One of the questions that parents often ask our interviewers is “What have you learned so far?” If you are one of the many who has asked this question, you were probably told that information must be gathered from many families in order to see any patterns. After three years of collecting information in six states across the US, we now have sufficient data to begin looking for patterns that will tell us more about Down syndrome.

We designed the National Down Syndrome Project (NDSP) as a multi-site project in order to enroll enough families to answer several important questions, including, how does Down syndrome occur, and why are some people with Down syndrome born with medical problems.

Since January 2001, 1,273 families have participated in the NDSP (see table below). Their time and energy have built a pool of data that we are now beginning to examine. Answers to questionnaires from participating families have been compiled in our database, and our molecular laboratory is midway in its analysis of the biological samples provided by parents and children. In the coming year, we will continue to enroll additional families whose participation should put us at our goal. Finally, our last step will be to examine the data carefully, draw our conclusions, and distribute important findings to the medical, scientific, and Down syndrome communities.

In this newsletter you will find information about another question parents frequently ask, “Is there a way to predict the severity in Down syndrome?” We also provide an update on our focus on heart defects associated with Down syndrome and on the institutions that have joined us in this study.

We continue to depend on the efforts of many families, and we are extremely grateful to each family for their participation and support of this project.
**Predicting Severity**

“**How seriously will my child be affected by Down syndrome?**” Without a doubt, this is the most common question new parents ask in clinic. They usually have a general idea that Down syndrome involves developmental delays and certain medical problems, but they want to know what the future will be for their own child. Because chromosome studies were used to diagnose Down syndrome in their baby, they often assume that the chromosome report holds the answer. That is, they think that the geneticist can look at the chromosomes through a microscope and predict the severity and, consequently, the course of a child’s future development. Why isn’t this possible?

To answer this question, we need to consider the chromosomes and their importance. Each child with Down syndrome has an extra copy of chromosome 21 in their cells. This extra chromosome can be either a separate, free-standing 21 (known as standard trisomy 21 Down syndrome) or it can be an extra 21 attached to another chromosome (translocation Down syndrome). First of all, there is no known difference in the physical and developmental outcome between individuals with standard trisomy 21 and those with the much less common translocation. It is the presence of the extra 21 that causes Down syndrome.*

**How does this extra chromosome 21 cause Down syndrome?**

Human chromosomes carry a total of approximately 30,000 genes. These act as blue prints to create a unique person from a single fertilized egg. Chromosomes can be seen and counted through the microscope, but genes are too small to be seen and studied in this way. Chromosome 21 is the smallest chromosome and, by the latest estimates, contains approximately 250-300 genes. A person without Down syndrome has two copies of chromosome 21 (one contributed by the mother in her egg and the other by the father in his sperm). Each chromosome of the pair has a copy of the same 250-300 genes. At the chromosome level, the only difference between persons with and without Down syndrome is that those with Down syndrome have three copies of 21. Their 21s are like anyone else’s, they just have one extra. It is the presence of this extra, normal chromosome that causes Down syndrome. Therefore, scientists have concluded that it is the presence of a normal chromosome 21 that causes the features of Down syndrome. Medical researchers around the world, including those of us with the National Down Syndrome Project, are now working to determine which genes are important in producing which features of Down syndrome. This knowledge will represent a tremendous leap forward in our understanding of Down syndrome and, perhaps offer insights into treatment.

**Why aren’t all children with an extra chromosome 21 alike?**

If all individuals with Down syndrome have an extra copy of the same 250-300 genes, why do they differ with regard to their medical problems and their development? Why are only about half of the children with Down syndrome born with a heart defect? Why do some children master speech better than others? Why are there different levels of developmental ability among the children? These are even more difficult questions. One current hypothesis is that, although all children with Down syndrome have the same extra set of chromosome 21 genes, each gene has some variation. This variation means that each child with Down syndrome is different in some ways from every other child with Down syndrome. An example of this type of variation that is familiar to everyone is eye color. We all have the same genes that determine eye color, so why do some of us have blue eyes, and others green or brown? It is because these genes vary slightly from one person to another. Something similar is probably happening in Down syndrome. All individuals with Down syndrome have three copies of each gene on chromosome 21 and that is enough to cause Down syndrome. However individual variation within each gene causes individual differences.

Learning about this variation is an exciting prospect and a priority of The National Down Syndrome Project. It is likely to take some time. First we need to find out the purpose of each of the important genes on chromosome 21. Only then will we be able to examine the effects of variation within each gene.

**In summary**, We are not able, at present, to predict the developmental potential and medical profile for a particular individual with Down syndrome. However, the future of our understanding of chromosome 21 genes seems very bright. With that understanding, should come the ability to predict what an extra chromosome 21 will mean for an individual child.

*Note: The rare individuals who have an extra chromosome in only some of their cells (mosaic trisomy 21) may have milder features, but it is not possible to predict the specific course for any individual with mosaicism.
**Celebrating Music with Daniel Skandera**

Each year, NDSP researchers and staff from across the country meet in Atlanta to discuss the business of research. Our last meeting was especially energized by the musical performance of Daniel Skandera, a.k.a. the Marimba Man.

Daniel is a professional musician who has Down syndrome and is hearing impaired. He began playing the marimba at 17 years old, and studied music at Georgia State University as a Guest Student for four years. Daniel has now been playing professionally for over 11 years, performing across the US and in Europe. Daniel’s career has earned a number of awards, including the National Exceptional Children’s Foundation “Yes I Can” Award and the National Itzhak Perlman Very Special Arts Young Soloist Award.

Daniel wowed our group with musical selections that ranged from rock n’ roll to classical, to Daniel’s own “Dance of the Chromosomes”. His performance brought new inspiration to our ‘traditional’ research conference. Thanks to Daniel, science took a back seat to music that evening.

Daniel Skandera will be performing at Spivey Hall on March 29, 2004.

**Coming Full Circle**

The National Down Syndrome Project (NDSP) began in 2001. However, those of us at its home-base at Emory University in Atlanta, had been conducting a similar study, recruiting Atlanta families since 1989. Our local success not only led to the NDSP, but also to an unexpected, very rewarding outcome. Over the 10-12 years of the first Atlanta study, we met many wonderful families solely because they had a child with Down syndrome. They gave so generously of their time and support that we wanted to find a way to give back. At the same time, we realized that many of the new families we met were hungry for accurate information about Down syndrome and what it means for their child. We decided that a clinic devoted to serving children with Down syndrome and their families was in order. Finally, the timing was right. In January of 2003, the Department of Human Genetics at Emory University established a Down Syndrome Center to include research, education, and a Down Syndrome Clinic. Currently, the clinic sees babies and toddlers under three years old. Our plans are to grow the clinic as the children grow. What’s the best part of this story? Our local parent group, The Down Syndrome Association of Atlanta, is behind our efforts to develop the clinic. Haven’t we always known that the families are at the heart of all our endeavors!

**Heart to Heart**

An important goal of the NDSP is to understand more about congenital heart defects in Down syndrome. Why do approximately half of all newborns with Down syndrome have a heart defect, and why is their most common heart defect (atrioventricular septal defect or AV canal) only seen rarely in babies without Down syndrome? As explained in the article on severity on page 2, researchers think the key is to find the genes on chromosome 21 that are important in heart development. Dr. Stephanie Sherman, the principal investigator for the NDSP, is directing an intensive team effort in her laboratory at Emory University to search for these genes. The project has been greatly strengthened by collaborations with researchers and physicians at Johns Hopkins University and the affiliated Kennedy Krieger Institute and more recently with Sibley Heart Center Cardiology in Atlanta, the largest pediatric cardiology practice in the southeastern USA and one of the largest in the nation.
Our Mission Statement

Trisomy 21, the leading cause of Down syndrome, occurs when a child receives three copies of chromosome 21 instead of the usual two copies. This is almost always due to a chromosome error during the formation of either the egg or the sperm (see figure at right). Our first goal is to discover how these errors occur and identify risk factors that affect this process.

Secondly, we want to understand why an extra chromosome 21 causes Down syndrome. We hope to identify specific genes on chromosome 21 that alter development and produce the mental retardation, congenital heart defects, and other health problems associated with Down syndrome.

Our hope is that increasing knowledge about Down syndrome will benefit families, educators, and health professionals.