

MEDIA RELEASE

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RESEARCHERS DISCOVER POTENTIAL TREATMENT FOR ORPHAN PAEDIATRIC CONDITION

The treatment uses the drug CHIR99021 administered during pregnancy to correct the condition in developing foetuses.

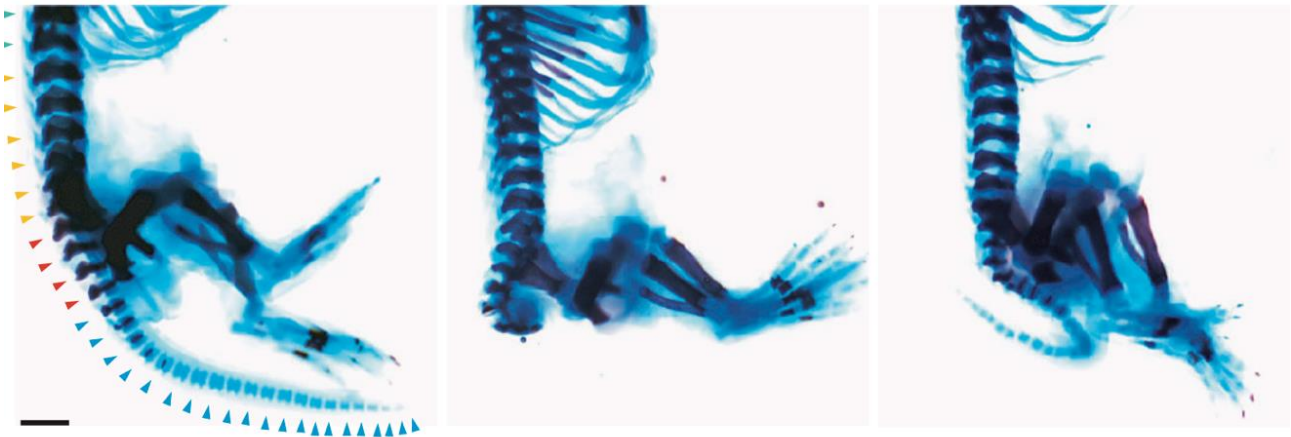


Image showing a normal mouse skeleton (left) with legs and tail, skeleton from a mouse carrying the patient mutation (middle) with its tail missing, and mouse (right) with the mutation now treated with the drug CHIR99021 and the tail (measured by the number of vertebrae) has regrown.

SINGAPORE – Researchers from the Agency for Science, Technology and Research's (A*STAR) Genome Institute of Singapore (GIS), and Rady Children's Institute for Genomic Medicine identified a previously unknown condition affecting children, which they discovered could be prevented by administering a drug during pregnancy.

Through a worldwide collaboration, the researchers identified children from Egypt, India, United Arab Emirates, Brazil, and USA affected by the same condition. Although different doctors were caring for these children, they all showed similar symptoms and had DNA mutations in the same gene.

The condition, which doctors named 'Zaki Syndrome' after one of the physicians who first identified it, impacts the development of several organs of the body including the eyes, brain, digit, kidney, hair, and heart. Using whole genome sequencing, doctors were able to find mutations in a previously mysterious gene called 'WNT-less', abbreviated *WLS*. The *WLS* gene controls the level of signalling of a hormone-like protein called WNT (pronounced wint).

Surprisingly, a drug that counteracts the loss of the WLS was able to mostly restore normal development in both pre-clinical trial model and a stem cell model of Zaki syndrome. Moving forward, researchers hope to discover how the drug could be administered to pregnant mothers to help correct the condition in developing fetuses.

“We were perplexed by this paediatric condition for many years,” said Dr Joseph Gleeson, senior author and paediatric neurogeneticist at Rady Children’s Institute for Genomic Medicine and the University of California, San Diego. “We observed children from across the globe with DNA mutations in the WNT-less gene, but did not recognise that they all had the same disease until doctors compared clinical notes. We then realised we were dealing with a new syndrome that can be identified by clinicians, and potentially prevented.”

Prof Bruno Reversade, co-senior author, head of the Laboratory of Human Genetics and Therapeutics at GIS, and Research Director at the Institute of Molecular and Cell Biology(IMCB), whose team helped to identify several families and studied the disease symptoms using patients’ cells, wondered if such a condition may be amenable to therapeutic intervention. He commented, “While we have shown that it is possible to mimic WNT-deficiency with dedicated drugs, the real challenge was to overcome, and possibly rescue, this congenital disease.”

To attempt this, researchers generated stem cells and mouse models for Zaki Syndrome, and treated it with a man-made drug that boosts WNT signalling, which is defective when WNT-less is mutated. In each model, they found that the drug, called CHIR99021, was able to boost WNT signals and restore development. The embryos regrew body parts that were missing (e.g. vertebrae), and organs began growing almost normally.

“The results were very surprising to us because it was previously assumed that structural birth defects like Zaki Syndrome could not be prevented with a drug,” said first author Dr Guoliang Chai, a member of the team at Rady Children’s Institute for Genomic Medicine, and currently at Capital Medical University in Beijing. “We could eventually see this drug, or drugs like it, being used to prevent birth defects if the fetuses are diagnosed early enough.”

Prof Patrick Tan, Executive Director of GIS, said, “Research into rare diseases helps scientists understand more common ailments. The findings from such research sometimes results in unexpected findings that may better inform diagnoses or therapies for patients suffering from these diseases. It always feels rewarding for GIS to be part of such collaborations that contribute to better health and social outcomes for Singapore, and beyond.”

The results appear in the issue of the New England Journal Medicine [<https://www.nejm.org/doi/10.1056/NEJMoa2033911>] on September 30, 2021.

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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.
For more information about the Reversade Laboratory, please visit www.reversade.com.

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Genome Institute of Singapore

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

ANNEX A – NOTES TO EDITOR

The research findings described in this media release can be found in the scientific journal *New England Journal Medicine*, under the title, “A Human Pleiotropic Multiorgan Condition Caused by Deficient Wnt Secretion” [<https://www.nejm.org/doi/10.1056/NEJMoa2033911>] by the following authors: Guoliang Chai, Ph.D., Emmanuelle Szenker-Ravi, Ph.D., Changuk Chung, Ph.D., Zhen Li, Ph.D., Lu Wang, Ph.D., Muznah Khatoo, B.S., Trevor Marshall, B.S., Nan Jiang, Ph.D., Xiaoxu Yang, Ph.D., Jennifer McEvoy-Venneri, B.S., Valentina Stanley, B.S., Paula Anzenberg, B.S., Nhi Lang, B.S., Vanessa Wazny, B.S., Jia Yu, Ph.D., David M. Virshup, M.D., Rie Nygaard, Ph.D., Filippo Mancina, Ph.D., Rijad Merdzanic, M.D., Maria B.P. Toralles, M.D., Paula M.L. Pitanga, M.Sc., Ratna D. Puri, M.D., Rebecca Hernan, M.Sc., Wendy K. Chung, M.D., Ph.D., Aida M. Bertoli-Avella, M.D., Ph.D., Nouriya Al-Sannaa, M.D., Maha S. Zaki, M.D., Ph.D., Karl Willert, Ph.D., Bruno Reversade, Ph.D., and Joseph G. Gleeson, M.D.

The authors’ affiliations are as follows: From the Rady Children’s Institute for Genomic Medicine, San Diego (G.C., C.C., Z.L., L.W., T.M., N.J., X.Y., J.M.-V., V.S., P.A., N.L., J.G.G.), and the University of California, San Diego, La Jolla (G.C., C.C., Z.L., L.W., T.M., N.J., X.Y., J.M.-V., V.S., P.A., N.L., K.W., J.G.G) — both in California; Xuanwu Hospital, Capital Medical University, Beijing (G.C.); the Genome Institute of Singapore (E.S.-R., M.K., V.W., B.R.) and the Institute of Molecular and Cellular Biology (B.R.), Agency for Science, Technology, and Research, and the Program in Cancer and Stem Cell Biology, Duke–NUS (National University of Singapore) Medical School (J.Y., D.M.V.) — all in Singapore; the Medical Genetics Department, Koç University School of Medicine, Istanbul, Turkey (B.R.); the Department of Pediatrics, Duke University, Durham, NC (D.M.V); the Department of Physiology and Cellular Biophysics, Columbia University Irving Medical Center (R.N., F.M.), and the Departments of Pediatrics and Medicine, Columbia University (R.H., W.K.C.) — both in New York; Centogene, Rostock, Germany (R.M., A.M.B.-A.); DNA Laboratório e Genética Médica, Salvador, Brazil (M.B.P.T., P.M.L.P.); the Institute of Medical Genetics and Genomics, Sir Ganga Ram Hospital, New Delhi, India (R.D.P.); Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia (N.A.-S.); and the Clinical Genetics Department, National Research Center, Cairo (M.S.Z.).

Address reprint requests to Dr. Gleeson at the University of California, San Diego, 9500 Gilman Dr., BRF2 3A25, La Jolla, CA 92093, or at jogleeson@ucsd.edu; or to Dr. Reversade at the Genome Institute of Singapore, Agency for Science, Technology, and Research, Biopolis, Singapore 138648, Singapore, or at bruno@reversade.com.

Drs. Reversade and Gleeson contributed equally to this article.

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Genome Institute of Singapore

60 Biopolis Street #02-01 Genome Singapore 138672

T + 6808 8000 W www.a-star.edu.sg/eis