Emerging New Treatments for Down Syndrome

Jeannie Visootsak, MD

Individuals with Down syndrome have an increased life span as a result of advances in medical and surgical interventions; however, treatments for cognition and memory problems have not kept up with this pace.

Emerging data from mouse models suggest that a number of potential drug therapies may help improve behavior and memory in individuals with Down syndrome. Scientists at Stanford University published a study in 2007 entitled “Pharmacotherapy for Cognitive Impairment in a Mouse Model of Down Syndrome”. The researchers studied Ts65Dn mice, an animal model of Down syndrome, which have extra chromosome 21 material, and a learning profile similar to individuals with Down syndrome. They wanted to see what effect a certain drug (called a GABA antagonist) would have on Ts65Dn mice. The Ts65Dn mice given the GABA antagonist drug developed normal learning behavior after 17 days. The researchers proposed that if the neurons of children with Down syndrome are similar to those in the Ts65Dn mice, then it may be possible to use a GABA blocking drug to improve learning in children with Down syndrome. This finding has paved the way for human trials to assess some of these potential therapies.

So, how do we translate laboratory animal studies to human trials? Clinical trials involving new drugs are classified into preclinical research and four phases. The drug development process proceeds through all four phases over many years. The path to drug approval includes 1) Preclinical research - does it work in animals? Once this phase is completed, the researchers inform the FDA by applying for an Investigational New Drug Application so that it may be tested in humans; 2) Phase I - Is it safe in humans both with and without the condition; 3) Phase II - Does the drug help humans and is it safe?; 4) Phase III – Does the drug help more than drugs already on the market. These studies have to be large to get a good understanding of the drug’s effectiveness, benefits, and adverse reactions. Phase III includes many patients and may last for many years; 5) Phase IV occurs after FDA approval, to monitor the drug’s long-term efficacy in a large population, and help further refine the safety information.

A Phase II clinical study sponsored by Roche Pharmaceuticals is now underway at ten academic centers across the United States. It is designed to assess the effectiveness of the GABA antagonist drug called R05186582 on learning, attention, memory, language, and adaptive (self-help) skills in 230 adults with Down syndrome. Improving these skills may potentially lead to better functioning and greater independence.

Emory University is one of the sites to conduct this clinical trial in adults 18 to 30 years with Down syndrome. If you are interested in learning more about the study and/or would like to participate, please call Jeannie Visootsak, MD at (404) 778-8590.
Introducing our new DS clinic coordinator

The Emory Down Syndrome Clinic is excited to introduce our new Clinic Coordinator and Certified Genetic Counselor, Kimmie Lewis, MS, CGC. She is originally from Cincinnati, Ohio and moved to Atlanta a little over a year ago. Kimmie will be sharing the Clinic Coordinator position with Meagan Smith, MS, CGC.

Kimmie earned her Master’s degree in Medical Genetics from University of Cincinnati/Cincinnati Children’s Hospital Medical Center Genetic Counseling Program in Cincinnati, Ohio.

Kimmie was previously working as a public health cancer genetic counselor on a CDC funded grant to improve the identification of young women at genetic risk for breast cancer and ovarian cancer. Prior to moving to Georgia, Kimmie worked for Cincinnati Children’s Hospital Medical Center as a Clinical Research Coordinator, where she coordinated multiple research studies within the Division of Behavioral and Community Pediatrics.

In her new role at Emory, Kimmie will be responsible for providing genetic counseling for families of newly diagnosed patients. She will also be available to answer questions or discuss any other needs that may arise. She is also looking forward to participating in the Down Syndrome of Association Atlanta social and community activities. You may contact her at 404-778-8484 or at Kimberly.M.Lewis@emory.edu.

Behind the Scenes

I grew up in China and graduated from Central South University. After graduate school, I was invited to join a research project in the US. That was the beginning of my research career in the US.

About 14 years ago, I joined Dr. Sherman’s team to explore a new field for me - human genetic disorders. Mostly, we focus on two human genetic syndromes: Down syndrome and Fragile X syndrome.

My kids often ask me: “Dad, what are you doing?” After I explain what I do, they will say “can you help them?” Right now, we definitely can tell the kids, we are getting close to that goal. That is the most exciting thing for me to work here everyday.
Within the collaborative Down Syndrome Heart Defects Project, we are continuing research to learn why many children with Down syndrome (DS) also have heart defects. We are focusing on a serious heart defect, atrioventricular septal defect (AVSD, sometimes called “hole in the heart”). This defect occurs in 1 in 5 children with Down syndrome.

All cells in our body have an instruction manual written in long strings of a molecule called DNA. The DNA is organized into 23 chromosomes. Each person inherits two sets of this DNA-encoded instruction manual: one from each parent for a total of 46 chromosomes. The 46 chromosomes together are called our genome—it’s the master instruction manual. A person with three copies of chromosome 21 has 47 total chromosomes and has DS. Cells using a genome instruction manual with three copies of chromosome 21 do not perform all functions in the typical way. This results in the features we see in DS. Having three copies of this chromosome is also known as copy number variation.

Copy number variation (CNV) happens not only on the scale of an entire chromosome, but also on a smaller scale affecting only small regions of DNA. In the general population, some regions of DNA are present in 0, 1, 2, 3 or even more copies in different people. CNVs are seen in all people. Some of these CNVs are part of normal variation while others cause medical or developmental problems.

We measured the number and location in the genome of CNVs in nearly 500 individuals with DS, half with AVSD and half without a heart defect. We asked if any of the CNVs are associated with AVSD. We found that children with AVSD had more large CNVs that are rare in the general population than those without a heart defect. We also saw evidence to suggest that these CNVs were more likely to cover regions of the genome important for cilia function.

Cilia are finger-like structures that stick out from cells. They help cells interact with each other. AVSD occurs when the cells in a developing heart fail to move to the right position. So this result makes biological sense. If the cilia are not functioning correctly, the cells of the developing heart might not get the right signals to know where to go.

It is important to understand that these are very early findings. They do not represent a “smoking gun.” For example, they don’t define what causes AVSD in all children with DS. But these results do highlight the uniqueness of each of our genomes. Each person has variation in their instruction manual and it can be read in different ways to produce different results, in this case a heart defect.

We want to thank all of the families who have helped us with this important research. We are eager to follow up these findings by continuing to explore these results and more in additional families who are willing to participate.
DOWN SYNDROME STUDY UPDATE: COGNITION

Emory University is part of a nationwide study to understand the differences and similarities in learning abilities among individuals with Down syndrome. Its purpose is to understand more about how children with Down syndrome learn and problem solve. We are also gathering information about certain medical conditions related to Down syndrome to determine how they may affect learning abilities. Finally, we plan to collect DNA samples to identify genes that play a role in these learning pathways. The other sites participating in the study include: Johns Hopkins University and Kennedy Krieger Institute in Baltimore, MD; University of Arizona in Tucson, AZ; Children’s National Medical Center in Washington, D.C.; The Waisman Center at the University of Wisconsin-Madison, WI; Children’s Hospital of Philadelphia, PA; and the MIND Institute in Sacramento, CA.

We have currently enrolled 167 participants across all sites with 98 families completing the study. This large scale, multi-site project will have the power to identify factors, both genetic and environmental, that lead to the variation in cognitive functioning seen in individuals with Down syndrome. If we can understand the systems involved in cognition and the factors that play a critical role, we will have a better chance of developing evidence-based intervention programs. The funding for this project has been provided by the Down Syndrome Research and Treatment Foundation. We are grateful for their support.

Participants come to Emory or one of the other sites for one testing session that may last about two hours. Participants will be asked to complete various cognitive tests. Most tests will be done on a computer and are just like a computer game. Other tests will be given by a trained researcher. In these tests participants will be asked to point to pictures or draw. While their child is being tested, we will ask parents to complete some short written questionnaires regarding the everyday skills and behavior of their child. We will also need a small blood sample from all participants which can be arranged during a routine medically necessary blood draw. We would need to collect a small saliva sample from both parents if available. We will ask parents to sign a form that will give us permission to obtain medical records on participants to find out if he or she has any of the medical problems often seen in children with Down syndrome. If you are interested in considering enrolling your child in this study or have questions about the project, please contact:

Tracie Rosser
Phone: 404-778-8474
Email: trosser@emory.edu
Our research group led by Dr. Leonard Abbeduto at the University of California, Davis MIND Institute wants to thank all of the families who have supported our effort to expand our research on Down syndrome! We have had a very successful year! Last January, we held a “Minds behind the MIND” event for the local Down syndrome (DS) community during which parents and service providers had the opportunity to ask questions about DS to a panel of researchers, a local advocacy group leader, and an adult with DS. In June, we hosted Dr. Sue Buckley, an internationally recognized expert on education in DS, who spoke at an open-house for our local community. Currently, our research group has three active projects that are focused on DS:

**Expressive Language Sampling in Down Syndrome and Fragile X Syndrome**
We are currently recruiting individuals with DS or fragile X syndrome, ages 6-23, to enroll in this multi-site study. The aim of this study is to learn how samples of spoken language can be used to detect change over time in language, problem solving, and behavior in individuals with genetic syndromes such as DS. In future research, it may be possible to use these measures to show whether drugs or other interventions can help individuals with DS learn to use language more effectively. **Funding Source:** National Institute of Child Health and Human Development  
**Collaborators:** Emory University, University of Wisconsin-Madison, University of Arizona, Rush University

**Down Syndrome Phenotype Study**
We are part of the nationwide DS Cognition Project led by researchers at Johns Hopkins University and Emory University. Its main purpose is to find out how individuals with DS ages 11-25 learn and problem solve. Other goals include determining whether certain medical conditions affect how individuals with DS learn and identifying the genes that may play a role in this process. **Funding Source:** Down Syndrome Research and Treatment Foundation

**Implicit Learning and Language in Youth with Down Syndrome**
Led by our collaborators at the University of Alabama, this 5-year longitudinal study tracks how children, adolescents, and young adults with DS learn new language skills over a two-year period. We are in the final year of the project and are beginning to look at study results! **Funding Source:** National Institute of Child Health and Human Development.

We are in the process of writing proposals for new projects related to understanding language, learning, and behavior in DS. We would like to thank the many families who have taken the time to participate in our research studies. Without you, none of this would be possible! We look forward to another productive year as we gain knowledge and strive toward our ultimate goal of finding better ways to support individuals and families with DS and other neurodevelopmental disorders.

**For more information, please contact:**
Lauren Bullard, Project Coordinator  
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Our Latest publications

Abstract
PURPOSE: Advanced maternal age and altered recombination are known risk factors for Down syndrome cases due to maternal nondisjunction of chromosome 21, whereas the impact of other environmental and genetic factors is unclear. The aim of this study was to investigate an association between low maternal socioeconomic status and chromosome 21 nondisjunction.

METHODS: Data from 714 case and 977 control families were used to assess chromosome 21 meiosis I and meiosis II nondisjunction errors in the presence of three low socioeconomic status factors: (i) both parents had not completed high school, (ii) both maternal grandparents had not completed high school, and (iii) an annual household income of <$25,000. We applied logistic regression models and adjusted for covariates, including maternal age and race/ethnicity.

RESULTS: As compared with mothers of controls (n = 977), mothers with meiosis II chromosome 21 nondisjunction (n = 182) were more likely to have a history of one low socioeconomic status factor (odds ratio = 1.81; 95% confidence interval = 1.07 - 3.05) and ≥2 low socioeconomic status factors (odds ratio = 2.17; 95% confidence interval = 1.02 - 4.63). This association was driven primarily by having a low household income (odds ratio = 1.79; 95% confidence interval = 1.14 - 2.73). The same statistically significant association was not detected among maternal meiosis I errors (odds ratio = 1.31; 95% confidence interval = 0.81 - 2.10), in spite of having a larger sample size (n = 532).

CONCLUSION: We detected a significant association between low maternal socioeconomic status and meiosis II chromosome 21 nondisjunction. Further studies are warranted to explore which aspects of low maternal socioeconomic status, such as environmental exposures or poor nutrition, may account for these results.


SOURCE: Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia, USA. jhunte4@emory.edu

The Emory Down Syndrome Project, better known as EDSP, has been underway since 2005. Currently, there are over 1,000 families enrolled with 472 families who have completed the study. The purpose of this study is to learn more about what triggers the extra chromosome to move incorrectly during the formation of the egg or sperm. Additionally, we are trying to learn more about why some children with Down syndrome have more medical problems, such as heart and gastrointestinal defects, than others. Recruitment for this study is still ongoing. The funding for this project has been provided by the National Institute of Child Health and Human Development (NICHD).

Research cannot be successful without support from the medical community, intensive effort by researchers, and most importantly commitment of motivated families. We are extremely grateful for the ongoing involvement and willingness of families to take time out of their busy lives to participate in a research study that will someday benefit others. Thank you so much to all who have participated.
Evidence for dysregulation of genome-wide recombination in oocytes with nondisjoined chromosomes 21.


**SOURCE:** Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA.

**Abstract**

In oocytes with nondisjoined chromosomes 21 due to a meiosis I (MI) error, recombination is significantly reduced along chromosome 21; several lines of evidence indicate that this contributes to the nondisjunction event. A pilot study found evidence that these oocytes also have reduced recombination genome-wide when compared with controls. This suggests that factors that act globally may be contributing to the reduced recombination on chromosome 21, and hence, the nondisjunction event. To identify the source of these factors, we examined two levels of recombination count regulation in oocytes: (i) regulation at the maternal level that leads to correlation in genome-wide recombination across her oocytes and (ii) regulation at the oocyte level that leads to correlation in recombination count among the chromosomes of an oocyte. We sought to determine whether either of these properties was altered in oocytes with an MI error. As it relates to maternal regulation, we found that both oocytes with an MI error (N = 94) and their siblings (N = 64) had reduced recombination when compared with controls (N = 2723). At the oocyte level, we found that the correlation in recombination count among the chromosomes of an oocyte is reduced in oocytes with MI errors compared with that of their siblings or controls. These results suggest that regulation at the maternal level predisposes MI error oocytes to reduced levels of recombination, but additional oocyte-specific dysregulation contributes to the nondisjunction event.

**SOURCE:** Division of Cardiovascular Medicine and the Heart Research Center, Oregon Health & Science University, Portland, OR 97239, USA.

**Abstract**

About half of people with trisomy 21 have a congenital heart defect (CHD), whereas the remainder have a structurally normal heart, demonstrating that trisomy 21 is a significant risk factor but is not causal for abnormal heart development. Atrioventricular septal defects (AVSD) are the most commonly occurring heart defects in Down syndrome (DS), and ~65% of all AVSD is associated with DS. We used a candidate-gene approach among individuals with DS and complete AVSD (cases = 141) and DS with no CHD (controls = 141) to determine whether rare genetic variants in genes involved in atrioventricular valvuloseptal morphogenesis contribute to AVSD in this sensitized population. We found a significant excess (p < 0.0001) of variants predicted to be deleterious in cases compared to controls. At the most stringent level of filtering, we found potentially damaging variants in nearly 20% of cases but fewer than 3% of controls. The variants with the highest probability of being damaging in cases only were found in six genes: COL6A1, COL6A2, CRELD1, FBLN2, FRZB, and GATA5. Several of the case-specific variants were recurrent in unrelated individuals, occurring in 10% of cases studied. No variants with an equal probability of being damaging were found in controls, demonstrating a highly specific association with AVSD. Of note, all of these genes are in the VEGF-A pathway, even though the candidate genes analyzed in this study represented numerous biochemical and developmental pathways, suggesting that rare variants in the VEGF-A pathway might contribute to the genetic underpinnings of AVSD in humans.
Preconception folic acid supplementation and risk for chromosome 21 nondisjunction: a report from the National Down Syndrome Project.

Abstract
Both a lack of maternal folic acid supplementation and the presence of genetic variants that reduce enzyme activity in folate pathway genes have been linked to meiotic nondisjunction of chromosome 21; however, the findings in this area of research have been inconsistent. To better understand these inconsistencies, we asked whether maternal use of a folic acid-containing supplement before conception reduces risk for chromosome 21 nondisjunction. Using questionnaire data from the National Down Syndrome Project, a population-based case-control study, we compared the use of folic acid-containing supplements among mothers of infants with full trisomy 21 due to maternal nondisjunction (n = 702) and mothers of infants born with no major birth defects (n = 983). Using logistic regression, adjusting for maternal age, race/ethnicity, and infant age at maternal interview, we found no evidence of an association between lack of folic acid supplementation and maternal nondisjunction among all case mothers (OR = 1.16; 95% CI: 0.90-1.48). In analyses stratified by meiotic stage and maternal age (<35 or ≥35 years), we found an association among older mothers experiencing meiosis II nondisjunction errors (OR = 2.00; 95% CI: 1.08-3.71). These data suggest that lack of folic acid supplementation may be associated specifically with MII errors in the aging oocyte. If confirmed, these results could account for inconsistencies among previous studies, as each study sample may vary by maternal age structure and proportion of meiotic errors.
As we expand our current research programs across the United States, we are moving towards a more comprehensive view of Down syndrome. We have decided to combine the current heart and cognition studies into one overall project with anticipation of expansion into other areas of DS research. This new program is our DS-360 project! We hope to investigate Down syndrome from more of an all-inclusive perspective. We plan to launch the new logo at the National Down Syndrome Conference in Indianapolis this summer. Please stop by and visit our table. See you there!

Dr. Jeannie Visootsak presenting at the Day to Day Strategies for Down Syndrome conference at Emory University in October 2013.
The Emory Down Syndrome Center, established in 2003, includes education, research, and an important clinical component, the Down Syndrome Clinic. The primary goal of the clinic is to meet the needs of individuals with Down syndrome and their families. For those of you who are not familiar with our services, we’d like to give you an introduction and answer some of your questions.

What is the age limit?
While our long-range goal is to see individuals of any age who have Down syndrome, we currently have the following limits:

New Patients. Birth to age 14 years
Returning Patients. We have raised our age limit so that children who we first saw before age three years can continue to return to clinic after their third birthday.

How do I make a clinic appointment?
To make an appointment call Jean Luan, Clinic Coordinator, at 404-778-8619. Spanish-speaking families can call Elizabeth Sablon, our medical interpreter, at 404-778-8476. We think it is important that parents are the ones to make the appointment. The 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 who you trust to provide all the best general pediatric care and who will be available for those midnight earaches! Our clinic combines genetics and developmental pediatrics.

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 for another child with Down syndrome in the family.

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 evaluation, she discusses her findings with parents. She makes recommendations for the timing and frequency of early interventional therapy (physical, occupational, 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, educational consultation, and developmental evaluation, we suggest appropriate specialists/therapists 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 understanding of what the diagnosis means 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 new facility just off the Emory 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?
Jean Luan, Clinic Coordinator, will be glad to answer questions related to the clinic 404-778-8619.

All of us in the Down Syndrome Clinic thank the Down Syndrome Association of Atlanta for its continuing support. We couldn’t do it without them!

Visit us online:
http://genetics.emory.edu/DSC
DS-Connect™: THE NEW DOWN SYNDROME REGISTRY

**DS-Connect™:**
A new tool to define the needs of individuals with Down syndrome and to find solutions

After many years of talking about the need to create a Down Syndrome Registry, it has finally happened. The community of stakeholders has come together and formed DS-Connect™ (https://dsconnect.nih.gov/). This is the effort of many families, health and education professionals, researchers, businesses and Down syndrome societies.

The National Institute of Child Health and Human Development (NICHD) took the lead once the Down Syndrome Consortium listed a registry as the highest priority. NICHD provided initial funds and their expertise. They got help from stakeholders and produced an excellent tool to allow people with DS and their families to share information and health history in a safe and confidential online database. The registry was launched in September of 2013. There are now over 1400 registrants. It is exciting to see the numbers of registrants grow!

Why do we need a registry? Let me describe the need for a registry from the viewpoint of research. First, information on the health and medical history of individuals with DS will pinpoint the gaps in our knowledge. Responses to surveys will identify the most pressing needs and show which problems should be addressed first. Second, this registry will connect researchers with families who want to hear about new research opportunities and potential clinical trials. That connection will be controlled by the registrant (“user”). The approved researcher will provided information about their study to each registrant. If the user is interested and wants to hear more, they will contact the researcher. This makes recruitment of study participants faster and less costly. Also, we expect that the registry will include a large pool of participants who are eligible for a project. This will help increase the value of each research study.

The registry is not only for research purposes. DS-Connect™ has many benefits in addition to moving research at a faster pace. Users will be able to create and edit their online profiles and share their profiles with other DS-Connect™ users. Users will be able to set reminders for medical care and other appointments and events. DS-Connect™ will also provide general information about Down syndrome. It will provide summary information from user responses to survey questions (never with names or personal identifiers).

The Emory Down Syndrome Center was honored to be part of the development of this registry. We are excited about its potential. We encourage each of the families with Down syndrome to go to the website and read more about DS-Connect™. We think you will be excited also and will want to join this community effort.

Important websites:
To learn more about DS-Connect™: https://dsconnect.nih.gov/
To learn more about the Down Syndrome Consortium: http://downsyndrome.nih.gov/Pages/default.aspx
To learn more about our ongoing research efforts that we will expand through DS-Connect™: http://genetics.emory.edu/DSC/
Emory Down Syndrome Project

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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 below). Our first goal is to discover how these errors occur and identify 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 intellectual disability, 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.

Si desea copia en español, por favor llame a la Sra. Elizabeth Sablon al 404-778-8476.

Both father and mother have 46 chromosomes or 23 pairs, including 2 copies of chromosome 21. Here we show only the pair of 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 forming in the egg.

Union of this egg with a normal sperm leads to a child with 3 copies of chromosome 21- trisomy 21 Down Syndrome.