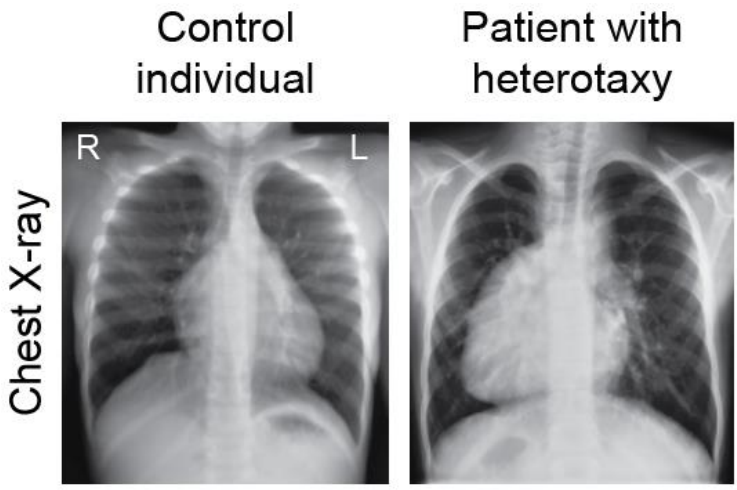
**MEDIA RELEASE**

**14 December 2021**

**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

**Genome Institute of Singapore**
60 Biopolis Street #02-01 Genome Singapore 138672
**T** + 6808 8000 **W** www.a-star.edu.sg/gis

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/

**Genome Institute of Singapore**
60 Biopolis Street #02-01 Genome Singapore 138672
**T** + 6808 8000 **W** www.a-star.edu.sg/gis

**Enclosed:**

**ANNEX A –** Notes to Editor

**For media queries and clarifications, please contact:**
Lyn Lai
Officer, Office of Corporate Communications
Genome Institute of Singapore, A*STAR
Tel: +65 6808 8258
HP: +65 8755 8759
Email: laiy@gis.a-star.edu.sg

---

## 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

physical sciences and engineering, with research entities primarily located in Biopolis and Fusionopolis. For ongoing news, visit www.a-star.edu.sg.

**Follow us on**
Facebook | LinkedIn | Instagram | YouTube

## 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:**

Emmanuelle SZENKER-RAVI[1,$,*], Tim OTT[2,$], Muznah KHATOO[1], Anne MOREAU DE BELLAING[3], Wei Xuan GOH[1], Yan Ling CHONG[4,34], Anja BECKERS[5,6], Darshini KANNESAN[1], Guillaume LOUVEL[7,35], Priyanka ANUJAN[4,36], Vydianathan RAVI[4], Carine BONNARD[8], Sébastien MOUTTON[9], Patric SCHOEN[10], Mélanie FRADIN[11], Estelle COLIN[12], André MEGARBANE[13,14], Linda DAOU[15], Ghassan CHEHAB[15,16], Sylvie DI FILIPPO[17], Caroline ROORYCK[18], Jean-François DELEUZE[19], Anne BOLAND[19 10], Nicolas ARRIBARD[20], Rukiye EKER[21], Sumanty TOHARI[4], Alvin Yu-Jin NG[22], Marlène RIO[23,24], Chun Teck LIM[25,37], Birgit EISENHABER[25,26], Frank EISENHABER[25,26,27], Byrappa VENKATESH[4,28 12], Jeanne AMIEL[23,29], Hugues ROEST CROLLIUS[7], Christopher T. GORDON[29], Achim GOSSLER[5,6 13], Sudipto ROY[4,28,30], Tania ATTIE-BITACH[23,31], Martin BLUM[2,*], Patrice BOUVAGNET[32,*] and Bruno REVERSADE[1,4,28,33,*]

1. Laboratory of Human Genetics and Therapeutics, Genome Institute of Singapore (GIS), A*STAR, Singapore
2. Institute of Biology, University of Hohenheim, Garbenstr. 30, 70599 Stuttgart, Germany
3. Laboratoire de Cardiogénétique, Groupe Hospitalier Est, Hospices Civils de Lyon, Lyon, France
4. Institute of Molecular and Cell Biology (IMCB), A*STAR, Singapore
5. Institute for Molecular Biology, OE5250, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
6. REBIRTH Cluster of Excellence, Hannover, Germany
7. Institut de Biologie de l'Ecole Normale Supérieure (IBENS), Ecole Normale Supérieure, CNRS, INSERM, PSL Research University, 75005, Paris, France
8. Skin Research Institute of Singapore (SRIS), A*STAR, Singapore
9. CPDPN, Pôle mère enfant, Maison de Santé Protestante Bordeaux Bagatelle, 33401 Talence, France
10. Praxis Dr Patric SCHÖN, Feierabendstrasse, 85764 OBERSCHLEISSHEIM, Germany

11. Service de Génétique Médicale, Hôpital Sud, CHU de Rennes, 35203, Rennes cedex, France
12. Service de Génétique Médicale, CHU d'Angers, Angers, France
13. Department of Human Genetics, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Lebanon
14. Institut Jérôme LEJEUNE, Paris, France
15. Department of Pediatric Cardiology, Hôtel Dieu de France University Medical Center, Saint Joseph University, Alfred Naccache Boulevard, Achrafieh, Beirut, Lebanon
16. Department of Pediatrics, Lebanese University, Faculty of Medical Sciences, Hadath, Greater Beirut, Lebanon
17. Service de Cardiologie Pédiatrique, Groupe Hospitalier Est, Hospices Civils de Lyon, 69677 Bron, France
18. University of Bordeaux, MRGM, INSERM U1211, CHU de Bordeaux, Service de Génétique, F-33000, Bordeaux, France
19. Université Paris-Saclay, CEA, Centre National de Recherche en Génomique Humaine (CNRGH), 91057, Evry, France
20. Service de Cardiologie Pédiatrique, Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Brussels, Belgium
21. Pediatric Cardiology Division, Pediatrics Department, Istanbul Medical Faculty, Istanbul University, 34093 Istanbul, Turkey
22. Molecular Diagnosis Centre (MDC), National University Hospital (NUH), Singapore
23. Fédération de Génétique, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, 75015 Paris, France
24. Université de Paris, Imagine Institute, Developmental Brain Disorders Laboratory, INSERM UMR 1163, 75015 Paris, France
25. Bioinformatics Institute (BII), A*STAR, Singapore
26. Genome Institute of Singapore (GIS), A*STAR, Singapore
27. School of Biological Sciences (SBS), Nanyang Technological University (NTU), Singapore
28. Department of Paediatrics, National University of Singapore (NUS), Singapore
29. Université de Paris, Imagine Institute, Laboratory of Embryology and Genetics of Malformations, INSERM UMR 1163, 75015 Paris, France
30. Department of Biological Sciences, National University of Singapore (NUS), Singapore
31. Université de Paris, Imagine Institute, Laboratory of Genetics and development of the cerebral cortex, INSERM UMR 1163, 75015 Paris, France
32. CPDPN, Hôpital MFME, CHU de Martinique, BP632, 97200 Fort de France, France
33. Medical Genetics Department, Koç University School of Medicine (KUSOM), Istanbul, Turkey
34. Present address: Department of Pathology, National University Hospital, Singapore

35. Present address: Écologie, Systématique et Évolution, UMR 8079 CNRS - Université Paris-Saclay - AgroParisTech, 91400 Orsay, France
36. Present address: Institute of Reproductive and Developmental Biology, Hammersmith Hospital, Imperial College, London, UK
37. Present address: Singapore Institute of Food and Biotechnology Innovation (SIFBI), A*STAR, Singapore

$ These authors contributed equally to this work

* Authors to whom correspondence should be addressed: Emmanuelle Szenker-Ravi (emmanuelle.szenker@reversade.com), Martin Blum (martin.blum@uni-hohenheim.de), Patrice Bouvagnet (patrice.bouvagnet@chu-martinique.fr), and Bruno Reversade (bruno@reversade.com).