Missed diagnosis: 22q11.2 deletion syndrome

July 1 2010

(PhysOrg.com) -- An article published in the June issue of the journal *Nature Reviews: Neuroscience* provides one of the first comprehensive overviews of the genetic, neural and cognitive bases of a frequently undiagnosed congenital disorder with an array of complex genetic, medical, neurological, behavioral and psychiatric features: the often baffling chromosome 22q11.2 deletion syndrome (22q11.2DS).

Those with 22q11.2DS can display a panoply of congenital heart and oral/palatal/facial defects, other medical problems, intellectual disabilities and psychiatric disorders, so it often is mistaken for other conditions, said Tony Simon, a professor of psychiatry and behavioral sciences at the UC Davis MIND Institute and an author of the article.

"There is such a huge variation in the manifestation of 22q11.2DS that few physicians recognize it for what it is," Simon said. "But it's important that doctors be more aware of it so children can receive early identification services and management for each of the problems that may develop."

The condition's name describes a location on the 22nd chromosome, where a tiny bit of genetic information is missing: a microdeletion. The submicroscopic loss of DNA affects expression of some 35 to 60 genes. While it can be inherited, the mutation usually arises spontaneously. It is diagnosed using a test called fluorescence in situ hybridization.

Among the first to encounter children with 22q11.2DS may be pediatric cardiologists, because many children with the disorder are born with

serious heart defects that require surgery at birth. Among these is tetralogy of Fallot, which occurs in nearly one quarter of people with 22q11.2DS. The defect, a complex of four heart malformations, is the most common cause of "blue baby" syndrome.

Abnormalities in the development of the palate and surrounding throat structures also are common in the disorder, as are facial abnormalities, learning disabilities, low calcium, thyroid and parathyroid levels, low muscle-tone and short stature. Immune-system abnormalities can make it dangerous for many affected children to receive certain live vaccinations.

Adding to the confusion about 22q11.2DS is its name. It also is known as DiGeorge syndrome, after the endocrinologist who first described four key features, and velocardiofacial syndrome, because of the heart/facial/oral/nasal cavity abnormalities. Other names for the condition that today are rarely used include Shprintzen syndrome, conotruncal anomaly face syndrome, Cayler craniofacial syndrome, congenital thymic aplasia and thymic hypoplasia. Today many professionals prefer the 22q11.2DS label, because it refers to the genetic lesion that occurs in most individuals given one of these diagnoses.

Those affected by 22q11.2DS have a significantly increased risk of developing schizophrenia. While most people with 22q11.2DS do not go on to develop the psychiatric disorder, schizophrenia does develop in approximately 25 to 30 percent of cases, but the reason is not well understood. It occurs in approximately 1 percent of the general population.

Children with 22q11.2 deletion syndrome generally have lower-than-average IQs, better verbal than nonverbal abilities and attention problems. They also may be diagnosed with autism or attention-deficit/hyperactivity disorder (ADHD). Some brain structures differ

between children with 22q11.2DS and typically developing children, and aberrant connectivity patterns or activity have been observed in different parts of the brain.

Recent research has focused on mice engineered to have genetic deletions similar to those found in humans. Mouse models vastly increase the potential for understanding the underlying genetic and neural bases of the condition, Simon said, and mouse-model research will accelerate understanding of the neural abnormalities involved in the cognitive impairments and in the development of schizophrenia in 22q11.2DS.

Simon is director of the MIND Institute's Cognitive Analysis and Brain Imaging Laboratory, whose mission is to investigate and examine neurodevelopmental disorders like 22q11.2DS. The laboratory also works closely with families of individuals with 22q11.2DS through its recently developed 22q11.2DS Translational Clinic, launched with support from the MIND Institute and the UC Davis Center of Excellence on Developmental Disabilities.

A major focus of the clinic is arming families with detailed neuropsychological and developmental and behavioral pediatric assessments to support their efforts to navigate the medical and education systems. By doing so, the laboratory team hopes to reduce some of the difficulties and frustrations of caring for children and adolescents with the condition.

"We are seeking to minimize learning difficulties and help reduce the stresses and anxiety that families who are caring for a loved one with 22q11.2 deletion syndrome may experience," Simon said. "We also are working to provide more education and support to help families advocate for services."

Simon's laboratory has produced several educational videos, including discussions of the medical issues present in 22q11.2DS, to help physicians understand the complex of symptoms that accompany the condition. The videos can be streamed on the laboratory's website, where DVDs also are offered for sale.

"The videos complement our research and give our lab a rich, holistic approach to the needs of individuals with 22q11.2DS. This is important because so few doctors, teachers and other professionals understand the problems associated with 22q11.2DS in children and how to respond to them appropriately," Simon said. "We're trying to reverse the situation where it is the parents of affected kids who are educating the providers."

Provided by UC Davis