Understanding the Aging “Chromosome Dance”

The process of forming an egg or a sperm includes a complicated, but fascinating, “dance of the chromosomes” called meiosis. Each cell of the human body typically contains 23 pairs of chromosomes, for a total of 46, and meiosis is the process that ensures each egg or sperm contains only half that total number — one from each of the 23 pairs of chromosomes. The reason this is so important is that when a sperm and an egg unite to form an embryo each usually brings their 23 chromosomes for the new cells of the embryo, and these are combined to provide the necessary 46 chromosomes carrying all the genes that form the building blocks of our bodies.

If you imagine that the chromosomes are being led through a dance, this is what they might hear their choreographer saying:

COPY: All 46 chromosomes, copy yourselves, but don’t let go. Glue your new “sister” tight to your side.

PAIR: Find your chromosome partner and make 23 pairs. To the two tall and skinny chromosomes, you get together. You two short ones, now move together. The rest of you get the idea.
LOCK: Link arms with your partner. (Remember you have four arms now, yours and your sisters’. So you have different ways to link together). Hold on tight! (For you eggs, hold on really tight, because you have to stay this way for at least 10 years!)

DIVIDE: On my signal, all pairs move to the center of the cell. Once you’re there, each partner needs to grab a rope that is tied to a pole at each side of the cell. One member of the pair grabs the rope tied to the right pole, the other one grabs the rope tied to the left pole. Now, pull yourselves to the opposite side of the cell. We are dividing equally to form two cells. Each cell now has 23 chromosome sister pairs. You have lost your glue, but that should be ok. You are in the last steps of the dance.

DIVIDE AGAIN: One more time, on my signal, all sisters move to the center of the cell. Now, each sister, grab a rope and separate yourselves! Pull to the other side of the cell. We are dividing into two more cells. Now each cell has 23 chromosomes.

As you can see, this is a very complicated “dance,” with a lot of props and a lot of precise movements. When chromosome pairs or their sister pairs are not “pulled” to the appropriate cell, too many or too few chromosomes can end up in the egg or sperm. In some cases, this can lead to Down syndrome, which is due to one extra copy of chromosome 21, for a total of three (trisomy).

One important safety measure in the dance is linking chromosome arms together tightly to stabilize chromosome pairs. For eggs, this is especially important, since the chromosome dance begins during the fetal life of a female. Then the music stops for years and only starts up again when that egg is ovulated. If the chromosome pairs do not link at all, or if they are linked only by their “fingertips,” they could become unstable.

We have studied this “dance” in eggs and focused on those links that hold the chromosome arms together during the first dance steps. We now know that these links (recombinations, for the experts) are very important and their location on the chromosome is key. We have found that links formed near the middle of the chromosome protect the chromosome pair from aging effects (sometimes referred to as “maternal age effects”). There is evidence that some links become weaker and the sisters start coming “unglued” as they age — that is, the glue degrades over time. Links that occur closer to the “rope” attachment point where the chromosome pairs are pulled apart are susceptible to these aging effects. But a link formed in the middle holds the chromosomes together better and protects those sisters from coming apart too early in the dance. On the other hand, links located at the end of the chromosomes (at their “fingertips”) are very weak. These weak links increase the chance that the sisters will separate too early in the first cell division, no matter how old the egg may be. We are now using resources developed through the Human Genome Project to determine whether there are differences between these links other than just their location.

This research will help us better understand the steps involved in egg formation. Information gathered through our studies may be used to investigate fertility problems that are related to the age of the egg. To reach either goal would mean major advances in reproductive biology.

We would like to thank all those who have graciously participated in our studies for helping us answer these important questions.
The Down Syndrome Clinic at Emory University celebrated its fourth birthday in January 2007. To date, our clinic has scheduled over 250 new family visits.

What age children are you currently seeing in your Down Syndrome Clinic? While our long-range goal is to see individuals of any age who have Down syndrome, we currently see children from birth to age five years.

How do I make a clinic appointment? To make an appointment call Shelley Dills, Clinic Coordinator, at 404-778-8524. Spanish-speaking families can call Elizabeth Sablon, our medical interpreter at 404-778-8476. We think it is important that parents make the appointment because that initial phone call gives us the opportunity to explain the clinic and determine if there is information about Down syndrome that the family needs immediately. If so, we can often provide it by phone or mail prior to their clinic appointment.

How is a visit to the Down Syndrome Clinic different from a visit to a pediatrician? We are not a substitute for a pediatrician. As for any child, your goal should be to select a pediatrician whom you trust to provide all the best general pediatric care and who will be available for those inevitable midnight earaches! Read on to find out more about our clinic.

What does a clinic visit include?

- A review of your child’s medical history. When parents schedule an appointment, we ask for permission to get their child’s medical records. Information from the birth hospital, pediatrician, and any specialists helps us get to know your child. For example, we can make sure that all recommended tests such as a hearing screen, thyroid test, and cardiac evaluation have been completed adequately.
- A discussion of your child’s chromosome report. Parents often want to know more about how Down syndrome occurs, what an extra chromosome 21 means for their child, and if there is an increased chance of another child in the family having Down syndrome
- A physical exam. We complete a basic physical exam of your child and make a special effort to answer any questions you have about features characteristic of Down syndrome.
- A developmental evaluation. Our medical director, Dr. Jeannie Visootsak, is a board-certified developmental pediatrician. After conducting a developmental screening she discusses her findings with parents and makes recommendations for the timing and frequency of early interventional therapy (physical, occupation, speech/language). Each child is an individual with developmental strengths and challenges. Our goal is to identify these strengths and challenges and make recommendations to maximize each child’s potential.
- An explanation of the Healthcare Guidelines for Children with Down Syndrome. These national guidelines provide parents and physicians with a concise outline of special items of care and their timing (e.g., cardiac evaluation, vision and hearing exams, thyroid tests.)
- Referrals. Based on each child’s medical history, physical examination, and developmental evaluation, we suggest appropriate specialists if needed.

Answer questions. This is perhaps the most important part of your visit. We urge parents to come with their questions. Each family who visits our clinic is in a different place in terms of their knowledge of Down syndrome and their acceptance of the diagnosis for their child. We try to tailor visits to each family’s needs.

Where is the Down Syndrome Clinic located? The clinic is located in our facility just off the Emory University campus near the corner of North Decatur and Clairmont Roads. The address is 2165 North Decatur Rd., Decatur, GA 30033 and parking is easy!

How do I find out more about the clinic? Shelley Dills, Clinic Coordinator, will be glad to answer questions related to the clinic (404-778-8524, sdills@genetic.emory.edu).
The Emory Down Syndrome and Congenital Heart Defects Study

For several years researchers at Emory University in the Departments of Human Genetics and Pediatrics have been working together to understand why some children born with Down syndrome also have a heart defect. We have worked with the Sibley Heart Center and Children’s Healthcare of Atlanta (CHOA) to identify children with Down syndrome and an atriocentric septal defect (AVSD or AV canal). This type of heart defect is rare in the general population but common among children with Down syndrome.

A study focused on the causes of heart defects is possible due to the network that we have built through the Atlanta Down Syndrome Project (1989-1999), National Down Syndrome Project (2000-2004) and Emory Down Syndrome Project (2005-present). Through these three studies, we have offered families in the 5-county metro Atlanta area, as well as nationwide, the opportunity to participate in research. Dr. Ken Dooley, a pediatric cardiologist at the Sibley Heart Center, has worked with our group to document the types of heart defects seen in children with Down syndrome. Although many of the children in these studies are eligible for the heart study, additional families needed to be identified.

In 2004 funding was granted by the Cardiac Research Committee at CHOA to identify children treated in Atlanta who were not eligible for the ongoing metro-Atlanta based studies. The response from Georgia families has been amazing. To date, 50 families with a child who was treated at CHOA have completed the study.

We have recently expanded our project to include families with a child who has been treated at Columbus Children’s Hospital in Columbus, OH. With the help of pediatric cardiologist Dr. Cliff Cua, an additional 14 families from Ohio have completed the study. More than 30 families have been recruited through collaboration with Dr. George Capone at the Kennedy Krieger Institute Down Syndrome Clinic.

A research study cannot be successful without support from the medical community, intensive efforts by researchers, and most importantly the time and effort of motivated families. We are continually impressed by and thankful for the willingness of busy families to make time for a study that will someday benefit others. Thank you to all who have participated.

For more information, contact Dr. Lora Bean at (404) 727-0485 or lbean@genetics.emory.edu.

Congenital Heart Defects and Folic Acid

Folic acid, or folate, is a vital dietary nutrient. Insufficient intake of folic acid during pregnancy increases the risk of neural tube defects in the fetus. Since 1998 the US food supply has been supplemented with folic acid and women who are pregnant or planning to become pregnant have been advised to take folic acid supplements, usually in the form of prenatal vitamins.

The process by which folic acid is broken down and used in the body is complex. Folic acid is needed both during fetal development and throughout life to make and repair DNA. Many genes contain information for proteins that play a role in folic acid processing. Human DNA is made up of long strings of building blocks referred to as “A”, “G”, “C”, and “T”. If, at a particular position in the DNA, some people have a “C” while others have a “T”, the site is called a variant. In the human population there are variants in genes that speed up or slow down folic acid processing.

These variants are common and have been associated with many diseases including congenital heart defects.

To investigate whether variants in folic acid processing genes play a role in heart defects in Down syndrome, DNA from approximately 125 children with Down syndrome and a complete atriocentric septal defect (AVSD) and their parents is being compared to DNA from approximately 125 children with Down syndrome and no heart defect and their parents. Variants in several genes necessary for folic acid processing are being tested to determine which variants each person has (a process called genotyping).

The frequency of variants from two groups, those with an AVSD and those without a heart defect, will be compared. If one version of a variant (i.e. “C”) occurs more often in cases than controls compared to the other version of the variant (i.e. “T”), this could indicate that the “C” variant confers a higher risk for having a heart defect with Down syndrome.

This genotyping study was made possible by an award from SeattleSNPs, a government-funded genotyping service at the University of Washington, Seattle, WA. Results from this study are expected soon.
What is a complete atrioventricular septal defect?

The human heart is divided into four chambers – the left and right atria and the left and right ventricles - by a combination of septa (partitions) and valves.

This heart structure ensures that blood entering the heart from the body is pumped to the lungs to pick up oxygen, returned to the heart, and pumped back to the body for oxygen delivery.

Efficient heart function is dependent upon the heart structures developing properly before birth.

An atrioventricular septal defect (AVSD) occurs when both septa and both valves do not develop properly. The resulting underdeveloped heart has difficulty pumping oxygen-carrying blood to the rest of the body. This heart defect requires surgical repair.

Did you know?

- 40% of children born with Down syndrome (or trisomy 21) have a congenital heart defect (CHD).
- The most common form of CHD in Down syndrome is an atrioventricular septal defect (or AVSD).
- Children born with Down syndrome are 2,000 times more likely to have a complete AVSD than children without Down syndrome.
Recruitment for the National Down Syndrome Project (NDSP) has concluded and the first article from this collaborative effort has been published (See abstract below.) The project involved six states: Arkansas, California, Georgia, Iowa, New Jersey, and New York, and during the four years of active recruitment, NDSP enrolled 1884 families in the study. We are continuing to analyze the data collected from this initiative and will have further publications soon. Although the recruitment for the national project has ended, Emory is continuing to enroll study participants through their new Emory Down Syndrome Project. This project began actively recruiting in 2005 and has currently enrolled 68 families. One new part of this project is the Family Study. We invite siblings and grandparents of children with Down syndrome to participate. The goal is to understand more about the links, or recombination, between chromosomes (see "Understand the Aging "Chromosome Dance"). We are also continuing our efforts to identify risk factors for congenital heart defects among individuals with Down syndrome. We have just received funding from the National Heart, Lung and Blood Institute and are collaborating with Johns Hopkins University (Dr. Reeves, Wilhour and Brenner), Kennedy Krieger Institute in Baltimore (Dr. Capone) and Oregon Health Science University (Dr. Maslen). We will expand enrollment of individuals with Down syndrome and a complete atriventricular septal defect and those with a structurally normal heart at all three sites. This combined effort will enhance our ability to identify genetic risk factors and understand the mechanisms that lead to abnormal heart development.

Our Latest Publication

The National Down Syndrome Project: Design and Implementation

SB Freeman, PhD; EG Allen, PhD; CL Oxford-Wright, MS; SW Tinker; C Druschel, MD, MPH; CA Hobbs, MD, PhD; LA O’Leary, PhD; PA Romitti, PhD; MH Royle, PhD; CP Torfs, PhD; SL Sherman, PhD

Objective. The National Down Syndrome Project (NDSP), based at Emory University in Atlanta, Georgia, represents a multi-site, population-based, case/control study with two major aims: (1) to identify molecular and epidemiological factors contributing to chromosome nondisjunction and the consequent packaging of an extra chromosome into an egg or sperm, and (2) to identify risk factors for Down syndrome-associated birth defects.

Methods. The six national sites represent approximately 11% of U.S. births. Cases were newborns with Down syndrome (trisomy 21), and controls were infants without major birth defects randomly selected from the same birth populations. Biological samples were collected from case infants and their parents, and genetic markers were typed to determine the parental origin of chromosome 21 nondisjunction. Each site interviewed parents of case and control infants addressing pregnancy, medical and family history, occupation, and exposures. Sites collected medical information on case infants.

Results. The NDSP enrolled 907 infants as cases and 977 infants as controls (participation rates: 60.7% for cases; 56.9% for controls). Participation rates varied widely by site as did important demographic factors such as maternal age, race, and education. Nondisjunction during oogenesis accounted for 93.2% of the cases. Errors in spermatogenesis were found in 4.1%, and 2.7% were post-zygotic errors.

Conclusions. This exceptional compilation of questionnaire, clinical, and molecular data makes the NDSP a unique resource for ongoing studies of the etiology and phenotypic consequences of trisomy 21. The combined approach increases study power by defining subgroups of cases by the origin of nondisjunction. This report describes the design and successful implementation of the NDSP.

The Down Syndrome Center at Emory University

Announces our new website: http://www.genetics.emory.edu/DSC/

Please visit our website for information regarding:

- Down syndrome research at Emory University
- The Emory Down Syndrome Clinic
- Educational resources

For more information, please call 404-778-8494.
Genotype & Phenotype

Genotype: The genetic makeup of an individual.
Phenotype: Our anatomical and physical characteristics.

The ‘instructions’ contained in the genotype determine the characteristics that make us each unique individuals.

In architectural terms, the genotype is a set of building plans, and the phenotype is the finished building.

Getting Involved

Enjoying the Buddy Walk. (L to R) Alex Bean, Lora Bean, and Helen Smith

Staffing the Down Syndrome Center booth at the Down Syndrome Congress Conference in Atlanta. (L to R) Helen Smith, Stephanie Sherman, and Lora Bean.
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.