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

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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.

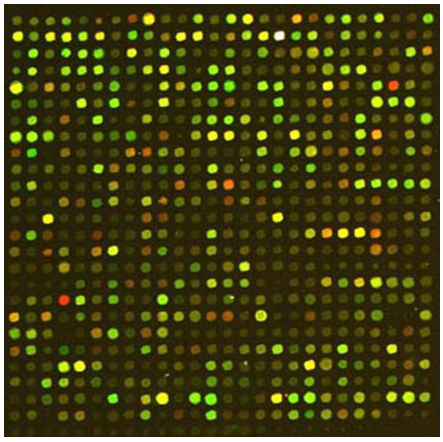
DNA Microarray: Detecting Chromosomal Abnormality through CGH

Genetics Center now offers comparative genomic hybridization via microarray testing

DNA microarray analysis is a new technology that may improve diagnosis by examining thousands of genes at once. Microarrays consist of a glass or silicon chip containing thousands of DNA oligonucleotides with specific sequences of interest.

Such testing has several advantages when combined with conventional testing. For example, microarray testing can detect smaller imbalances than traditional karyotype or FISH analysis, which may have implications for genetic counseling. Furthermore, it can detect multiple microdeletions or duplications throughout the genome in a single test.

Currently, microarray analysis is used to detect the subtle gain or loss of genetic material in patients with developmental delay or mental retardation. Often, these patients are tested using conventional cytogenetics, and the results are usually negative. Microarray analysis allows a much deeper study of the chromosomes on a molecular level, which will give a greater chance of diagnosing a patient. This testing can be offered prenatally by way of amniocentesis or CVS when there is a known family history and increased risk of recurrence. Essentially, microarray analysis allows for a comprehensive survey of the entire patient genome. However, this information must be used with caution and not without genetic counseling for interpretation.



Example of microarray hybridization

All biological functions are regulated by proteins synthesized by messenger RNA (mRNA). If a particular gene is very active, it produces many molecules of mRNA from a DNA template. Because the mRNA is complementary, it will bind to the original portion of the DNA from which it was copied.

In order to detect the activity of a particular gene, fluorescent dye is introduced to a blood, prenatal, or tumor cell specimen. The dye binds to the mRNA, which then binds to a microarray containing the segments of complementary DNA (probes) of interest. Using a computer to measure the brightness of the fluorescent signals on the microarray, we can determine the activity of the gene and create a "gene expression profile."

Previously, scientists have classified cancers based on the organs in which tumors and leukemias have developed. Through CGH gene expression profiling, cancers may be further classified based on the patterns of gene activity in cancer cells.

DNA Microarray

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By examining the differences in gene activity between treated and untreated cells, scientists may understand how different therapies affect tumors and be able to develop more effective treatments.

Another important application of microarray analysis is comparative genomic hybridization (CGH). CGH is a molecular-cytogenetic method for the analysis of copy number changes (gains/losses), also known as copy number variants (CNVs), in the DNA content of tumor cells.

There are several limitations of CGH. CGH cannot detect abnormalities such as triploidy, nor can it pick up balanced translocations or inversions. Additionally, it is not easy to interpret arrays. CNVs are abundant in the cells of healthy individuals; therefore, CGH may detect CNVs that have no known clinical significance. Finally, microarray testing is more expensive and has a longer turnaround time than routine karyotyping.

Because of these limitations, microarray testing is generally offered after routine testing has been performed. For example, prenatal CGH testing may be performed if an amniocentesis detects an apparently balanced translocation. This is to determine if it is truly balanced. Other examples would be if a previous child has a diagnosis of chromosome abnormality by CGH, or if ultrasound abnormalities have been detected. If microarray analysis shows gain or loss of genetic material, FISH analysis may be performed on the amniocentesis to examine the chromosome structure in the affected area. Since CNVs may be benign, parental blood may be tested to see if they have the same CNV. If the parents have learning problems or minor dysmorphic features, then the CNV may not be benign. There are additional issues that might also arise in the future.

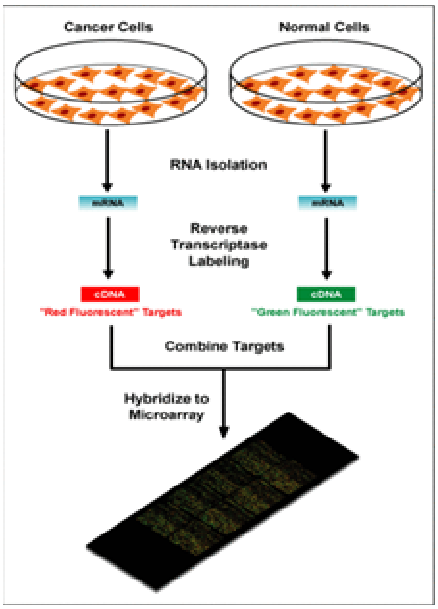

Diagram of dual-color microarray experiment

Genetic counseling may become more complex as not enough is known in terms of the benefits and limitations of this type of testing. There may be issues with compliance (i.e. obtaining paternal blood). Finally, it is unclear whether insurance will cover this relatively new technology.

Still, when provided in conjunction with routine karyotyping, microarray DNA analysis is a powerful tool that can detect a wide range of anomalies even when conventional testing shows a normal result. In the coming years, improvements in microarray technology will have a tremendous impact on the diagnosis and treatment of many genetic diseases.

Genetics Center is offering microarray DNA analysis. For further information, please feel free to contact us.

Fragile X DNA Screening

Detecting the most common inherited cause of mental impairment

Fragile X syndrome is the most common inherited cause of mental retardation and learning difficulties, affecting as many as 1 out of every 1,500 males and 1 out of every 2,500 females. One out of every 250 females has a mutation in the gene, FMR-1, that causes fragile X syndrome. The gene is inherited in an X-linked manner, and manifestation of the condition is extremely variable depending upon gender, mosaicism, methylation patterns, and other gene-gene interactions.

In addition to intellectual disability, fragile X syndrome is associated with behavioral characteristics such as aggression, mood liability (easily overstimulated, impulsive, or withdrawn), hand flapping and/or biting, autistic behaviors (poor eye contact, obsessive interests, or echolalia), and social anxiety. Physical characteristics include a long narrow face, large ears, high arched palate, post-pubertal enlargement of testes in males, hyper-extensible joints, and flat feet.

Fragile X syndrome is caused by an expansion of a single gene sequence (CGG repeats) in the FMR-1 gene on the X chromosome (Xq27.3) and results in a failure to express the FMR-1 protein. In the normal range (29-31 repeats), individuals do not have symptoms. In the gray zone (41-55 repeats), individuals do not have symptoms, but the repeats may occasionally expand into a full mutation in their offspring. In the premutation range (56-200 repeats), females are at risk to have a child with fragile X syndrome (because the repeats can expand from parent to child).

The carriers of a premutation usually do not have developmental disabilities themselves. However, females with premutations are at an increased risk for premature ovarian failure (POF), which is the cessation of menses before age 40 years. The risk of POF in those with premutations is ~21% compared to a 1% background risk in the general population. Female carriers of full mutations are not at an increased

Fragile X DNA

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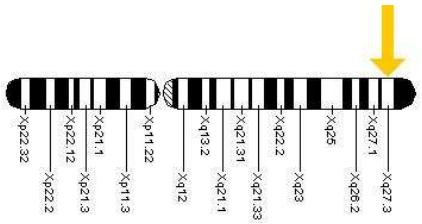
risk for POF.

Males with premutations are at risk for fragile X-associated tremor/ataxis syndrome (FXTAS), which is characterized by late-onset, progressive cerebellar ataxia and intention tremor. Other neurologic findings include short-term memory loss, executive function deficits, cognitive decline, parkinsonism, peripheral neuropathy, lower-limb proximal muscle weakness, and autonomic dysfunction. The penetrance of FXTAS is age related, with symptoms seen in 17% of males ages 50-59, 38% of males ages 60-69, 47% of males ages 70-79, and 75% of males over 80 years of age.

Males with a full mutation (>200 repeats) will have fragile X syndrome. Approximately 50% of females with a full mutation have characteristics of fragile X syndrome, due to the fact that females have only one active X chromosome in each cell. The more cells that have the full mutation in the active X, the more affected the female will be.



Location of the FMR1 gene on the X chromosome

Potential issues with fragile X syndrome screening are that it is difficult to predict future cognitive function in the fetus, the fact that 50% of female "carriers" may actually have the full mutation, the need to address possible premature ovarian failure in females that are carriers, the need to address FRAXTAS in male premutation carriers, and patient options during the pregnancy.

Fragile X syndrome carrier testing should be considered for any individual with, or having a family history of, an unexplained developmental delay or mental retardation. If a pregnant woman learns that she is at risk of having a child with fragile X syndrome early in her pregnancy, she will be able to make a more informed decision regarding her reproductive choices. This information may also allow parents more time to prepare themselves by learning about the syndrome and its consequences. Genetics Center's on-site laboratory is proud to offer DNA analysis for fragile X syndrome.

The Genetic Information Nondiscrimination Act (GINA)

Giving patients the security to proceed with genetic testing without fear of discrimination

The Genetic Information Nondiscrimination Act (GINA) was signed into law on May 21, 2008. GINA, which is similar to federal laws making race and gender discrimination illegal, is designed to prohibit improper use of genetic information in health insurance and employment. Insurers may not deny coverage or charge higher premiums based solely on genetic predisposition to disease. Employers will be prohibited from using genetic information to make hiring or firing decisions.

Prior to GINA, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 provided the first federal protections against genetic discrimination. The act prohibited health insurers from excluding individuals from group coverage and stated that genetic information in the absence of a current diagnosis of illness did not constitute a preexisting condition. GINA expands upon HIPAA by adding specific provisions relating to genetic privacy and nondiscrimination.

Fear of genetic discrimination is a major concern among patients considering predictive genetic testing. Patients can make more informed healthcare decisions if they know their risk of developing disease; however, they may choose not to undergo testing due to real or perceived economic consequences. When individuals decline predictive testing, they lose the opportunity for monitoring and preventative care that will benefit them in the long-term. Other patients may undergo testing, but choose to pay out-of-pocket for testing their insurance would otherwise cover.

Because genetic testing can be more specific than family history regarding the chances of inheriting disease, the opportunities for discrimination are much greater. GINA encourages patients to undergo genetic testing by alleviating the fear that results may be used against them by their employer or insurance company. This legislation is important not only for the health of individual patients, but also furthers genetic research and clinical practice. Linking gene variants to health outcomes requires studies of large numbers of people. GINA eases the fear from potential study participants that they may be discriminated against for providing this information. GINA also allows patients to be more comfortable having the results of genetic tests included in their medical records and to be able to share this information with other doctors or specialists.

Some states, such as California, have had varying protections in place for patient privacy and against discrimination. Like HIPAA, GINA is also a federal act that provides baseline protections across the country.

It is crucial that health care professionals understand and be able to communicate these new protections to their patients. The field of medical genetics is expanding rapidly and promises to revolutionize research and healthcare. GINA's protections are essential in giving patients the freedom to make informed decisions regarding their personal care and well-being.

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 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, signed into federal law.

For referrals and laboratory services please contact us at:

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We are celebrating our 22nd 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 22 years of success possible.

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