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

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GENETICS UPDATE **December 2011**
*A publication of **GENE**TICS CENTER*

25+ Years
of Services

INSIDE THIS ISSUE:

Genetics Center provides a full range of genetic services, such as clinical genetics, genetic counseling, and laboratory services. We have CAP accredited on-site cytogenetics and molecular genetics laboratories, including fluorescence in situ hybridization (FISH), microarray, and sequencing. Genetics Center is a state-approved and contracted 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 association and inquires.

Genetics Center Celebrates a *Quarter Century* of Service

Providing Human Genetics Services Since 1986

Genetics Center is pleased to observe its ***25th year*** of serving the healthcare community. The field of genetics has significantly evolved over the past 25 years. Genetics Center has also advanced with consistant and substantial growth since our doors opened in 1986.

The most recent highlights include the addition of a second medical geneticist (Neda Zadeh, M.D.), as well as a multitude of additional Ph.D. scientists who have received their educations from our best institutions in southern California, including Caltech and UCLA.

We have also physically expanded our operation (which is now our third expansion over the past 10 years), have become a CAP accredited laboratory, and have continuously added to and improved our diagnostic test menu that includes 180k array comparative genomic hybridization (microarray analysis), spinal muscular atrophy carrier screening, connexin 26 targeted mutation analysis, connexin 26 full gene sequencing, connexin 30 targeted deletion testing, and cystic fibrosis full gene sequencing.

Genetics Center at 211 S. Main St In Orange

Comprehensive Genetics Services

Our 25th anniversary coincides with the completion of construction of an additional 3,000 square feet for our laboratory and clinical facilities. Our aim is to continuously provide exceptional service to our patients, their families, and our referring physicians and business partners. Our commitment to quality and excellence has been constant and reliable over the past 25 years. (Please see the items highlighted in blue on page 4 for Genetics Center's full chronology.)

Throughout the years, we have maintained and increased our ability to meet all your needs for comprehensive, high-quality, and personalized genetic services at the Genetics Center. We wish to thank you for your continued support and look forward to a long and prosperous association. Our goal is to remain the "*Experts in Genetics and Specialists in Caring*."

Genetic Hearing Loss

Genetics Center now offering the latest in molecular testing for common causes of genetic hearing loss

Genetic hearing loss is a relatively common occurrence in the population that affects all ethnic groups. It is estimated that 2 out of 1000 children under the age of 3 years and 4 out of 1000 children under the age of 19 years are hearing impaired. Identifying the cause of hearing loss early in life is important to determine appropriate medical management and to provide accurate genetic counseling.

Hearing loss is classified into several categories according to different parameters. Of individuals with congenital hearing loss, 35% have genetic hearing loss, 35% have acquired hearing loss, and the remaining 30% have hearing loss due to unknown/unidentifiable causes. The category of genetic hearing loss can be further subdivided into "syndromic hearing loss" and "nonsyndromic hearing loss." Seventy percent of children with genetic hearing loss have the nonsyndromic form of hearing loss, in which deafness is not associated with any other medical issues or birth defects.

Fifty percent of individuals with autosomal recessive nonsyndromic hearing loss have involvement of the *GJB2* (connexin 26) and *GJB6* (connexin 30) nuclear genes. Mutations in *GJB2* and/or *GJB6* are associated with mild to profound hearing impairment that is present at birth. Affected individuals will have two mutations in either the *GJB2* or *GJB6* genes, or one mutation in each gene. Individuals with one mutation in the *GJB2* gene and another mutation in the *GJB6* gene are called compound heterozygotes. Individuals with only one mutation in either the *GJB2* or *GJB6* gene are considered to be carriers.

To date, more than 80 causative mutations have been reported in the *GJB2* gene; however, a common frameshift mutation (35delC) is seen in more than 90% of the European Caucasian population. In the Ashkenazi Jewish population, another mutation (167delT) is more commonly observed. In the *GJB6* gene, the most commonly observed mutations are in the form of two deletions (D13S1830 and D13S1854). Targeted mutation testing of *GJB2* and *GJB6,* as well as sequence analysis of the *GJB2* gene, is now offered by the Genetics Center.

Genetic hearing loss can also be inherited through changes in mitochondrial genes. Mutations in two mitochondrial genes are commonly associated with nonsyndromic hearing loss: *MT-RNR1* and *MT-TS1*. Furthermore, mutations in *MT-RNR1* can be associated with a predisposition to develop profound bilateral hearing loss after exposure to an aminoglycoside antibiotic. Mitochondrial genes are inherited only from the mother. Thus, if a mother has a mutation in a mitochondrial gene that is known to cause hearing loss, the chance to have a child with hearing loss may be as high as 100%. Genetics Center offers sequence analysis of select mitochondrial regions that include the *MT-RNR1* and *MT-TS1* genes.

We are pleased to announce the availability of the **Genetics Center Hearing Loss Panel**. This comprehensive panel provides the latest in molecular genetic testing for the common causes of nonsyndromic hearing loss. The Genetics Center is also able to provide clinical genetic evaluations and genetic counseling for individuals with hearing loss, or for prospective parents with a family history of hearing loss. Genetics Center is a CLIA approved and CAP accredited laboratory. For further information, please feel free to contact our center.

Genetics Center Hearing Loss Panel

The following tests are offered as a comprehensive panel or can be performed as individual tests:

- Targeted mutation analysis of the *GJB2* gene (Connexin 26).
- Sequence analysis of the *GJB2* gene (Connexin 26).
- Targeted mutation analysis of the *GJB6* gene (Connexin 30).
- Sequence analysis of the *MT-RNR1* and *MT-TS1* mitochondrial genes.

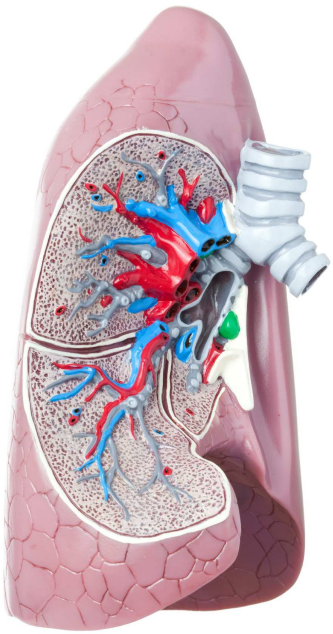
Cystic Fibrosis

Genetics Center offers CFTR full gene sequencing for Cystic Fibrosis

Cystic fibrosis (CF) is one of the most common autosomal recessive conditions in the Caucasian population (1:3200 live births) with lower incidences in other populations (1:15,000 in African-Americans and 1:31,000 in Asian Americans). This condition is caused by defective electrolyte and chloride ion transport in the apical membrane of specialized epithelial cells present in the respiratory tract, exocrine pancreas, intestine, hepatobiliary system, sweat glands, and male genital tract. Thus, individuals with cystic fibrosis have characteristic findings of thick, viscous mucus that affects the function of multiple organ systems as listed above.

Chronic sinopulmonary disease is commonly observed in most individuals with CF, with frequent symptoms of shortness of breath, persistent coughing, and recurrent respiratory illness. Pancreatic function can be compromised, as digestive enzyme production may be suboptimal resulting in poor growth and difficulty gaining weight. There are now a variety of modern treatments to better manage pulmonary and pancreatic symptoms; however, early diagnosis of cystic fibrosis is essential in providing the most accurate and adequate medical management.

Current modern treatments have transformed CF from a once devastating childhood disease to a manageable illness, where affected individuals may have a life expectancy beyond the fourth decade. The most recent treatment modalities for CF involve management of the long-term effects of the disease, with a focus on preventing and treating lung infections. Patients have regular monitoring of their respiratory health and take care to avoid dust, smoke, and



other lung irritants, as well as dehydration. Individuals with pancreatic insufficiency are given enzyme supplements and special dietary formulas.

The diagnosis of CF can be performed at multiple levels. In children over the age of four months, two positive sweat chloride tests (qualitative pilocarpine iontophoresis) is one approach. With the presence of two positive sweat tests in an older child, or if presented with a newborn infant with a suspected diagnosis of CF, molecular genetic testing is recommended.

The Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene located on chromosome 7q31.2 is the only gene known to be associated with cystic fibrosis. The Genetics Center is offering two testing methods for analysis of the *CFTR* gene. The first test is a targeted mutation assay to screen for 42 of the most common mutations, including the 23 alleles recommended by the American College of Medical Genetics (ACMG). This assay has a mutation detection rate of up to 97% of the mutations in Ashkenazi Jewish populations and 90% in non-Jewish Caucasians. The second method involves *CFTR* full gene sequence analysis, which improves detection to 98% of all mutations reported in the medical and scientific literature. Full gene sequencing is quite valuable in detecting private mutations not screened for in the targeted assay.

Sequencing at the Genetics Center is currently performed via the Sanger method. This method generates truncated copies of the sequence of interest, each copy ending with a fluorescent label specific to the nucleotide at that position (i.e. A, T, G or C). These products are then size-sorted by running them through capillary electrophoresis, which allows us to determine the order of nucleotides in the sequence. Mutations are easily and reliably detectable by this method. Full gene sequence analysis involves the entire coding region of the *CFTR* gene, including splice sites, 5' and 3' untranslated regions and two intronic regions where pathogenic mutations have been previously identified. Sequences are then analyzed by our team of Ph.D. scientists and clinical & molecular geneticists with access to the current CF literature and databases. Genetics Center is a CLIA approved and CAP accredited laboratory. For further information, please feel free to contact our center.

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 is 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 receives Outstanding Orange Business award.

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

2002: Genetics Center offers additional services such as:
- ACOG recommended cystic fibrosis testing
- Factor V Leiden testing

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

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

Completion of the Human Genome Project.

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

Genetics Center is approved by the California DHS-LFS as a training program for clinical cytogeneticist scientists.

2005: Genetics Center is 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 starts offering prenatal aneuploidy FISH analysis for trisomies 13, 18, 21, and sex chromosome aneuploidy.

2006: National Cancer Institute and National Institutes of Health starts The Cancer Genome Atlas Project to identify the genes associated with various forms of cancer.

2007: Genetics Center starts 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.

2009: The State of California launches its new Prenatal Screening Program, which includes 1st trimester screening.

Genetics Center becomes a CAP accredited laboratory.

2010: Discovery of the MLL2 gene associated with Kabuki syndrome, a congenital cognitive impairment syndrome.

Genetics Center starts offering 180k Array CGH (microarray) testing for postnatal, prenatal, and products of conception.

Genetics Center is approved by the California DHS-LFS as a training program for clinical genetic molecular biologist scientists.

2011: Genetics Center adds a 2nd medical geneticist to its team.

Genetics Center starts offering Spinal Muscular Atrophy Carrier Screening.

Genetics Center starts offering an enhanced hearing panel (Connexin 26 and 30 targeted mutation analysis & Connexin 26 sequencing, and sequencing of the MT-RNR1 and MT-TS1 genes).

Genetics Center starts offering full gene sequencing for Cystic Fibrosis.

Genetics Center completes its 3rd physical expansion.

We are grateful to all of the people who have supported us and have made possible our 25th year as a provider of a full-range of genetics services.

CAP ACCREDITED™

GENETICS CENTER 25th ANNIVERSARY 1986 2011 ORANGE, CA

For referrals and laboratory services, please contact us at:

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