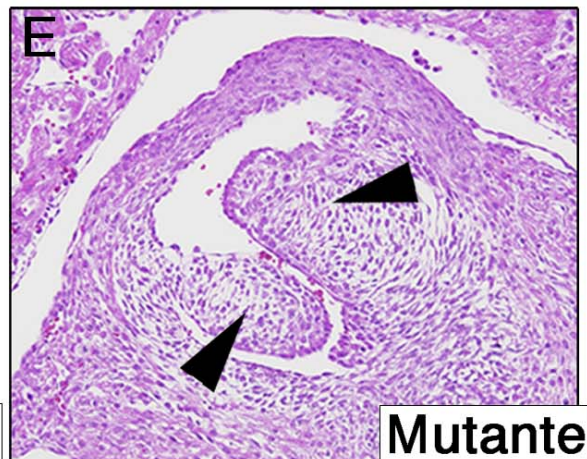
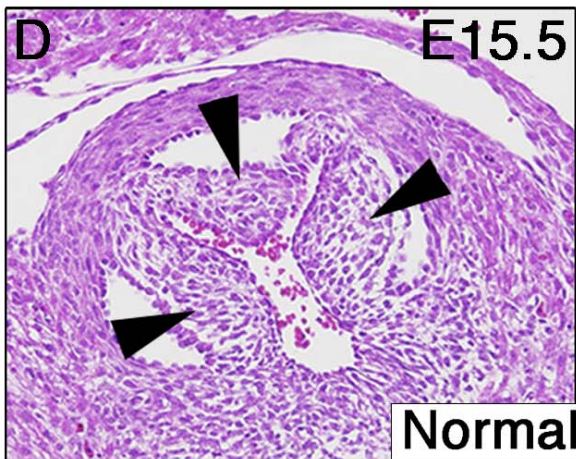
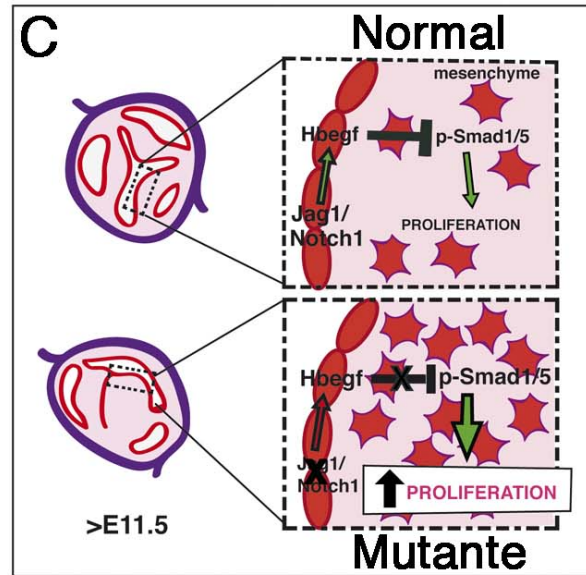
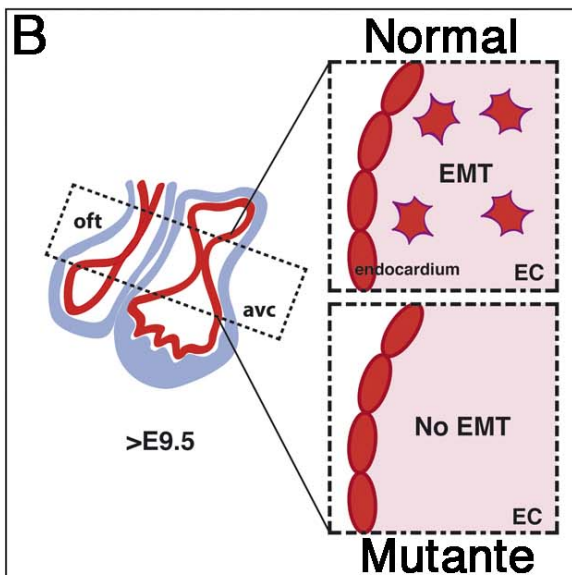
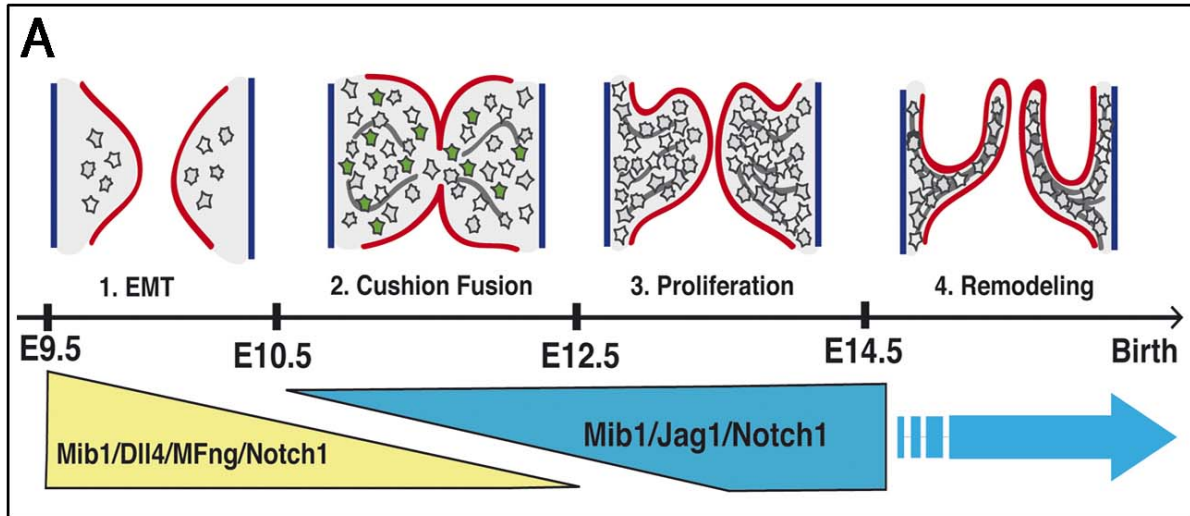


Researchers identify a new signaling mechanism implicated in congenital aortic valve disease

April 29 2016



The function of NOTCH is crucial for valve development. (A) NOTCH action

occurs in 2 phases, early (E9.5-10.5) and late (E14.5-birth), which involve the activation of the receptor by distinct ligands. E9.5, E10.5, etc. indicate the day of embryonic development in the mouse. (B) Early valve development via the process of epithelial to mesenchymal transition (EMT), giving rise to the primitive valves at E9.5 (E22 in humans). (C) From E11.5 (E33 in humans), NOTCH negatively regulates the proliferation of valve tissue; inactivation of this pathway triggers an overproliferation of valve tissue and eventually the formation of a bicuspid aortic valve (BAV). (D) Normal aortic valve at E15.5 (E55 in humans); arrowheads mark the 3 valve leaflets. (E) Bicuspid aortic valve in a NOTCH mutant; as a result of overproliferation and fusion, only 2 valves are present (arrowheads). Credit: CNIC

Researchers at the Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) have demonstrated the crucial role of the NOTCH signaling pathway in the development of a fundamental heart structure, the heart valves. These valves ensure unidirectional bloodflow with each heartbeat, and open and close millions of times during a person's lifetime. The results, published in *Circulation Research*, could help to improve the genetic diagnosis and treatment of patients with a bicuspid aortic valve (BAV), a highly prevalent condition (affecting 1-2% of the population) that seriously compromises cardiovascular health.

Using genetically modified mouse strains, the research team showed that the NOTCH signaling pathway plays an essential role throughout the process of heart valve formation. NOTCH is required for the formation of the primitive valves that function during fetal development and later for the acquisition of the definitive form of the mature valves. The study identifies a new NOTCH-regulated molecular mechanism that controls proliferation during late valve development. The research team, led by José Luis de la Pompa, showed that this control is inactivated by alterations to genes encoding NOTCH [pathway](#) components. The resulting excessive growth results in the fusion of the original 3 valves

into 2, producing a [bicuspid aortic valve](#) instead of the normal tricuspid valve.

Congenital defect

BAV is the most frequent congenital heart defect and affects 3 times as many men as women. The bicuspid valve is predisposed to premature calcification, and as a result the valve normally needs to be surgically replaced at a relatively young age (30-40 years). First author Donal MacGrogan added that the effects of BAV are not limited to valve formation, but also affect the development of the aorta.

The research findings could have important clinical implications in relation to both early [genetic diagnosis](#) and the classification of patients with heart valve malformations, and could contribute to the eventual development of therapies aimed at controlling excessive valve growth.

More information: Sequential Ligand-Dependent Notch Signaling Activation Regulates Valve Primordium Formation and Morphogenesis , [circres.ahajournals.org/content/115.308077.abstract](https://circres.ahajournals.org/content/115/3/308077) , DOI: [10.1161/CIRCRESAHA.115.308077](https://doi.org/10.1161/CIRCRESAHA.115.308077)

Provided by Centro Nacional de Investigaciones Cardiovasculares

Citation: Researchers identify a new signaling mechanism implicated in congenital aortic valve disease (2016, April 29) retrieved 26 April 2024 from <https://medicalxpress.com/news/2016-04-mechanism-implicated-congenital-aortic-valve.html>

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