Eleven years of Down syndrome research - thanks to you!

The Emory University Down Syndrome Study is beginning its 12th year! Thanks to all the families who have taken time out of their busy lives to join our study, we can brag about a wonderful participation rate of over 70%. Each year approximately 30-40 babies with Down Syndrome (DS) are born to families in the Atlanta area and, over the past 11 years, almost 300 of these families have joined our study. This may sound like a lot of families. Why do we need so many? The answer is complex, but one of the main reasons is that we are doing a statistical study of DS and studies of this type require large numbers to make sure any finding is statistically significant and not just something that could happen by chance. For example, say we find that there were more smokers among parents who had a child with DS than among those who did not. If we base this finding on only 50 parents, there would be a possibility that just by chance, we enrolled more smokers among our parents of children with DS. But if this finding remained true after we collected information on 500 parents, we would begin to seriously investigate possible connections between smoking and DS.

For this reason, we recently submitted a new grant application to the National Institutes of Health (NIH) in which we proposed to add five additional sites across the country. These sites are in New York, New Jersey, Arkansas, Iowa, and California. Scientists in these states are excited about joining our study and, with the help of the Centers for Disease Control and Prevention (CDC), we will be able to enroll families from all of these locations as well as Atlanta and combine the information into one large database. This will speed up our work. We submitted the grant in June and then waited nervously while a panel of experts reviewed our proposal. We recently received the good news that we got a terrific score on our application and should be able to start the project in early 2000, just as the funding for our current study ends. This national study of DS will be the first of its kind ever undertaken.

We want you to know that one of the main reasons our proposal received such a high rating is that we could demonstrate our success over the past 11 years and that success, in large part, was due to all of you who made our participation rate so spectacular. We look forward to working with you and all of the new families as we begin this next exciting chapter and we'll say it again - Thank you!
Examining maternal age at the millennium

As we enter the 21st century we are reminded that the pace of science can be maddeningly slow! We have known for 40 years that 95% of the time, Down syndrome (DS) is caused by an extra chromosome 21, referred to as trisomy 21. However, we still don’t know what causes that extra chromosome to be packaged into an egg or a sperm. Advanced maternal age, the only well-established risk factor for trisomy 21, was actually recognized during the 19th century when physicians observed that children with DS were often the last born in a large family. Now, at the beginning of the 21st century, scientists are still struggling to understand this maternal age effect.

In our own Atlanta study, we have discovered that over 90% of trisomy 21 is due to an error in the formation of the egg. What clues have we found to explain the maternal age effect? First, let’s review what is known about the formation of human eggs.

Eggs form before birth

Did you know that women are born with all of the eggs they will ever have? These eggs begin to form during the first few weeks after the woman herself begins development as an embryo. At about the 20th week (5th month) of her fetal life she has several million eggs in her two ovaries. Then, for reasons we do not understand, the numbers begin to decline and the decrease continues throughout a woman’s life until essentially no eggs remain at menopause (see figure above). Thus, at any time in a woman’s life, her eggs are as old as she is.

Meiosis: the chromosome “dance”

Each month during a woman’s reproductive lifetime, one egg is singled out for ovulation. Immediately before the egg is released from the ovary, hormones trigger an elaborate chromosome “dance” known as meiosis in which one half of the set of 46 chromosomes is discarded leaving an exact half-set (23) in the egg. At fertilization, the egg unites with a sperm containing the father’s 23 chromosomes. An error in this meiotic dance is what causes an extra chromosome to remain in the egg. Less often errors occur in sperm. We think this is because new sperm are produced continuously throughout a man’s life and as a result do not “age”.

Do hormone imbalances play a role?

The fact that the age of the egg depends on the age of the woman makes the maternal age effect more understandable, but we still don’t know why an older egg might be more likely to have an extra chromosome. We do know that, as a woman ages, the smaller egg supply disrupts the balance of female hormones that control egg development. Could the maternal age effect be caused by the imbalance of hormones that occur with the decline in the number of eggs? We finally have evidence that the answer may be yes. As we interviewed Atlanta women who had given birth to a child with DS (cases) and women who had a child without DS (controls), we asked if they had ever had an ovary removed. We found that significantly more cases than control mothers said they were missing all or part of an ovary either because they were born with only one ovary or because they had undergone ovarian surgery. It is interesting that women who have had an ovary removed show changes in their hormone levels similar to those seen in women as they age. Scientists believe that these hormone levels are dependent upon the number of eggs remaining in a woman’s ovaries. This early finding must be repeated with larger numbers of mothers. Still, it suggests that the maternal age effect may be tied to the declining number of eggs in a woman’s ovaries over time. It also suggests that, in order to understand the maternal age effect, we must examine the impact of changing hormone levels on meiosis, the chromosome dance. Of course, like most scientific research, what we have found provides more questions than answers, but, thanks to all of our participants, we may be closer to understanding the maternal age effect than ever before. We enter the new millennium with optimism and excitement!

Our thanks to R. Dwain Blackston & Dorothy Pettay

The Emory University Down Syndrome Study wishes to recognize the efforts of two members of the medical and scientific community who have done so much to advance the progress of our research: R. Dwain Blackston, MD, our medical consultant, and Dorothy Pettay, the former director of our laboratory. A plaque has been created for each of these individuals with the following inscription:

“The Emory University Down Syndrome Study hereby expresses appreciation in recognition of contributions of time and self to Down syndrome research.”

Both Dr. Blackston and Ms. Pettay have been instrumental in the continued success of our project, and we are grateful for their services.
Is Down syndrome an inherited disorder?

Many new parents learn that the most common kind of Down syndrome (DS), called free trisomy 21, involves the presence of an extra copy of the number 21 chromosome in each of the child’s cells. As mentioned in the previous article, our chromosomes are normally present in 23 numbered pairs (for a total of 46), with each pair containing a chromosome contributed by mother and a complementary chromosome contributed by father. Sometimes an extra copy of one of the chromosomes is present, and in the case of DS, it is the number 21 chromosome that is present in three copies. The extra copy is sometimes the mother’s, and sometimes the father’s. However, it would be incorrect to say that the child who has DS inherited the syndrome from one parent or the other.

What is behind this distinction? Parents of children with free trisomy 21 do not have any extra genetic material. They have 46 chromosome and all are structurally normal. The child’s extra copy of chromosome 21 is not something that was passed from generation to generation in the family. This explains why most families who have a child with DS tell us that there is little or no history of DS in their families. Rather, the extra chromosome originated during the formation of an egg in the mother or a sperm in the father.

An example of an inherited disorder: sickle cell anemia

A well-known example of a genetic condition that is inherited in a simple way from one generation to the next is sickle cell anemia. The basis for this disease is a mutation, or chemical change, in a specific gene, one of the 100,000 genes present in humans. In this case, this gene is found on chromosome 16. If an individual has two mutated copies of the gene, meaning that he or she received one mutated copy from mother and one from father, then the individual will have sickle cell anemia. If the individual has two normal copies of the gene, then he or she will not have sickle cell anemia. If the individual has a mutated copy of the gene received from one parent and a normal copy of the gene received from the other, then he or she will be considered a carrier. A carrier is someone who does not have the disease but may pass a mutated copy of the gene to one or more children.

Trisomy: not a mutation, but extra normal genetic material

Trisomy 21 Down syndrome works very differently. It is not caused by a mutation in a gene, but rather by the presence of an extra amount of normal genetic material. It is most correctly referred to as a chromosome abnormality rather than a genetic condition. The process of egg and sperm formation requires the chromosomes to go through the complex “dance” we mentioned before. They duplicate once and divide twice so that each egg or sperm will contain 23 chromosomes (the half set). Errors can occur at different points in this process, resulting in a mature egg or sperm with one too many copies of chromosome 21, so that when the egg and sperm come together at fertilization, the child also has this extra chromosome. The figure shows an example of an error in the egg. This error in chromosome division happens only rarely in eggs or sperm. This explains why a family may have one child with DS and others without DS. So again, Down syndrome is a chromosome abnormality that does not happen by inheritance.

Both father and mother have the usual number of chromosomes, including 2 copies of chromosome 21. Here we show only chromosome 21.

The father’s sperm have 1 copy of each pair of chromosomes, including chromosome 21.

The mother’s eggs have 1 copy of each pair of chromosomes, including chromosome 21.

Occasionally, an egg or sperm is formed with an extra copy of chromosome 21.

This example shows the extra chromosome originating in the egg.

Union of this egg with a normal sperm leads to a child with three copies of chromosome 21 - Down syndrome.
The journey ahead: thoughts from Dr. Stephanie Sherman, principal investigator.

As we pause to take a breath before starting the next exciting research project, we want to give a big thanks to all of you who have made this work possible. We completely depend on your efforts in these studies. We are committed to doing the best research on Down syndrome that we can. We want to make sure that your work will count in moving us closer to understanding Down syndrome and its associated birth defects, such as heart abnormalities.

As you have read through our newsletter, you may have picked up on a recurring “theme”: our gains in understanding Down syndrome are measured in inches, not miles. Although this is sometimes frustrating to parents and to us, we have to remind ourselves that we are very complex “organisms” and each of us lives within a unique environment that changes over time. So it makes sense that it is going to take a long time, many approaches, and persistence to find out how all this works together.

We are very hopeful that, soon, we may start measuring our gains in feet instead of inches! New resources, new approaches, new ways of communicating between scientists and physicians are here and more are coming. The Human Genome Project is just one of the many new resources. Its goal is to discover the sequence all of our genes—that is, to find the order of the “alphabet” that determines the blueprint of our bodies. This should be finished by 2003! This is several years earlier than originally thought because of the rapid progress in technology. You can find out more about this project at http://www.ornl.gov/TechResources/Human_Genome.

We are committed to doing the best research on Down syndrome that we possibly can.

What will this bring us? If computer technology can keep up with processing the huge amount of data, we will be able to identify all the genes that play a role in development of the egg or the sperm, or all the genes that are involved in heart development. With the new approaches that are being developed, we will be able to alter these genes in systems that mimic those in humans to see what happens. These model systems include things you sometimes find in your kitchen—yeast (for you bread or beer makers), fruit flies (for you who like ripe fruit) and mice (for you who don’t have cats around!). Once we identify the important genes, we can go on to see how the environment may affect the action of those genes. Granted, this is still very complicated, but it will open up doors that may have the answers behind them!

Our project is only one of many that will use these new resources and help all of us better understand our development and progression through life. This will be an exciting time and, hopefully, will help us appreciate our similarities and celebrate our differences!

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