Holt-Oram Syndrome vs Heart-Hand Syndrome

To the Editor:
In a recent article, Brockhoff et al\(^1\) provide an elegant example of a patient affected by a heart-hand syndrome. Their findings also highlight the importance of modern cardiovascular genetics in clinical diagnosis. Although the patient presented certainly has both a cardiac septation defect and an upper limb deformity, recent DNA-based studies have demonstrated that the hand abnormalities shown would actually make a diagnosis of Holt-Oram syndrome unlikely.

Heart-hand syndromes are a broad category of disease, of which Holt-Oram syndrome is the most common form. Other heart-hand syndromes (reviewed in Reference 2) include Tabatznik’s syndrome and heart-hand syndrome type III. Holt-Oram syndromes (reviewed in Reference 2) include which Holt-Oram syndrome is the most common form. Other heart-hand syndromes, including the patient described by Brockhoff et al, may have primary upper limb malformation in the postaxial ulnar ray distribution and can even have a lower limb deformity. Our previous studies\(^2\) have demonstrated that the class of disorders referred to as heart-hand syndromes is genetically heterogeneous and that only Holt-Oram syndrome\(^4,5\) is due to mutations in the TBX5 transcription factor gene at human chromosome 12q24.1.

Although it would be technically feasible to screen DNA samples from Brockhoff et al’s patient for the TBX5 mutations that cause Holt-Oram syndrome, the absence of upper limb radial ray abnormalities suggests that such a search is unlikely to be fruitful. Diagnostic precision in heritable heart-hand syndromes is essential for the informed clinical evaluation of other family members who may be affected,\(^5\) and it is critical for the ongoing basic molecular genetic analyses of these disorders. We believe that TBX5 is only one member of a morphogenic pathway that is critical for cardiac development. It is likely that mutations in other members of this pathway account for a variety of other congenital heart and limb malformation syndromes. In the future, further genetic analyses of these heart-hand syndromes will elucidate a panoply of basic mechanisms underlying cardiac morphogenesis and clarify diagnostic and potentially therapeutic approaches to these congenital heart diseases.

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Response
We appreciate the comments of Dr Basson on our article, “Holt-Oram Syndrome.” The primary goal of our article was to enhance awareness in clinical cardiologists of the association between hand defects and congenital abnormalities of the heart. Remarkably, our patient had survived to her forties without being diagnosed with a congenital cardiac defect, despite her obviously hypoplastic ring fingers. Our secondary goal was to document a remarkable case of successful late correction of an atrial septal defect in the presence of marked pulmonary hypertension.

In cardiovascular textbooks, the term “Holt-Oram syndrome” is often used to describe atrial septal defects associated with upper limb deformities. This was the definition used in our article. We fully agree that for purposes of genetic counseling and research the stricter definition, as described by Basson et al\(^1–3\) should be used.

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