cells contain extra material from chromosome 21.

Chorionic villus sampling, conducted at 9 to 11 weeks of pregnancy, involves extracting a tiny amount of chorionic villi, tissue extensions that will eventually develop into a placenta. The tissue can be tested for the presence of extra material from chromosome 21. The villi can be obtained through the pregnant woman's abdomen or cervix. This type of sampling carries a 1-2% risk of miscarriage.

The third diagnostic method, percutaneous umbilical blood sampling or PUBS, is the most accurate method and can be used to confirm the results of CVS or amniocentesis. However, PUBS cannot be performed until later in the pregnancy, during the 18th to 22nd weeks, and carries the greatest risk of miscarriage.

New prenatal diagnostic techniques are currently being developed. The NICHD has supported the development of a new, noninvasive test performed during the first trimester of pregnancy, that samples and separates fetal cells from the mother's blood. The goal is to compare the accuracy of this type of cellular level analysis with results obtained by amniocentesis or CVS.

Diagnostic Tests For Down Syndrome

AMNIOCENTESIS

The removal and analysis of a small sample of fetal cells from the amniotic fluid.

Cannot be done until the 14-18th week of pregnancy

Lower risk of miscarriage than chorionic villus sampling

CHORIONIC VILLUS SAMPLING (CVS)

Extraction of a tiny amount of fetal tissue at 9 to 11 weeks of pregnancy

The tissue is tested for the presence of extra material from chromosome 21

Carries a 1-2% risk of miscarriage

PERCUTANEOUS UMBILICAL BLOOD SAMPLING (PUBS)

Most accurate method used to confirm the results of CVS or amniocentesis.

The tissue is tested for the presence of extra material from chromosome 21

PUBS cannot be done until the 18-22nd week
Carries the greatest risk of miscarriage
Researchers outside the NICHD are also developing a new method of diagnosis, called preimplantation diagnosis or blastomere analysis before implantation (BABI), which allows clinicians to detect chromosome imbalances before an embryo is implanted during in vitro fertilization. This technique would primarily be used in couples who are at risk of passing on X-linked disorders, couples who have suffered repeated terminations of pregnancy, subfertile couples, or those at risk for single gene disorders. This technique, which allows the clinician to provide a genetic diagnosis prior to implantation, has been successful so far for cystic fibrosis, Tay Sachs disease, and Lesch-Nyhan syndrome. BABI allows a couple to begin their pregnancy knowing that the fetus is unaffected with the genetic disease of concern. For couples at high risk, this procedure provides an alternative to prenatal testing in the first or second trimester.

A Diagnosis of Down Syndrome

A newborn baby with Down syndrome often has physical features the attending physician will most likely recognize in the delivery room. These may include a flat facial profile, an upward slant to the eye, a short neck, abnormally shaped ears, white spots on the iris of the eye (called Brushfield spots), and a single, deep transverse crease on the palm of the hand. However, a child with Down syndrome may not possess all of these features; some of these features can even be found in the general population. To confirm the diagnosis, the doctor will request a blood test called a chromosomal karyotype. This involves “growing” the cells from

the baby's blood for about two weeks, followed by a microscopic visualization of the chromosomes to determine if extra material from chromosome 21 is present.
Medical care for infants with Down syndrome should include the same well-baby care that other children receive.

When parents are told that their newborn baby has Down syndrome, it is not unusual for them to have feelings of sadness and disappointment. Many parents report that at the time their child is first diagnosed with Down syndrome and during the weeks that follow, they feel overwhelmed by feelings of loss and anxiety. While caring for a child with Down syndrome frequently requires more time and energy, parents of newborn children with Down syndrome should seek the advice of a knowledgeable pediatrician and/or the many Down syndrome support groups and organizations available (see Additional Resources for a listing). The doctor making the initial diagnosis of Down syndrome has no way of knowing the intellectual or physical capabilities this child, or any other child, may have. Children and adults with Down syndrome have a wide range of abilities. A person with Down syndrome may be very healthy or they may present unusual and demanding medical and social problems at virtually every stage of life. However, every person with Down syndrome is a unique individual, and not all people with Down syndrome will develop all the medical disorders discussed below.

Down Syndrome and Associated Medical Disorders

During the first days and months of life, some disorders may be immediately diagnosed. Congenital hypothyroidism, characterized by a reduced basal metabolism, an enlargement of the thyroid gland, and disturbances in the autonomic nervous system, occurs slightly more frequently in babies with Down syndrome. A routine blood test for hypothyroidism that is performed on newborns will

detect this condition if present.
Several other well-known medical conditions, including hearing loss, congenital heart disease, and vision disorders, are more prevalent among those with Down syndrome.
Recent studies indicate that 66 to 89% of children with Down syndrome have a hearing loss of greater than 15 to 20 decibels in at least one ear, due to the fact that the external ear and the bones of the middle and inner ear may develop differently in children with Down syndrome. Many hearing problems can be corrected. But, because of the high prevalence of hearing loss in children with Down syndrome, an objective measure of hearing should be taken to establish hearing status. In addition to hearing disorders, visual problems also may be present early in life. Cataracts occur in approximately 3% of children with Down syndrome, but can be surgically removed.
Approximately half of the children with Down syndrome have congenital heart disease and associated early onset of pulmonary hypertension, or high blood pressure in the lungs.
Echocardiography may be indicated to identify any congenital heart disease. If the defects have been identified before the onset of pulmonary hypertension, surgery has provided favorable results. Seizure disorders, though less prevalent than some of the other associated medical conditions, still affect between 5 and 13% of individuals with Down syndrome, a 10-fold greater incidence than in the general population. There is an unusually high incidence of infantile spasms or seizures in children less than one year of age, some of which are precipitated by neonatal complications and infections and cardiovascular disease. However, these seizures can be treated with anti-epileptic drugs.
The incidence and severity of these associated medical ailments will vary in babies with Down syndrome and some may require surgery.

Newborns

Babies with Down syndrome often have hypotonia, or poor muscle tone. Because they have a reduced muscle tone and a protruding

tongue, feeding babies with Down syndrome usually takes longer. Mothers breast-feeding infants with Down syndrome should seek advice from an expert on breast feeding to make sure the baby is getting sufficient nutrition. Hypotonia may affect the muscles of the digestive system, in which case constipation may be a problem. Atlantoaxial instability, a malformation of the upper part of the spine located under the base of the skull, is present in some individuals with Down syndrome. This condition can cause spinal cord compression if it is not treated properly.

Infants and Preschool Children

Medical care for infants with Down syndrome should include the same well-baby care that other children receive during the first years of life, as well as attention to some problems that are more common in children with Down syndrome. If heart, digestive, orthopedic or other medical conditions were identified during the neonatal period, these problems should continue to be monitored. During the early years of life, children with Down syndrome are 10-15 times more likely than other children to develop leukemia, a potentially fatal disease. These children should receive an appropriate cancer therapy, such as chemotherapy. Infants with Down syndrome are also more susceptible to transient myelodysplasia, or the defective development of the spinal cord. Compared to the general population, individuals with Down syndrome have a 12-fold higher mortality rate from infectious diseases, if these infections are left untreated and unmonitored. These infections are due to abnormalities in their immune systems, usually the t-cell and antibody-mediated immunity functions that fight off infections. Children with Down syndrome are also more likely to develop chronic respiratory infections, middle ear infections, and recurrent tonsillitis. In addition, there is a 62-fold higher incidence of pneumonia in children with Down syndrome than in the general population.

Children with Down syndrome may be developmentally delayed. A child with Down syndrome is often slow to turn over, sit, stand, and

respond. This may be related to the child's poor muscle tone. Development of speech and language abilities may take longer than expected and may not occur as fully as parents would like. However, children with Down syndrome do develop the communication skills they need. Parents of other children with Down syndrome are often valuable sources of information and support. Parents should keep in mind that children with Down syndrome have a wide range of abilities and talents, and each child develops at his or her own particular pace. It may take children with Down syndrome longer than other children to reach develop mental milestones, but many of these milestones will eventually be met. Parents should make a concerted effort not to compare the developmental progress of a child with Down syndrome to the progress of other siblings or even to other children with Down syndrome.

Early Intervention and Education

The term "early intervention" refers to an array of specialized programs and related resources that are made available by health care professionals to the child with Down syndrome. These health care professionals may include special educators, speech therapists, occupational therapists, and social workers. It is recommended that stimulation and encouragement be provided to children with Down syndrome. The evaluation of early intervention programs for children with Down syndrome is difficult, due to the wide variety of experimental designs used in interventions, the limited existing measures available that chart the progress of disabled infants, and the tremendous variability in the developmental progress among children with Down syndrome, a consequence in part of the many complicating medical factors. While many studies have been conducted to assess the effects of early intervention, the information is limited and contradictory regarding the long-term success of early intervention for children with Down syndrome.

However, federal laws (Public Law 94-12) are in place to ensure

each state has as a goal that “all handicapped children have available to them a free public education and related services designed to meet their unique needs.” The decision of what type of school a child with Down syndrome should attend is an important one, made by the parents in consultation with health and education professionals. A parent must decide between enrolling the child in a school where most of the children do not have disabilities (inclusion) or sending the child to a school for children with special needs. Inclusion has become more common over the past decade.

Adolescence

Like all teenagers, individuals with Down syndrome undergo hormonal changes during adolescence. Therefore, teenagers with Down syndrome should be educated about their sexual drives. Scientists have medical evidence that males with Down syndrome generally have a reduced sperm count and rarely father children. Females with Down syndrome have regular menstrual periods and are capable of becoming pregnant and carrying a baby to term.

Adults with Down Syndrome

The life expectancy for people with Down syndrome has increased substantially. In 1929, the average life span of a person with Down syndrome was nine years. Today, it is common for a person with Down syndrome to live to age fifty and beyond. In addition to living longer, people with Down syndrome are now living fuller, richer lives than ever before as family members and contributors to their community. Many people with Down syndrome form meaningful relationships and eventually marry. Now that people with Down syndrome are living longer, the needs of adults with Down syndrome are receiving greater attention. With assistance from family and caretakers, many adults with Down syndrome have developed the skills required to hold jobs and to live semi-independently.

Premature aging is a characteristic of adults with Down syndrome. In addition, dementia, or memory loss and impaired judgment similar to that occurring in Alzheimer disease patients, may appear in adults with Down syndrome. This condition often occurs when the person is younger than forty years old. Family members and caretakers of an adult with Down syndrome must be prepared to intervene if the individual begins to lose the skills required for independent living.

Down Syndrome in the Workplace

The Americans with Disabilities Act (ADA) makes it illegal for an employer of more than 15 individuals to discriminate against qualified individuals in application procedures, hiring, advancement, discharge, compensation, job training, and other terms of employment. The ADA requires that an employer provide reasonable accommodation for individuals who are qualified for a position. More information about the ADA can be obtained from the Office of Civil Rights of the U.S. Department of Health and Human Services, Washington, DC, 20201.

Future Directions in Down Syndrome Research

Recently, it has been suggested that children with Down syndrome might benefit from medical intervention that includes amino acid supplements and a drug known as Piracetam. Piracetam is a psychoactive drug that some believe may improve cognitive function. However, there have been no controlled clinical studies conducted to date using Piracetam to treat Down syndrome in the U.S. or elsewhere that show its safety and efficacy.

Down syndrome researchers have developed a mouse model to analyze the developmental consequences of Down syndrome. Mice are used because a large stretch of mouse chromosome 16 has many genes in common with those on human chromosome 21.

Studying these models at varying stages of development will enhance our basic understanding of Down syndrome and facilitate the development of effective interventions and treatment strategies.
Questions and Answers about Down Syndrome
Is Down syndrome a rare genetic disorder? Down syndrome occurs in 1 in 800 births.

Do only older women give birth to babies with Down syndrome?

Researchers have established that the likelihood that a reproductive cell will contain an extra copy of chromosome 21 increases dramatically as a woman ages. Therefore, an older mother is more likely than a younger mother to have a baby with Down syndrome, but older mothers account for only about 9% of all live births each year and 25% of Down syndrome births.

Are all people with Down syndrome severely retarded?

Most people with Down syndrome have IQ's that fall in the mild to moderate range of retardation. Some are so mildly affected that they live independently and are gainfully employed.

Can people with Down syndrome receive proper care at home?

Home-based care and community living give them the opportunity to socialize and benefit from such interactions.

Should all children with Down syndrome be placed in special

education classrooms?

While federal laws have been established to ensure that all handicapped children have access to public education, children with Down syndrome can and have been included into a regular classroom.

Is there a cure for Down syndrome?

Researchers have identified the genes that cause the characteristics of Down syndrome and are working to further develop mouse models, at varying stages of development, in order to enhance their basic understanding of Down syndrome and facilitate the development of effective interventions and treatment strategies.