Folate Helps to Reduce the Risk of Congenital Heart Defects in Down Syndrome

Folate is a nutrient we all need. It is essential for making and maintaining DNA, the blueprint for human cells. In the 1980’s, folate deficiency was recognized as a cause of brain and spinal cord birth defects (called neural tube defects). Deficiency of folate has also been associated with heart defects, urinary tract defects, and limb defects. The evidence that we need folate to stay healthy is so strong that folate has been added to United States food supply (check the ingredients in your breakfast cereal). It is recommended that all women who are pregnant or planning a pregnancy take a folate supplement.

Infants with Down syndrome (DS) have a high risk of being born with a heart defect. Since lack of folate has been associated with heart defects in general, we thought it was important to look at this risk factor among mothers whose child with DS had or did not have a heart defect. To do this, we asked mothers who participated in the National Down Syndrome Project (2001-2004) about their use of prenatal vitamins or other folate containing supplement during their pregnancy.

To learn as much as possible about folate use, we asked each mother when she started taking folate (starting before or during the pregnancy) and how much folate she took (once a day or less than once a day). Since the human heart is formed between 4 and 8 weeks of pregnancy, we needed to figure out if a woman was taking folate during this time period.

In total, we had information on over 1000 mothers of children with DS. About 40% were taking folate during the time period of heart developmental and 40% were not. Our first general finding was that mothers taking folate seemed to correlate with a lower risk of a heart defect in the infant with DS. Folate use does not prevent all heart defects, but any preventative measure that reduces the risk of heart defects is important.

Our second finding was specific to atrioventricular septal defects (AVSD, sometimes called a “hole in the heart”), a severe heart defect often seen in infants with DS. We found that folate supplementation seems to reduce the risk for AVSD in males, but not females, with DS. Combined with our previous finding that females with DS have a higher risk for AVSD than males with DS, these new results might explain some of this difference between sexes: the males with DS, not the females, seem to be protected from AVSDs when mothers take folate. This finding is important to help us understand how folate is working during heart development.

The take home message is that folate seems to offer some protection against heart defects in all infants, including those with DS. But folate is only part of the story. We are also looking at genes that help process the folate as well as other genes involved in heart development. Our studies will be important to help ensure that all babies born with DS have healthy hearts.

We plan to publish this work this year.
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 seven 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 Pat Olney, Clinic Coordinator, at 404-778-8484.

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, 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/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?** Pat Olney, Clinic Coordinator, will be glad to answer questions related to the clinic 404-778-8484, polney@emory.edu).

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!

Jeannie Visootsak, MD
Pat Olney, MS, CGC
Lillie Huddleston, M.Ed., Ed.S.
Helen Smith, BSN
Elizabeth Sablon, BSW
Neurodevelopmental Outcome of Children with Down Syndrome and Congenital Heart Defects

We are currently conducting a study to understand the neurodevelopmental outcome in children with Down syndrome, specifically the impact of heart problems on development. There have been studies on the neurodevelopmental outcome in typically-developing children who have congenital heart defects (CHD). However, almost no studies have examined the neurodevelopmental challenges experienced by children with Down syndrome and CHD.

About 50% of all individuals with Down syndrome have CHD. Of those congenital heart defects, atrioventricular septal defect (AVSD) is the most common. Routine echocardiogram screening of all newborns with Down syndrome has increased detection of CHD and is a contributing factor to the growing number of early survivors. Furthermore, rapid advancements in surgical procedures have also increased the survival of individuals with Down syndrome and CHD. Thus, as children with Down syndrome and AVSD increasingly survive cardiac surgery live longer, understanding their early developmental profiles (cognitive, motor, language, adaptive, and social) is critical in designing early interventions to maximize their potential.

Our study is the first to assess the very early developmental course in children with Down syndrome and AVSD compared to children with Down syndrome who do not have CHD. The study visit consists of physical examination, medical interview, and developmental assessment. We will evaluate the cognitive, motor, language, social, and adaptive profiles of children with Down syndrome and AVSD compared to age-matched Down syndrome children without CHD. Children must be between the ages of 2 – 4 months at study entry, and we will track their developmental progress for two years. Studying young children allows us to identify early problems that may lead to further delayed development.

For further information, please contact Dr. Jeannie Visootsak Jvisoot@emory.edu or (404) 778-8590.

Emory Down Syndrome Studies Update

The Department of Human Genetics at Emory University School of Medicine has been studying Down syndrome for twenty years. Previous studies include the Atlanta Down Syndrome Project which was from 1989 to 1999 and the National Down Syndrome Project which was from 2001 to 2005. Current studies include the Emory Down Syndrome Project and the Congenital Heart Defects Study.

The Emory Down Syndrome Project began in 2005 and is currently tracking over 300 families, with approximately 200 complete cases. The purpose of the study is to combine information from interview questions with laboratory data on the behavior of chromosomes to further understand what causes Down syndrome and its related medical problems. More specifically, why do some children with Down syndrome have more medical problems such as heart defects and gastrointestinal defects than others?

Another component of the Emory Down Syndrome Project is the Family Study which includes siblings and grandparents of children with Down syndrome. By studying many three-generation families, we will be able to learn more about how chromosomes behave and explore the importance of specific genes on chromosome 21, including how those genes affect heart development. To date, there are almost 150 families participating in the Family Study.

We are also recruiting children with Down syndrome to participate in an NIH funded study to identify genetic and environmental factors related to congenital heart disease (CHD) in Down syndrome. The goal is to understand why some children with Down syndrome have heart defects and others do not. This study is a collaborative effort between sites at the Kennedy Krieger Institute and Johns Hopkins University, both in Baltimore, MD, Emory University in Atlanta, GA, Oregon Health & Science University in Portland, OR., and Children’s National Medical Center in Washington, D.C. Findings from this project will help us to understand congenital heart defects in all children. We have enrolled almost 800 families since 2001.
Emory’s Down Syndrome Clinic Visits St. Croix

In 1993, six babies were born with Down syndrome in a small town on the island of St. Croix named Frederiksted. Fifteen years later, three of us from Emory University’s Down Syndrome Clinic had an opportunity to meet two of these children and their mothers still living on the island.

Just about a year ago, Rebecca “Becky” and her family visited our clinic in Atlanta and proposed the idea of a trip to their island to present an educational conference on Down syndrome. I would never have imagined that parents would raise the funds to make this trip possible.

Becky and several parents organized a “Buddy Walk”, solicited local hotel owners, as well as a rental car company, to help make this idea become a reality. After a journey of 1700 miles, the Emory University Down Syndrome Clinic staff, Jeannie Visootsak, Pat Olney, and Lillie Huddleston landed in St. Croix.

We were greeted by Becky, her family, Gladys and her one year old son at the airport. They escorted us to our hotel overlooking the harbor of Christiansted with beautiful beaches, excellent food and friendly staff.

The next day we presented seven lectures between the three of us. Dr. Visootsak spoke about development and behavior of children with Down syndrome, I spoke about genetics and growing into adulthood, and Lillie spoke about education, social development and sexuality. We wrapped the sessions up with a discussion of resources, or I might say lack thereof.

The islanders are resourceful people, but even the most assertive parents are frustrated with the lack of appropriate services to meet the needs of their children. In spite of federal laws that apply to education for children with disabilities, the islanders are isolated and often faced with teachers who lack the skills to teach them.

If a child needs specialized medical attention, for example an echocardiogram, those with the means travel to San Juan, Puerto Rico. The situation may be improving now that a group of cardiologists comes to the island a couple times a year to evaluate the children. But, there’s a cap on Medicaid if you don’t have private health insurance.

In spite of the lack of adequate services, these children are flourishing. They are integrated into their island culture and accepted. They have active social lives, accompany their parents everywhere, and grow to love and appreciate the beauty of their island.

The day after our lectures, we arranged a time to meet with parents informally, sort of like a parent support group. Their individual stories were just like a common thread that binds all families of children with Down syndrome; we listened with interest. Some of the mothers brought their children and we delighted in their enthusiasm and social personalities.

One of the 15 year old, Jordan, from the small town of Frederiksted was so engaging that we wanted to somehow sponsor a trip for him to come to the mainland! We also had the pleasure of meeting the senator of St. Croix. He encouraged us to live our life with a positive attitude.

After a couple of days of sightseeing, we sadly packed our bags for the long journey home. We will cherish the memories of our visit to St. Croix and remind ourselves of how life with children with Down syndrome ought to be.
New insights into human nondisjunction of chromosome 21 in oocytes.

Oliver TR, Feingold E, Yu K, Cheung V, Tinker S, Yadav-Shah M, Masse N, Sherman SL.

Abstract: Nondisjunction of chromosome 21 is the leading cause of Down syndrome. Two risk factors for maternal nondisjunction of chromosome 21 are increased maternal age and altered recombination. In order to provide further insight on mechanisms underlying nondisjunction, we examined the association between these two well established risk factors for chromosome 21 nondisjunction. In our approach, short tandem repeat markers along chromosome 21 were genotyped in DNA collected from individuals with free trisomy 21 and their parents. This information was used to determine the origin of the nondisjunction error and the maternal recombination profile. We analyzed 615 maternal meiosis I and 253 maternal meiosis II cases stratified by maternal age. The examination of meiosis II errors, the first of its type, suggests that the presence of a single exchange within the pericentromeric region of 21q interacts with maternal age-related risk factors. This observation could be explained in two general ways: 1) a pericentromeric exchange initiates or exacerbates the susceptibility to maternal age risk factors or 2) a pericentromeric exchange protects the bivalent against age-related risk factors allowing proper segregation of homologues at meiosis I, but not segregation of sisters at meiosis II. In contrast, analysis of maternal meiosis I errors indicates that a single telomeric exchange imposes the same risk for nondisjunction, irrespective of the age of the oocyte. Our results emphasize the fact that human nondisjunction is a multifactorial trait that must be dissected into its component parts to identify specific associated risk factors.

Ethnicity, sex, and the incidence of congenital heart defects: a report from the National Down Syndrome Project.


Abstract: PURPOSE: The population-based National Down Syndrome Project combined epidemiological and molecular methods to study congenital heart defects in Down syndrome. METHODS: Between 2000 and 2004, six sites collected DNA, clinical, and epidemiological information on parents and infants. We used logistic regression to examine factors associated with the most common Down syndrome-associated heart defects. RESULTS: Of 1469 eligible infants, major cardiac defects were present in 44%; atrioventricular septal defect (39%), secundum atrial septal defect (42%), ventricular septal defect (43%), and tetralogy of Fallot (6%). Atrioventricular septal defects showed the most significant sex and ethnic differences with twice as many affected females (odds ratio, 1.93; 95% confidence interval, 1.40-2.67) and, compared with whites, twice as many blacks (odds ratio, 2.06; 95% confidence interval, 1.32-3.21) and half as many Hispanics (odds ratio, 0.48; 95% confidence interval, 0.30-0.77). No associations were found with origin of the nondisjunction error or with the presence of gastrointestinal defects. CONCLUSIONS: Sex and ethnic differences exist for atrioventricular septal defects in Down syndrome. Identification of genetic and environmental risk factors associated with these differences is essential to our understanding of the etiology of congenital heart defects.
Smarter Clustering Methods for SNP Genotype Calling
Lin Y, Tseng G, Cheong SY, Bean LJ, Sherman SL, Feingold E.

Abstract: MOTIVATION: Most genotyping technologies for single nucleotide polymorphism (SNP) markers use standard clustering methods to "call" the SNP genotypes. These methods are not always optimal in distinguishing the genotype clusters of a SNP because they do not take advantage of specific features of the genotype calling problem. In particular, when family data are available, pedigree information is ignored. Furthermore, prior information about the distribution of the measurements for each cluster can be used to choose an appropriate model-based clustering method and can significantly improve the genotype calls. One special genotyping problem that has never been discussed in the literature is that of genotyping of trisomic individuals, such as individuals with Down syndrome. Calling trisomic genotypes is a more complicated problem, and the addition of external information becomes very important. RESULTS: In this article, we discuss the impact of incorporating external information into clustering algorithms to call the genotypes for both disomic and trisomic data. We also propose two new methods to call genotypes using family data. One is a modification of the K-means method and uses the pedigree information by updating all members of a family together. The other is a likelihood-based method that combines the Gaussian or beta mixture model with pedigree information. We compare the performance of these two methods and some other existing methods using simulation studies. We also compare the performance of these methods on a real dataset generated by the Illumina platform (www.illumina.com). AVAILABILITY: The R code for the family-based genotype calling methods (SNPCaller) is available to be downloaded from the following website: http://watson.hgen.pitt.edu/register.

A novel procedure for genotyping of single nucleotide polymorphisms in trisomy with genomic DNA and the invader assay.
Duffy KJ, Littrell J, Locke A, Sherman SL, Olivier M.

Abstract: Individuals with trisomy 21 display complex phenotypes with differing degrees of severity. Numerous reliable methods have been established to diagnose the initial trisomy in these patients, but the identification and characterization of the genetic basis of the phenotypic variation in individuals with trisomy remains challenging. To date, methods that can accurately determine genotypes in trisomic DNA samples are expensive, require specialized equipment and complicated analyses. Here we report proof-of-concept results for an Invader(R) assay-based genotyping procedure that can determine SNP genotypes in trisomic genomic DNA samples in a simple and cost-effective manner. The procedure requires only two experimental steps: a real-time measurement of the fluorescent Invader(R) signal and analysis with a specifically designed clustering algorithm. The approach was tested using genomic DNA samples from 23 individuals with trisomy 21, and results were compared to genotypes previously determined with pyrosequencing. Additional assays for 15 SNPs were tested in a set of 21 DNA samples to assess assay performance. Our method successfully identified the correct SNP genotypes for the trisomic genomic DNA samples tested, and thus provides an alternative to determine SNP genotypes in trisomic DNA samples for subsequent association studies in patients with Down syndrome and other trisomies.
Congenital gastrointestinal defects in Down syndrome: a report from the Atlanta and National Down Syndrome Projects.
Freeman SB, Torfs CP, Romitti PA, Royle MH, Druschel C, Hobbs CA, Sherman SL.

Abstract: We report Down syndrome (DS)-associated congenital gastrointestinal (GI) defects identified during a 15 year, population-based study of the etiology and phenotypic consequences of trisomy 21. Between 1989 and 2004, six sites collected DNA, clinical and epidemiological information on live-born infants with standard trisomy 21 and their parents. We used chi-squared test and logistic regression to explore relationships between congenital GI defects and infant sex, race, maternal age, origin of the extra chromosome 21, and presence of a congenital heart defect. Congenital GI defects were present in 6.7% of 1892 eligible infants in this large, ethnically diverse, population-based study of DS. Defects included esophageal atresia/tracheoesophageal fistula (0.4%), pyloric stenosis (0.3%), duodenal stenosis/atresia (3.9%), Hirschsprung disease (0.8%), and anal stenosis/atresia (1.0%). We found no statistically significant associations between these defects and the factors examined. Although not significant, esophageal atresia was observed more often in infants of younger mothers and Hispanics, Hirschsprung disease was more frequent in males and in infants of younger mothers and blacks, and anal stenosis/atresia was found more often among females and Asians.

Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects.
Allen EG, Freeman SB, Druschel C, Hobbs CA, O'Leary LA, Romitti PA, Royle MH, Torfs CP, Sherman SL.

Abstract: We examined the association between maternal age and chromosome 21 nondisjunction by origin of the meiotic error. We analyzed data from two population-based, case-control studies: Atlanta Down Syndrome Project (1989-1999) and National Down Syndrome Project (2001-2004). Cases were live born infants with trisomy 21 and controls were infants without trisomy 21 delivered in the same geographical regions. We enrolled 1,215 of 1,881 eligible case families and 1,375 of 2,293 controls. We report four primary findings. First, the significant association between advanced maternal age and chromosome 21 nondisjunction was restricted to meiotic errors in the egg; the association was not observed in sperm or in post-zygotic mitotic errors. Second, advanced maternal age was significantly associated with both meiosis I (MI) and meiosis II (MII). For example, compared to mothers of controls, mothers of infants with trisomy 21 due to MI nondisjunction were 8.5 times more likely to be >/=40 years old than 20-24 years old at the birth of the index case (95% CI = 5.6-12.9). Where nondisjunction occurred in MII, mothers were 15.1 times more likely to be >/=40 years (95% CI = 8.4-27.3). Third, the ratio of MI to MII errors differed by maternal age. The ratio was lower among women <19 years of age and those >/=40 years (2.1, 2.3, respectively) and higher in the middle age group (3.6). Lastly, we found no effect of grand-maternal age on the risk for maternal nondisjunction. This study emphasizes the complex association between advanced maternal age and nondisjunction of chromosome 21 during oogenesis.
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.

Occasionally, an egg or sperm is formed with an extra copy of chromosome 21. This example shows the extra chromosome forming in the egg.

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 an normal sperm leads to a child with 3 copies of chromosome 21 - trisomy 21 Down syndrome.

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 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.