

The University of Chicago Genetic Services Laboratories



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CLIA #: 14D0917593 CAP #: 18827-49

Microdeletion/duplication Syndromes

FISH analysis is available for detection of small deletions and duplications responsible for a variety of disorders. The following is a list of the microdeletion and microduplication syndromes that we currently test for.

Clinical Features/Molecular Genetics:

Angelman syndrome (AS) occurs in approximately 1 in 12,000 to 1 in 20,000 live births. It is associated with severe mental retardation, gait ataxia, seizures and a happy disposition. Most individuals with AS do not develop speech. AS results from the absence of the maternal copy of the 15q11.2-q13 region by one of several mechanisms. Approximately 68% of patients have a deletion in this region that can be detected by FISH analysis. The recurrence risk for deletions is less than 1% [1]. In addition to FISH analysis for deletions of 15q11-q13, our laboratories offer methylation-specific PCR (M-PCR), polymorphic microsatellite analysis for UPD15, real-time quantitative PCR (RT-PCR) for imprinting center deletions, and *UBE3A* sequencing. We recommend M-PCR along with chromosome analysis to rule out chromosomal abnormalities, as the initial test for AS.

Autism is associated with impaired social behavior and communication skills, as well as stereotypic behaviors. It affects an estimated 1 in 500 live births. A maternally inherited duplication of 15q involving the *SNRPN* gene is responsible for autism in approximately 3% of cases [1]. These duplications can also be detected by chromosome analysis. Other abnormalities of 15q, including deletions, have been associated with autism as well [1].

CHARGE syndrome is characterized by coloboma, heart defects, choanal atresia, growth retardation, genital hypoplasia, and ear abnormalities. It occurs in approximately 1 in 10,000 to 1 in 15,000 live births and is caused by mutations or microdeletions in the *CHD7* gene at 8q12.1. Most cases of CHARGE syndrome are caused by *de novo* mutations or deletions of this gene [2]. Up to 10% of individuals with CHARGE syndrome have microdeletions that can be detected by FISH analysis [3]. We also offer mutation analysis by DHPLC and sequencing of the *CHD7* gene.

Cri-du-Chat syndrome is characterized by a cat-like cry, growth retardation, microcephaly, and mental retardation. The incidence is approximately 1 in 30,000 live births. Approximately 80% of individuals have a *de novo* deletion in the short arm of chromosome 5 [4]. Chromosome analysis detects these deletions in >95% of cases. FISH analysis is very accurate in identifying these deletions as well, and can be used alone or to supplement cytogenetic testing [5].

Lissencephaly is characterized by decreased or absent gyration in the brain, and is associated with mental retardation and epilepsy. Mutations or deletions in the *LIS1* gene at 17p13.3 cause approximately 60% of cases of isolated lissencephaly [6]. FISH analysis of *LIS1* detects deletions in approximately 40% of these patients [7]. We also offer sequencing of the *LIS1* gene to detect mutations in patients with isolated lissencephaly.

Miller-Dieker syndrome is caused by large deletions in 17p13.3, which disrupt *LIS1* and other contiguous genes. It is associated with dysmorphic facial features and severe lissencephaly, and other congenital anomalies such as cardiac and gastrointestinal defects can be present as well [8].

Prader-Willi syndrome (PWS) is characterized by hypotonia in infancy, obsessive eating that can lead to obesity and some degree of cognitive impairment. The incidence is approximately 1 in 10,000 to 1 in 25,000 live births. PWS is caused by the absence of the paternal copy of the region 15q11.2-q13 by one of several mechanisms. Approximately 70% of cases will have a deletion in this region that can be detected by FISH analysis. When a deletion is identified, the recurrence risk is less than 1% [1]. In addition to FISH analysis for deletions of 15q11-q13, our laboratories offer methylation-specific PCR (M-PCR), polymorphic microsatellite analysis for UPD15, and

real-time quantitative PCR (RT-PCR) for imprinting center deletions. We recommend M-PCR along with chromosome analysis to rule out chromosomal abnormalities, as the initial test for PWS.

Smith-Magenis syndrome (SMS) is associated with distinct facial features, mental retardation, sleep disturbances, and self-injurious behaviors. The incidence is approximately 1 in 20,000 live births. Approximately 90% of individuals with SMS have a *de novo* deletion in the short arm of chromosome 17, including the *RAI1* gene [1]. Our lab uses the commercially available SMS probe along with a probe containing the *RAI1* gene.

Sotos syndrome is an autosomal dominant condition that occurs in approximately 1 in 14,000 live births. It is associated with overgrowth of height and head circumference, characteristic facial features, advanced bone age, and cognitive impairment. Over 95% of cases of Sotos syndrome are *de novo* [1]. Mutations or deletions in the *NSD1* gene located at 5q35 have been identified in approximately 80% of individuals with a clinical diagnosis of Sotos syndrome. Deletions in *NSD1* can be detected by FISH analysis in approximately 50% of Japanese patients and 10% of non-Japanese patients [1]. We also offer mutation detection by DHPLC and sequencing of the *NSD1* gene.

SRY, or sex-determining region Y protein, is responsible for sex determination in males. It is associated with XX male syndrome, in which phenotypically male individuals have a 46,XX karyotype. This syndrome occurs in approximately 1 in 20,000 newborn males. Most cases are caused by a *de novo* translocation of genetic material, including the *SRY* gene, between the X and Y chromosomes [9]. *SRY* can be detected by FISH analysis in approximately 80% of individuals with this syndrome [1]. FISH analysis is also a reliable way to detect *SRY* in phenotypic females whose genotype is 46,XY.

22q duplication syndrome is a rare syndrome characterized by varying degrees of cognitive impairment and dysmorphic features. Velopharyngeal incompetence and urogenital anomalies may also be present. The phenotype is variable both between and within families. The majority of these duplications are *de novo*, although several cases of inherited 22q duplications have been reported. Few of these duplications can be detected by chromosome analysis, especially at lower resolutions. Interphase FISH analysis accurately detects duplications in the 22q11.2 region [10].

Velocardiofacial/DiGeorge syndrome (VCFS/DS) is associated with congenital heart disease (most commonly conotruncal defects), immunodeficiency, learning disabilities, palate abnormalities and dysmorphic features. The incidence is approximately 1 in 4,000 live births. VCFS/DS is caused by a deletion in the 22q11.2 region, which can be detected by FISH analysis in >95% of cases. Approximately 7% of deletions are inherited [1].

Williams syndrome (WBS) occurs in an estimated 1 in 20,000 live births. It is characterized by cardiac defects (usually supra-valvular aortic stenosis), some degree of mental retardation, distinctive facial features, and a sociable personality. Deletions in the elastin (*ELN*) gene at 7q11.2 are responsible for WBS and can be detected by FISH analysis in approximately 99% of cases. The majority of cases are *de novo*, and the recurrence risk for future pregnancies is <5% when the parents are unaffected [1].

Wolf-Hirschhorn syndrome (WHS) occurs in approximately 1 in 50,000 live births. It is characterized by growth retardation, "Greek helmet" facial features, and mental retardation. Individuals with this condition can also have seizures, cardiac and skeletal anomalies, and hearing loss. WHS is caused by deletion of 4p16, and approximately 75% of these deletions are *de novo*. Chromosome analysis detects approximately 60-70% of these deletions. FISH analysis can detect over 95% of these deletions [1].

XIST, or X-inactivation specific transcript, is responsible for X-inactivation in females. X-inactivation is normally a random event. In cases where a female has a structurally abnormal X chromosome (ring or marker chromosome), XIST is responsible for selective inactivation of the abnormal chromosome. If XIST is not present or the abnormal chromosome is not selectively inactivated, a more severe phenotype involving mental retardation and congenital anomalies can present [11].

Test methods:

We offer deletion and duplication analysis by FISH. Sample submission paperwork and instructions are included with this packet.

Deletion/duplication analysis (FISH)

Sample specifications:	3 to10 cc of blood in a green top (sodium heparin) tube
Cost:	\$325
CPT codes:	88230, 88271, 88291, 88273
Turn-around time:	10-12 days

Testing for a known deletion/duplication in additional family members

Sample specifications:	3 to10 cc of blood in a green top (sodium heparin) tube
Cost:	\$325
CPT codes:	88230, 88271, 88291, 88273
Turn-around time:	10-12 days

Prenatal testing for a known deletion/duplication

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	\$325
CPT codes:	88230, 88271, 88291, 88273
Turn-around time:	5-6 days

Results

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

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