Guidelines for 22q11 Deletion Screening of Patients With Conotruncal Defects

Goldmuntz et al. (1) have reported the frequency of 22q11 deletions in a prospectively ascertained sample of 251 patients with conotruncal defects. Deletions were found in 17.9% of the patients, including 50% with interrupted aortic arch (IAA), 34.3% with truncus arteriosus (TA), and 15.9% with tetralogy of Fallot (TOF). Although this study was designed to determine the frequency of deletions in patients recruited solely on the basis of cardiac findings independently from extracardiac features, the authors have recommended deletion screening of all patients with IAA, TA and TOF. Personal experience does not support these conclusions and rather suggests that general clinical evaluation, including extracardiac features, and the analysis of the anatomical subtypes of cardiac defects are mandatory for selecting patients undergoing 22q11 deletion testing. Following the first report of Goldmuntz et al. (2), who found 22q11 deletion in 29% of their patients with “non-syndromic” conotruncal defects, careful clinical evaluation of larger series of patients has shown that one or more additional features of 22q11 deletion syndrome, including characteristic or subtle facial dysmorphisms, palatal anomalies, absent thymus, T-lymphocyte deficit, hypocalcemia or developmental disabilities, occur in deleted patients with conotruncal defect (3–9). Interestingly, 80% of the patients with “isolated” conotruncal defects in the study of Goldmuntz et al. (2) had associated extracardiac symptoms. Other investigations have corroborated these results by showing that 22q11 deletion is virtually never found in nonsyndromic patients with conotruncal defects (3,10–14). In a personal series of 204 nonsyndromic patients with conotruncal defects, we detected only one deleted patient (12). Formerly, we have shown that “isolated” cleft palate, another feature of 22q11 deletion phenotype, is never associated with 22q11 monosomy (15).

It has been also shown that distinct subtypes of conotruncal defects are likely to be found in association with 22q11 deletion. For example, IAA type A and B are distinct defects, and only IAA type B is found in patients with 22q11 deletion (16,17). In addition, TA with major aortopulmonary collateral arteries, crossing pulmonary arteries and pulmonary ostial stenosis is often associated with 22q11 deletion (18). We disagree with the suggestion to perform large-scale screening of all TOF patients irrespective of their clinical phenotype (1). Tetralogy of Fallot is a heterogeneous defect, which can be either isolated or associated with genetic disorders or extracardiac malformation (3,19,20). We found 22q11 deletion in less than 10% of the patients with “classic” TOF (3,12,21), excluding children with TOF and pulmonary atresia, which are often related to 22q11 deletion (21–24). The occurrence of this deletion in one-third of our patients with TOF and pulmonary atresia has suggested the inclusion of this defect in the list of features related to 22q11 deficiency (21). Similarly, TOF with right aortic arch, absent infundibular septum and absent pulmonary valve must be included among the manifestations of 22q11 deletion syndrome (20,25).

No evidence is supporting, at present, that an early detection of 22q11 deletion predicts outcome in patients with conotruncal defects (26). Therefore, we favor 22q11 deletion testing only in patients in which heart defects are associated with “classic” or “subtle” clinical anomalies falling within the phenotypic spectrum of 22q11 deletion, and in those presenting with distinct anatomic conotruncal defect subtypes. The only conotruncal defect that “per se” deserves screening for 22q11 deletion, independently from clinical phenotype, the screening for 22q11 deletion is the IAA type B, which is related to this microdeletion in about 30%–80% of the cases (16,17).

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REFERENCES
It is clinically important to identify the patient with the 22q11 deletion in infancy for several reasons. First, the infant recognized to have the deletion is at risk for multiple extracardiac anomalies that warrant early detection and intervention. These include palatal abnormalities, feeding disorders, hypocalcemia, immune deficiencies, renal anomalies, and speech and learning disabilities (1,2). Many of these abnormalities are not apparent on examination alone but are only identified by specialized tests. Although all patients with congenital heart disease should be examined carefully for noncardiac features, infants with a 22q11 deletion are at risk for known anomalies that are best managed by early identification and intervention.

It is also important to identify the infant with a 22q11 deletion for family counseling purposes. Approximately 8% to 28% of cases are familial in origin. Most affected parents are not diagnosed as deletion positive until their child is diagnosed (2,3). The parent with a deletion carries a 50% chance of passing the deletion-bearing chromosome to additional offspring. Although one cannot predict the outcome for the fetus that inherits the deletion bearing chromosome, appropriate monitoring and counseling can be offered to the family because many affected infants have severe forms of heart disease that carry significant morbidity and mortality (1,2). Thus, screening neonates with specific cardiac defects and parental origin. Clin Genet 1998;53:63–9.

Many of these abnormalities are not apparent on examination alone

Additional studies are likely to answer this question more precisely. However, since identification of the syndromic infant is likely to depend upon the experience of the clinicians, careful monitoring for noncardiac features is recommended.