GENETICS CENTER:
Experts in Genetics...Specialists in Caring.

February 2009

A publication of
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GENETICS Update

Inside this issue:

Genetics Center provides a full range of genetic services, including clinical genetics, genetic counseling, laboratory services, and fluorescence in situ hybridization (FISH). We have on-site cytogenetics and molecular genetics laboratories. Genetics Center is a state-approved comprehensive prenatal diagnosis center. Genetics Center is recognized by the Children's Oncology Group (COG) as an approved laboratory. We publish this periodic newsletter, *Genetics Update*, as a service to our referring physicians, the healthcare community at large, and our patients. We appreciate your inquiries.

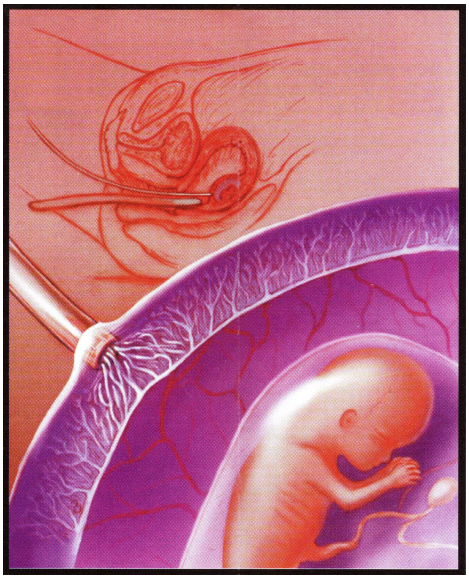
Chorionic Villus Sampling

Genetics Center Offers CVS Testing for Identification of Fetal Chromosome Abnormalities

The Genetics Center team has been performing chorionic villus sampling (CVS) routinely since July 1988. We are the pioneers of the procedure in Orange County and were the first center on the West Coast to perform CVS on a triplet pregnancy.

CVS is a diagnostic test performed during the first trimester of pregnancy for identification of fetal chromosome abnormalities. The indications for CVS referral include most of those for which amniocentesis would be offered: advanced maternal age, previous pregnancy with chromosome abnormality, and risk for a prenatally identifiable genetic disorder. There are some disorders (such as collagen abnormalities) for which prenatal diagnosis can only be performed via CVS. Furthermore, a woman may choose to pursue a CVS due to First Trimester Screening results showing her to be at increased risk for a chromosome abnormality.

For patients considering CVS, certain prerequisites must be completed by 8-9 weeks of pregnancy.



Chorionic villus sampling is a diagnostic test that can detect many problems early in pregnancy

Cervical cultures should be obtained and tested for *chlamydia* and *gonococcus* to rule out a preexisting vaginal infection. Also, an ultrasound evaluation is performed to locate the developing placenta and to date the pregnancy.

CVS can be performed by one of two methods, and the placental location determines which method is appropriate. In the transcervical approach, a catheter is introduced through the vagina and cervix and guided via ultrasound to the early placenta. A small sample of chorionic villi is then aspirated into a media-filled syringe. CVS can also be performed via transdominal approach, where a needle is placed through the patient's abdomen and uterine wall and directed to the placenta. After either method, the villi are cultured in the laboratory for chromosome analysis. If further testing is required, DNA extracted from the villi can be analyzed for a known familial mutation.

There are several reasons for selecting CVS over amniocentesis. CVS can be performed 10-12 weeks into the pregnancy (with results available at 12-15 weeks), as opposed to 15-18 weeks for an amniocentesis (with results available at 17-

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20 weeks). Unlike amniocentesis, chorionic villus sampling allows for a preliminary chromosome result (referred to as the "direct prep") in 1-2 days. While not considered a final, definitive analysis, it is a good predictor of the final cultured result. Earlier knowledge that no abnormalities were detected can bring greater peace of mind to the patient. However, if a patient decides to discontinue the pregnancy, first trimester pregnancy terminations can be safer, more easily performed, and less emotionally difficult than second trimester terminations.

Once a woman is into the second trimester of her pregnancy, CVS is no longer an option and amniocentesis should be considered. Amniocentesis may be more useful to parents who have a family history of neural tube defects, because alphafetoprotein (AFP) testing can be done on amniotic fluid but cannot be done on CVS specimens. For women who have had CVS, follow-up ultrasound evaluation of fetal anatomy and maternal serum AFP screening for neural tube defects is recommended at 16-18 weeks of pregnancy.

As with any invasive prenatal diagnosis procedure, CVS does have an associated risk for complications. When performed by a skilled practitioner, the overall risk is equivalent to that of amniocentesis. Moreover, most miscarriages occur early in pregnancy regardless of whether any invasive testing has been performed. After the procedure, it is important for the OB/GYN to follow the patient closely to ensure that no infection develops.

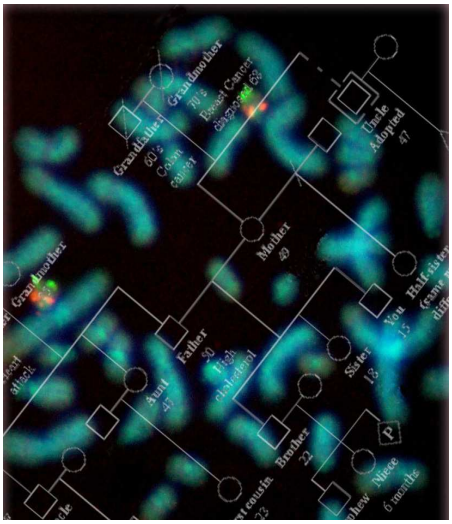
When a patient is referred for genetic counseling and is early enough in her pregnancy for diagnostic testing, CVS is presented to her as an option along with other options, such as amniocentesis. In the near future, we will also be able to perform microarray analysis on the chorionic villius sample, to detect a greater range of anomalies. CVS is a good choice for microarray analysis because DNA/RNA extraction is much easier from chorionic villi compared to an amniotic fluid specimen. Furthermore, microarray analysis of CVS can be performed at an earlier stage of pregnancy compared to the amniocentesis. For further information, please feel free to contact us.

Genetic Counseling and Cancer

The Benefit of Genetic Counseling in the Treatment of Cancer

Cancer affects nearly one-third of the U.S. population and accounts for about twenty percent of all deaths in this country. All cancers are genetic, resulting from the disruption of the normal genetic regulatory mechanisms of cell growth and proliferation. However, only 15 percent of cancer cases involve inherited factors. Those who have inherited a germline mutation in a tumor suppressor gene have a higher risk of developing cancer compared to the general population. For example, two genes known to be involved in hereditary breast and ovarian cancers are BRCA1 and BRCA2. Either parent can pass on these mutations, and this can increase an individual's risk for cancer over his or her lifetime. Based on this information, an individual may decide to take preventative measures, such as medication or prophylactic surgery.

Factors that would raise suspicion of a possible tumor suppressor mutation include unusually early age of onset of cancer, cancer affecting both of paired organs (such as the breasts, kidneys, or ovaries), and multiple affected family members with related types of cancers. The finding of a mutation in a cancer-related



Genetic counseling can help patients understand their genetic risk status and management strategies

gene does not automatically mean one will develop cancer, but it is an indication of an increased lifetime risk. Persons at increased risk may benefit from more frequent surveillance (such as mammography or colonoscopy), adoption of a healthier lifestyle, and avoidance of environmental risk factors. Additionally, those found to have inherited factors can inform relatives about their increased risk and the options that may be available to them.

Many individuals have been introduced to topics in cancer genetics through the media. This exposure may lead patients to be concerned about their family history of cancer and to seek genetic counseling to discuss these concerns. Genetic counseling regarding cancer involves obtaining a detailed personal and family history about cancer, risk assessment and explaining cancer risk figures, exploring options for genetic testing, discussing methods for early detection and possible prevention, and providing support. Apart from the benefits of prevention and early treatment, counseling may reassure patients if their cancer risk is found to be less than what the person had anticipated. Patients may also gain satisfaction from having a chance to talk to someone about their cancer concerns.

There are tests available for many specific genes known to be associated with an increased risk for cancer. If a family history can be established, then testing a family member affected with the cancer of concern maximizes the chance of identifying a mutation that can be used to screen other family members

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at risk. For instance, if a mutation associated with inherited risk is detected in the affected family member, then other family members may be tested for the presence or absence of the same mutation. However, if no mutation is found in the affected individual, then testing for an inherited basis of the cancer in unaffected family members is not possible.

Genetics Center has on-site cytogenetic and molecular genetic laboratories that can assist in the risk assessment and genetic testing. Working with a select group of cancer professionals, geneticists, and genetic counselors, the Genetics Center is able to provide not only genetic testing when appropriate, but also provide pre-test and post-test support services that are vital in case management.

Autism and Genetics

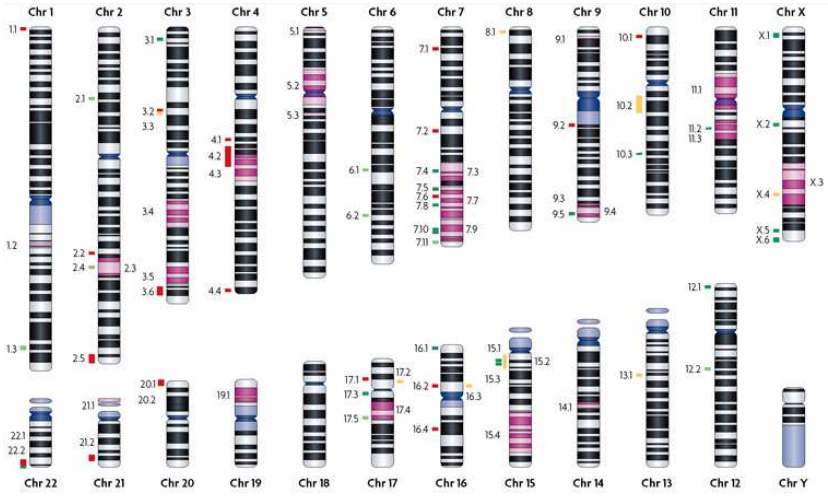
Current Perspectives on the Link between Autistic Disorder and Genetics

Autistic spectrum disorders (ASDs) are a group of developmental disabilities characterized by a lack of social interaction, impairments in communication, and repetitive and stereotypic behaviors. Autistic disorder, or autism, is the most common type of ASD, but there are other clinically defined conditions, including pervasive developmental disorder and Asperger syndrome.

By definition, autism develops prior to the age of three years. Fifty to seventy percent of autistic children are defined as having cognitive delay. About 25% of children who fit the diagnostic criteria for autism at age two or three subsequently begin to talk and communicate and blend in with the regular population by six or seven years. The remainder continue to have a lifelong disability requiring intensive support.

Early normal or near-normal nonverbal IQ is the best predictor of adequate functioning by grade school. Seizures develop in approximately 25% of children with autism. Approximately 24% of autistic individuals have macrocephaly (head circumference above the 98th percentile), while 15.1% have microcephaly (head circumference below the 3rd percentile).

According to the Centers for Disease Control and Prevention, the prevalence rate for autistic spectrum disorders is as high as 1 in 166 children. For families with one autistic child, the risk of having another child with autism rises to approximately 10 percent. Twin studies show that the concordance of autism among identical twins is as high as 98 percent. These numbers suggest that genetic factors are largely responsible for the occurrence of autism related disorders. During the past decade, scientists have made significant breakthroughs in understanding the genetics of autism. Researchers are now seeing evidence for the existence of autism-related genes on specific chromosomal regions.



Loci implicated in ASD etiology. Red and yellow bars correspond to de novo losses and gains, respectively, that are observed in ASD cases but not in controls. Green bars correspond to genes that are observed to modulate autistic spectrum disorder (ASD) risk.

Approximately 3% of individuals with autism have a maternally inherited chromosomal duplication in the Prader-Willi syndrome/Angelman syndrome region of 15q11-q13. This duplication can be detected by routine cytogenetic studies or interphase FISH analysis of the SNRPN gene. An additional 3-5% of individuals with autism have other chromosome abnormalities, including apparently balanced and unbalanced translocations, inversions, rings, interstitial deletions and duplications, and marker chromosomes. These abnormalities support a current study about a significantly higher frequency of copy number variation (CNV) found in children with ASDs. Furthermore, in early 2008, it was found that deletions and duplications at chromosome 16p11.2 and a deletion on chromosome 22 are associated with ASD. These latest research results also demonstrate the vital role of CNVs in the pathogenesis of ASDs.

Although it may not be possible to locate a single 'autism gene,' Genetics Center offers genetic testing that can determine whether a child has an inherited disorder or genetic syndrome associated with autistic behavior. Routine chromosome analysis can detect many abnormalities; however, high-resolution chromosome studies and subtelomeric FISH will detect most of the chromosomal anomalies which may attribute to CNVs associated with ASDs. Also, DNA microarray analysis is recommended for some patients. In particular, molecular genetic testing can be performed for fragile X syndrome, as at least half of children with fragile X syndrome have autistic behaviors. Testing for other conditions can be arranged based on a patient's features. Please feel free to contact us for additional information.

CHRONOLOGY

of selected milestones in genetics / and our Genetics Center's history

1980: The Human Genome Project is proposed.

1986: Genetics Center opens its doors offering clinical genetics, cytogenetics, genetic counseling, and amniocentesis.

1987: Genetics Center is approved by the State of California as a Comprehensive Prenatal Diagnosis Center (PDC).

1988: Genetics Center is the first in Orange County to offer chorionic villus sampling (CVS) for first trimester prenatal diagnosis.

1989: The gene for cystic fibrosis is identified by researchers at Toronto's Hospital for Sick Children and University of Michigan.

1993: Discovery of the gene for Huntington disease, an adult onset neurological disease.

1994: Genetics Center laboratory begins performing amniotic fluid AFP analysis.

1995: Genes that account for the majority of hereditary breast cancers are identified.

Genetics Center offers fluorescence in situ hybridization (FISH).

1998: Genetics Center establishes a molecular genetics laboratory.

2000: Working draft of the entire human genome sequence was announced in June 2000, with analyses published in February 2001.

2001: Genetics Center moves into our new facilities at 211 S. Main St. in Orange.

Genetics Center received Outstanding Orange Business award.

FDA approves Gleevec©/imatnib, a genetics-based drug to treat CML.

2002: Genetics Center continues to grow with additional services offered such as:
- ACOG recommended cystic fibrosis testing
- Factor V Leiden testing

Genetics Center upgraded its computer facility to a web-based computer system and integrated electronic karyotyped documentation. This is a major step toward paperless operation and HIPAA compliance.

2003: Genetics Center started offering Connexin 26 testing for detecting a form of genetic deafness.

Completion of the Human Genome Project.

2004: Genetics Center started offering a Thrombotic Panel test for venous thrombosis and other various risk factors.

2005: Genetics Center was recognized by Childrens Oncology Group (COG) as an approved laboratory.

Completion of HapMap Project; a database of human variation useful for identification of genes associated with common diseases such as diabetes

Genetics Center started offering prenatal aneuploidy FISH analysis for trisomies 13, 18, 21, and sex chromosome aneuploidy.

2006: Genetics Center started offering genetic testing to establish optimal warfarin dosage for cardiovascular disease.

National Cancer Institute and National Institutes of Health started The Cancer Genome Atlas Project to identify the genes associated with various forms of cancer.

2007: Genetics Center started offering JAK2 testing for diagnosing myeloproliferative disorders.

2008: The Genetic Information Nondisclosure Act (GINA), designed to prohibit improper use of genetic information in health insurance and employment, is signed into federal law.

For referrals and laboratory services please contact us at:

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We are celebrating our 23rd year as a provider of a full-range of genetic services, from hospital consults and genetic counseling to cytogenetic and molecular genetic laboratory testing.

We are grateful to all of the people who have supported us and have made our 23 years of success possible.

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