MEDIA RELEASE

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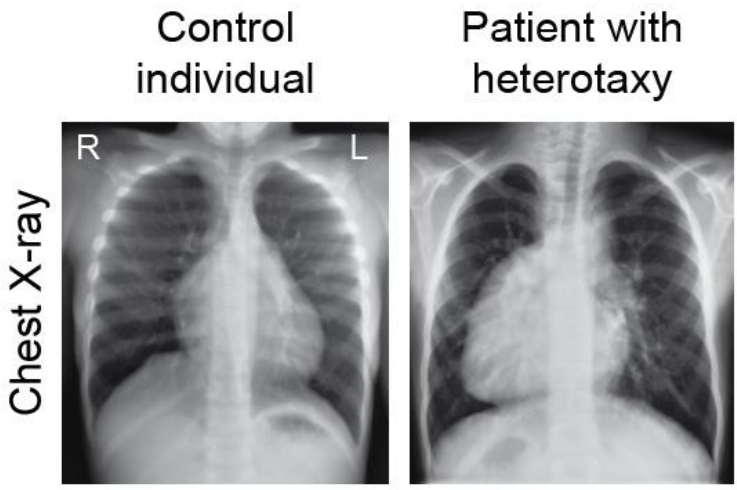
SCIENTISTS DISCOVER AND NAME NOVEL GENE THAT GOVERNS LEFT-RIGHT ASYMMETRY WITHIN THE HUMAN BODY

Shedding light on this novel gene has helped diagnose congenital heart defects and heterotaxy syndromes, which affect 1 in 10,000 live births.



Chest X-ray of a control individual (left), with his heart pointing to the left (L), while the chest X-ray of a patient with heterotaxy (right) revealed that his heart is inversely positioned pointing instead to the right (R).

SINGAPORE – A team of researchers, led by the Agency for Science, Technology, and Research's (A*STAR) Genome Institute of Singapore (GIS), in collaboration with A*STAR's Institute of Molecular and Cell Biology (IMCB) and Bioinformatics Institute (BII), and clinicians from six different countries, has discovered a novel gene, **Ci**liated Left-**R**ight **O**rganizer Metallo**p**eptidase (CIROP), that is crucial for establishing proper left-right asymmetry during vertebrate embryonic development. Babies that carry mutations in *CIROP* had internal organs randomly positioned, leading to severe birth defects consistent with heterotaxy[1].

[1] Heterotaxy syndrome is a condition in which the internal organs are abnormally arranged in the chest and abdomen. https://medlineplus.gov/genetics/condition/heterotaxy-syndrome

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At first glance, the human body looks symmetrical because our left side appears to be a mirror image of the right side. This symmetry is in fact only skin-deep since our internal organs are asymmetrically placed – the heart and spleen are on the left side while the liver is on the right side of our body. This is governed by a set of genes – comprising *CIROP*, *PKD1L1*, *MMP21*, *DAND5* and *C1orf127* – which act early during embryonic development to assign each organ a stereotypical position. When this is not achieved properly, babies can be born with birth anomalies such as congenital heart defects and misplacement of internal organs along the left-right axis. On average, these diseases occur once every 10,000 births and are grouped under syndromes of heterotaxy.

By performing an evolutionary analysis of genomes from many vertebrate species, *CIROP*, *PKD1L1*, *MMP21*, *DAND5* and *C1orf127* were found to be present in ancestral animals such as fish and frogs, but absent in reptiles, birds, and certain mammals such as cetaceans. This pattern of gene disappearance during evolution correlates with the loss of motile cilia in the transient organ that establishes left-right patterning during embryogenesis.

Prof Bruno Reversade, Senior Group Leader of the Laboratory of Human Genetics and Therapeutics at GIS and IMCB, said, “Our phylogenetic screen for genes that have disappeared in vertebrate species yielded important evolutionary insights into the development of left-right patterning. Our findings suggest that these five genes have only one function, which is to distinguish left from right. Active during a small window in the course of development, these genes may never be used again after birth.”

Dr Emmanuelle Szenker-Ravi, Research Scientist from the Laboratory of Human Genetics and Therapeutics at GIS, and first author of this study, was struck that *CIROP*, which is such an essential gene, had never been characterised before, “*CIROP’s* incomplete annotation in the human genome prevented it from being used for diagnostic purposes via exome sequencing. We are thrilled that this is now remedied and will immediately benefit affected families.”

Prof Patrick Tan, Executive Director of GIS, said, “The study illustrates the power of Mendelian genetics[2] which assigns gene functions and provides indisputable causality. Birth defects due to genetic mutations have devastating impact on both the children and their families. These findings will serve as the basis for research on potential therapies.”

– END –

[2] https://www.nature.com/scitable/topicpage/gregor-mendel-and-the-principles-of-inheritance-593/

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Enclosed:

ANNEX A – Notes to Editor

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About A*STAR's Genome Institute of Singapore (GIS)

The Genome Institute of Singapore (GIS) is an institute of the Agency for Science, Technology and Research (A*STAR). It has a global vision that seeks to use genomic sciences to achieve extraordinary improvements in human health and public prosperity. Established in 2000 as a centre for genomic discovery, the GIS pursues the integration of technology, genetics and biology towards academic, economic and societal impact, with a mission to "read, reveal and write DNA for a better Singapore and world".

Key research areas at the GIS include Precision Medicine & Population Genomics, Genome Informatics, Spatial & Single Cell Systems, Epigenetic & Epitranscriptomic Regulation, Genome Architecture & Design, and Sequencing Platforms. The genomics infrastructure at the GIS is also utilised to train new scientific talent, to function as a bridge for academic and industrial research, and to explore scientific questions of high impact.

For more information about GIS, please visit www.a-star.edu.sg/gis.

About the Agency for Science, Technology and Research (A*STAR)

A*STAR is Singapore's lead public sector R&D agency. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit the economy and society. As a Science and Technology Organisation, A*STAR bridges the gap between academia and industry. Our research creates economic growth and jobs for Singapore, and enhances lives by improving societal outcomes in healthcare, urban living, and sustainability. A*STAR plays a key role in nurturing scientific talent and leaders for the wider research community and industry. A*STAR's R&D activities span biomedical sciences to

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ANNEX A – NOTES TO EDITOR

Paper published in *Nature Genetics*.

Discovery of a genetic module essential for assigning left-right asymmetry in humans and ancestral vertebrates:

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