Atrial Fibrillation and Other Clinical Manifestations of Altered TBX5 Dosage in Typical Holt–Oram Syndrome

To the editor:

We were pleased to read the recent study in Circulation Research by Postma et al that describes an activation mutation in TBX5 that causes Holt–Oram syndrome. These exciting findings validate prior studies (reviewed elsewhere) showing that cytotypic abnormalities that produce TBX5 duplication (and presumed TBX5 overexpression) result in phenotypes that include Holt–Oram syndrome associated abnormalities. Moreover, we and others have previously demonstrated in experimental models that cell biological consequences of diminished and augmented Tbx5 expression are similar. In aggregate, these prior findings and the current data support a model in which Tbx5 dosage must be finely controlled to avoid cardiovascular pathology. The findings of Postma et al provide an important platform to dissect the mechanisms underlying such regulation.

However, we would like to provide clarity for clinicians evaluating patients with potential Holt–Oram diagnoses. We note potential misinterpretation of our prior reports that may have contributed to the conclusion by Postma et al that their family has “atypical” Holt–Oram syndrome. Classically, Holt–Oram syndrome findings do include grossly obvious absent or triphalangeal thumb. In fact, though, mild hypoplasia of the thenar bones or eminence or of any structure within the radial ray is more commonly the only evidence of Holt–Oram syndrome.

In some cases of typical Holt–Oram syndrome, delayed bone age by carpal bone assessment may be the only evidence of disease. Unfortunately, these subtle abnormalities are often initially overlooked, as in the initial clinical report of the family in the study by Postma et al. The relative paucity of cardiovascular manifestations in that family is also a common observation in families with TBX5 missense mutations. Such mutations regularly display a predominance of either skeletal or cardiac findings compared with families with haploinsufficient mutations, although predicting the organ preferences of a specific mutation remains controversial.

In addition, Holt–Oram syndrome patients frequently exhibit paroxysmal atrial fibrillation on ambulatory ECG recordings. Yet, despite the assertion by Postma et al that this is usually a consequence of abnormal hemodynamics in congenital heart defects, this is not our experience. Atrial fibrillation is a primary manifestation of Holt–Oram syndrome conduction disease, sometimes associated with progressive atrioventricular block, and frequently in the absence of overt congenital structural heart disease. Thus, the family reported here appears to have typical Holt–Oram syndrome that well meets the strict diagnostic criteria we previously proposed and validated. We caution clinicians against predicting specific classes of TBX5 mutations based on Holt–Oram syndrome phenotypes that exhibit marked inter- and intrafamilial variability. The presence of lone atrial fibrillation should not be used to predict activating versus inactivating TBX5 mutations. Moreover, we counsel clinicians and genetic investigators that meticulous physical and radiographic examinations of the hands and upper limbs are required elements of the Holt–Oram syndrome diagnostic evaluation, along with detailed cardiovascular imaging studies such as echocardiography, MRI, and/or CT, as well as resting and ambulatory electrocardiography.

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