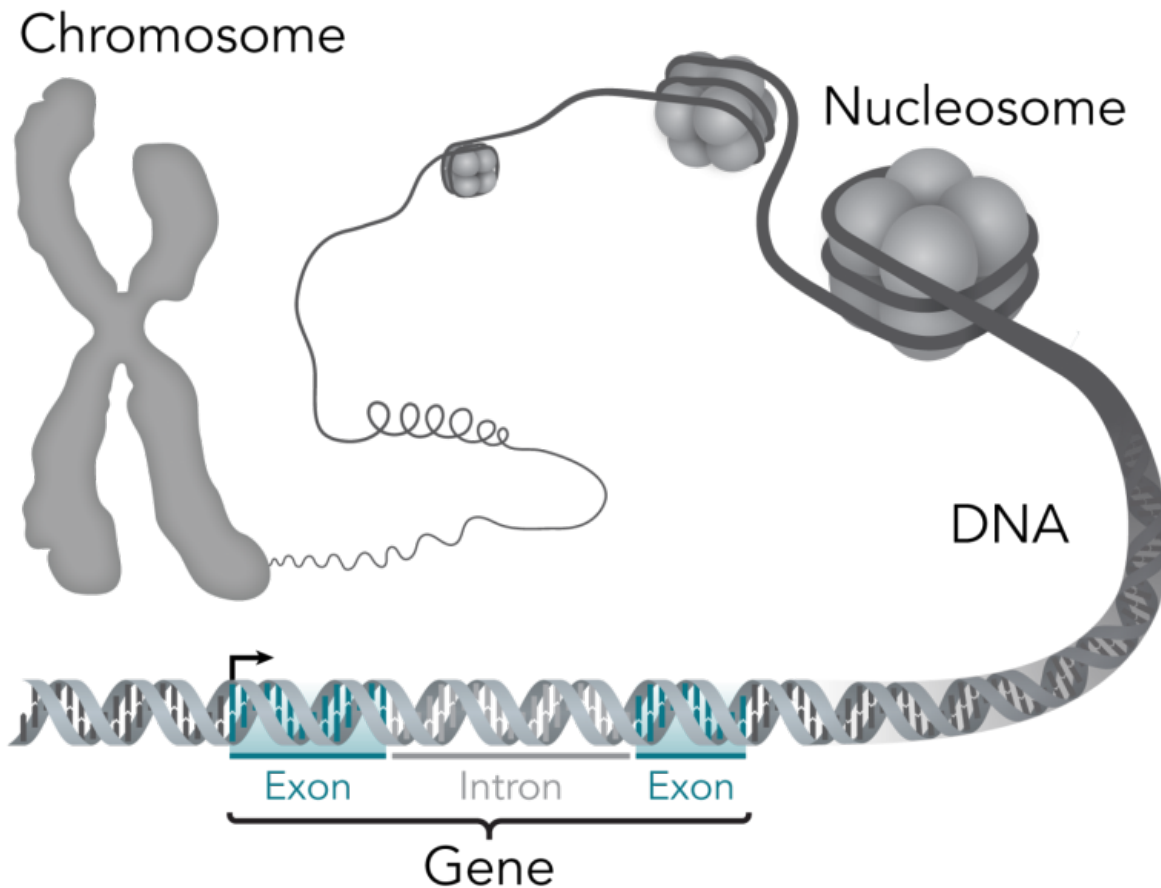


One gene closer to helping sufferers of rare genetic disorder

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This stylistic diagram shows a gene in relation to the double helix structure of DNA and to a chromosome (right). The chromosome is X-shaped because it is dividing. Introns are regions often found in eukaryote genes that are removed in the splicing process (after the DNA is transcribed into RNA): Only the exons encode the protein. The diagram labels a region of only 55 or so bases as a gene. In reality, most genes are hundreds of times longer. Credit: Thomas

A new study has separately confirmed and significantly built on recent research, identifying mutations of a gene that causes the uncommon but potentially fatal Adams-Oliver syndrome.

A leading team of medical and genetics experts from institutions across Europe independently identified a gene called NOTCH1 while also discovering the largest range of [mutations](#), both consolidating and expanding previous research published in 2014.

The new findings, published in the journal *Circulation: Cardiovascular Genetics*, solidify Notch signalling as a major factor in Adams-Oliver syndrome (AOS) and further advance diagnosis and treatment of this neonatal disorder - characterised by limb and scalp defects, accompanied by a host of cardiac and vascular complications.

The identification of the gene was driven by Professor Richard Trembath and Dr Laura Southgate, from Queen Mary University of London, with subsequent functional analyses primarily conducted by Dr Rajiv Machado and colleagues at the University of Lincoln, UK.

The study's joint senior author Dr Machado, from the School of Life Sciences, University of Lincoln, said: "Our study, which provides the largest collection of NOTCH1 mutations to date, clearly places this gene as a major causal genetic factor in AOS and in particular when associated with major cardiovascular defects, both developmental and structural.

"This insight into NOTCH1 offers the potential to explain its function in the development of key systems in the body – notably cardiovascular,

skeletal and pulmonary systems. The ultimate hope is further research in this area will result in more effective diagnoses, but most importantly treatment therapies, for those affected with this debilitating condition."

The initial gene identification process was based on sequencing the genomes of 12 families affected with AOS. They found that two people from different families had mutations in the NOTCH1 gene. Confirmation of these findings was obtained by screening a cohort of 52 additional patients, which led to the identification of a further eight unique mutations.

This study, combined with the earlier publication of NOTCH1 mutations in AOS, is a significant breakthrough in the understanding of this developmental disorder, which currently has no cure.

In 2011, Dr Machado and Dr Southgate were integral to efforts that led to the discovery of the ARHGAP31 gene - the first identified molecular defect associated with AOS. This finding was noted by international publications including the *American Journal of Medical Genetics* which provided an editorial to mark the work.

Since then four additional genes, including NOTCH1, have been identified indicating this is a disease underpinned by multiple genetic factors.

The collaboration is currently further examining the impact of NOTCH1 mutations described in this study and exploring the possibility of additional mutations in as yet unidentified [genes](#) in an extensive cohort of patients.

More information: Laura Southgate, Maja Sukalo, Anastasios S. V. Karountzos, Edward J. Taylor, Claire S. Collinson, Deborah Ruddy, Katie M. Snape, Bruno Dallapiccola, John L. Tolmie, Shelagh Joss,

Francesco Brancati, M. Cristina Digilio, Luitgard M. Graul-Neumann, Leonardo Salviati, MD, Wiltrud Coerdts, Emmanuel Jacquemin, Wim Wuyts, Martin Zenker, Rajiv D. Machado, Richard C. Trembath. 'Haploinsufficiency of the NOTCH1 receptor as a cause of Adams-Oliver syndrome with variable cardiac anomalies' *Circulation: Cardiovascular Genetics*.

Provided by University of Lincoln

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