# Correspondence

## Letter by Gourdie and Sedmera Regarding Article, "Abnormal Conduction and Morphology in the Atrioventricular Node of Mice With Atrioventricular Canal–Targeted Deletion of Alk3/Bmpr1a Receptor"

*To the Editor:*

A study by Stroud et al on a transgenic mouse (cGATA6-Cre/Alk3) in which a bone morphogenetic protein receptor had been conditionally deleted in the atrioventricular (AV) canal, reported a "dual" AV node in some of the mutants.[1] Interpretation focused on the hypothesis that disrupted bone morphogenetic protein signaling had prompted fibrosis, causing separation of the node into 2 components. This explanation follows from the group's earlier work on the LacZ-ccs mouse in which it was proposed that the AV conduction system (CS) develops from a single contiguous structure specified early in cardiac morphogenesis. However, an alternative hypothesis is worth consideration: namely, that the AV-CS may develop from independent modules that establish mature patterns of electrical linkage during cardiac development. The observed "dual" node could thus represent a failure of coupling between distinct AV-CS components.

What is the evidence? First, lineage analyses of clonally related myocytes in chick have demonstrated that terminal Purkinje fibers show closer lineage relationships to adjacent myocytes than to cells of the central CS.[2] On the basis of this finding, it was deduced that peripheral and central components of the CS differentiate independently and undergo linkage to form the mature and electrically continuous AV-CS. Further evidence for discontinuity in chick CS morphogenesis comes from a shift in ventricular activation from an anterior-basal to an apex-first origin identified by Watanabe, Rosenbaum and colleagues, a change accounted for by a switch to preferential conduction through the His-Purkinje system.[2] Interestingly, the anterior-basal origin identified as aberrant in cGATA6-Cre/Alk3 mice is normal in the rat heart at the looped-tube stage.[3]

Further evidence comes from other work in mice and rats. The histological location illustrated in Stroud et al[1] corresponds to a discrete transition in the rodent AV junction. Within this region, Coppen, Severs, and Gourdie described a sharp interfacial boundary within the node between a Cx45-expressing compartment and an anterior modular compartment expressing both Cx40 and Cx45.[2] Three-dimensional reconstruction studies in rat embryos by Aoyama and coworkers have demonstrated initially noncontiguous atrial and ventricular domains expressing HNK-1. Studies of mice with compound haploinsufficiency of Nkx2.5 and Tbx5 or id2 have identified segregated transcriptional programs for atrial-nodal and ventricular CS modules.[4] In the latter study, Moskowitz et al concluded that their results were consistent with modular fusion, also citing our work on nonmammalian vertebrates that suggests a more recent phylogenetic history of the ventricular component of mammalian AV-CS compared with those of the atria.

It remains to be determined whether the dual nodal phenotype results from fibrotic disruption, failed coalescence of CS modules, bifurcation, or another mechanism. But it is our view that this important article arrives at an opportune moment. Determining the basis of structural/functional discontinuity in the developing AV junction will provide insight into the operation of the adult node. Choi and Salama have already concluded that AV delay is more consistent with a barrier-like function than the conventionally accepted decremental mechanism.[5] For this reason, the cGATA6-Cre/Alk3 mouse conceivably points the way for unraveling long-standing enigmas on development and function of the AV node.

## Disclosures

None.

**Robert G. Gourdie, PhD**
*Childrens' Research Institute*
*Cardiovascular Developmental Biology Center*
*Medical University of South Carolina*
*Clemson*

**David Sedmera, MD, PhD**
*Laboratory of Cardiovascular Morphogenesis*
*Institute of Animal Physiology and Genetics*
*Charles University*
*Prague, Czech Republic*

## References

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