GENETIC ANALYSES IN TWO EXTENDED FAMILIES WITH DELETION 22Q11 SYNDROME: IMPORTANCE OF EXTRACARDIAC MANIFESTATIONS

KERRY A. SHOONER, MS, ALAN F. ROPE, MD, ROBERT J. HOPKIN, MD, GREGOR U. ANDELFINGER, MD, AND D. WOODROW BENSON, MD, PHD

Objectives **Cardiovascular malformations (CVMs) are reported to be common (~75%) in patients with deletion 22q11.2 (del22q11) syndrome. To better understand why deletions go unrecognized, we characterized the phenotype in deleted individuals in two large kindreds with particular emphasis on the presence or absence of CVM.**

Study design **After the diagnosis of del22q11 in two unrelated probands with CVM, we sequentially evaluated family members with clinical evaluation and cytogenetic analysis.**

Results **Del22q11 was identified in 13 individuals; all exhibited characteristic dysmorphic facial features, but a CVM was present in only 6 of 13 (46%) individuals.**

Conclusions **We speculate that in the absence of CVM, diagnosis of del22q11 is hampered by a failure to recognize extracardiac features of the del22q11 syndrome spectrum. The data highlight the need for primary care physicians and specialists to familiarize themselves with the extracardiac stigmata of del22q11 to ensure timely diagnosis in all family members.** ***(J Pediatr 2005;146:382-7)***

The deletion 22q11.2 syndrome, which includes DiGeorge, Shprintzen, velocardiofacial syndrome, conotruncal anomaly face syndrome, and cardiac defects, abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia (CATCH-22), results from a submicroscopic deletion on chromosome 22q11.2 at the DiGeorge chromosomal region (DGCR).[1-5] The associated phenotype is variable, and more than 150 manifestations have been acknowledged by the advocacy group Velo-Cardio-Facial Syndrome Educational Foundation.[6] More common manifestations include palatal abnormalities; oromotor apraxia; growth retardation; cardiovascular malformations (CVMs); characteristic facies including tubular nose, hooded eyes, and small mouth; psychologic and cognitive disorders; and renal, skeletal, and immunologic manifestations.[7-9]

CVMs are common in patients with deletion 22q11 (del22q11) syndrome, and infant patients frequently come to medical attention because of symptoms of heart disease. In reviewing the three largest groups of patients reported to date (total n = 810) in which cardiac phenotypes were analyzed, the most common types of CVMs were tetralogy of Fallot (22% to 35%), interrupted aortic arch (15% to 19%), ventricular septal defect (13% to 18%), truncus arteriosus (7% to 12%), and vascular ring (5%).[10-12] Overall, CVMs have been reported to be present in approximately 75% of individuals with del22q11.[10-12] However, the prevalence is much lower in pediatric patients diagnosed after 6 months (38%) and in adult patients (~30%), suggesting that the prevalence figure of 75% probably is an overestimation caused by selecting sporadic cases presenting with CVM.[7,13-15]

Although approximately 90% of del22q11 cases are thought to occur sporadically, family occurrence has been well documented since the syndrome was first recognized in 1968.[16-22] In these reports, most familial occurrences are detected when an infant with overt features of the syndrome has del22q11, and, subsequently, a parent with less obvious clinical features is also tested and found to have the deletion.[12,23-25] If older children and adults in families with del22q11 were diagnosed earlier, families could benefit sooner from early intervention strategies, medical management options, and reproductive counseling.

We identified two large kindreds in which members with del22q11 were diagnosed only after an infant relative with a CVM was found to have the deletion. To better

CVM	Cardiovascular malformation	DGCR	DiGeorge chromosomal region
del22q11	Deletion on the long arm of chromosome 22 at band 11.2	FISH	Fluorescence in situ hybridization

From the Divisions of Cardiology and Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

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Reprint requests: Dr D. Woodrow Benson, Cardiology, ML 7042, Children's Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229-3039.

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understand why deletions went unrecognized in these large kindreds, we characterized the phenotype in deleted individuals, with particular emphasis on the presence or absence of CVM. Based on previous estimates, the prevalence of CVM in the families we studied was lower than expected. Underrecognition of the deletion in these families may have been a direct result of the failure to appreciate characteristic syndromic features other than CVM.

METHODS

Two families were identified through a proband with clinical suspicion of del22q11 and a fluorescence in situ hybridization (FISH) analysis confirming this diagnosis. Family history was recorded, and, per standard testing protocol, parents were tested by FISH. Once a parent was identified as having the deletion, informed consent for a research protocol was obtained from that person's first-degree relatives. Participating family members were sequentially evaluated with physical examinations, review of medical records, and cytogenetic testing. Individuals with del22q11 underwent cardiac evaluations. The study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center.

Assessment for Dysmorphic Features

All subjects (n = 17) were examined by a medical geneticist. The assessment for dysmorphic features consisted of examinations of the craniofacial and oral areas, eyes, ears, limbs, skeleton, and skin. Medical, educational, and social histories were also collected to uncover additional features of the syndrome.

Analysis for the 22q11.2 Deletion

FISH was used to evaluate the presence of a DGCR deletion in 17 subjects. FISH analysis was performed with the use of a standard protocol.[26] A patient's sample was considered to exhibit the deletion if the control probe labeled both homologs of chromosome 22, whereas the critical region probe only bound to one homolog.

Cardiac Evaluation

Cardiac evaluation, consisting of medical record review and physical examination, was performed by a cardiologist on all individuals having the deletion (n = 13), including probands and family members. All individuals having the deletion but no history of cardiac surgery underwent a standard complete transthoracic 2-D and Doppler echocardiogram, which evaluated the intracardiac anatomy and the laterality and branching pattern of the aortic arch.

RESULTS

Family 1

The proband of family 1 (III-1, Figure 1, *A*), a white male infant, 5 weeks old, was suspected to have del22q11 syndrome when he was also found to have thymic aplasia during surgery for malalignment-type ventricular septal defect. FISH analysis revealed del22q11. Both parents of the proband were noted to have learning problems. The mother additionally had dysmorphic facial features, speech difficulty, and a previous stillbirth at 36 weeks' gestation (III-2). Autopsy of the stillborn infant revealed a heart defect (partial atrioventricular canal defect); cytogenetic analysis of the stillborn infant was not performed. FISH analysis identified the proband's mother (II-2) as having the deletion. Photographs of the proband's mother at various ages from infancy to adulthood show salient dysmorphic facial features, even in early life (Figure 2). Subsequently, the mother's first-degree relatives were evaluated. Evaluation of additional family members identified dysmorphic features, major and minor anomalies, history of speech and learning problems, and del22q11 in the maternal grandmother (I-2) and maternal uncle (II-5). The age range of affected family members was 12 to 44 years. Cardiac examinations in family 1 identified one previously unknown cardiac diagnosis, bicuspid aortic valve (I-2, Figure 1, *A*). This diagnosis made the prevalence of heart disease in affected family members 2 of 4. The Table provides a summary of the clinical characteristics of family members with the deletion.

Family 2

The proband of family 2 (IV-2, Figure 1, *B*) is a white male infant who was diagnosed with interrupted aortic arch type B and thymic aplasia shortly after birth; FISH identified del22q11. His mother (III-6) exhibited dysmorphic facial features, had a history of speech problems, and had learning disabilities; she was found to have the deletion. During evaluation of 10 additional family members, 7 more individuals with del22q11 were identified (age range, 2 to 54), each with characteristic dysmorphic features. Of 9 members of family 2 with del22q11, 4 demonstrated CVMs. Three of these individuals had a history of cardiac surgery, for interrupted aortic arch type B and atrial septal defect (IV-2), tetralogy of Fallot (III-2), and aortic stenosis (status post–valve replacement) resulting from bicuspid aortic valve (II-3). Left aortic arch with aberrant right subclavian artery was identified in one individual (III-4). Clinical findings are summarized in the Table.

When both families 1 and 2 are included, an overall prevalence of CVM in unselected individuals is 6 of 13 (46%). When only those individuals with a history of cardiac surgery are considered, this prevalence falls to 4 of 13 (31%).

DISCUSSION

Despite characteristic dysmorphic facial features, affected members of the families we studied were not identified until the diagnosis of an infant with CVM requiring surgery. The findings in these families support the observations that previously undiagnosed older children and adult family members often exhibit mild manifestations.[13-15,17,18] To an experienced observer, the phenotype may be apparent in