

**MEDIA RELEASE
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SCIENTISTS UNCOVER A NEW LAYER OF COMPLEXITY BEYOND THE HUMAN GENOME

In-depth study and new discoveries of RNA editing process provide better understanding of what makes us human

Singapore – Singaporean researchers have made significant inroads in the study of Ribonucleic Acid (RNA) editing¹ to further explain how, although we have roughly the same number of protein-coding genes as other living things, the developmental and cognitive complexity of humans are at a significantly higher level than other organisms. Jointly led by A*STAR's Genome Institute of Singapore (GIS), Nanyang Technological University, Singapore (NTU Singapore) and Stanford University, USA, the study was recently published in *Nature*.

The genome contains all the necessary information that dictates cellular and organismal behaviour. Given the developmental and cognitive complexity of humans, one would have thought that our genome would contain many more protein-coding genes than most other living organisms. Surprisingly, however, the Human Genome Project has uncovered only approximately 20,000 protein-coding genes in our genome, a number not much different from other mammals, vertebrates, flies, or even worms. Part of the answer to this apparent paradox lies in the complex processing of RNA after it has been transcribed² from the genome, which formed the basis for this study.

Different types of RNA processing are known to exist in humans. One particularly important kind is known as RNA editing, whereby genome-encoded information is altered in the transcripts. As a result, the sequence of an edited transcript does not correspond exactly to the sequence of the gene position from which the transcript originates. RNA editing provides a powerful method to diversify the transcriptome³ and to fine-tune biological function. Adenosine-to-inosine (A-to-I) editing is the most common kind of editing in animals, and over a million A-to-I editing sites are present in the human transcriptome. However, the extent to which each site is edited in different biological contexts is largely unknown.

Co-lead author of the study Prof Tan Meng How, together with his team has comprehensively profiled A-to-I editing in multiple human tissues and compared editing

¹ RNA editing is a fundamental biological process whereby RNA molecules in the cell are modified so that their sequences do not match up perfectly with the DNA from which they are derived.

² Transcription is the first step of gene expression, in which a particular segment of DNA is copied into RNA by the enzyme called RNA polymerase.

³ The sum total of all RNA molecules expressed from the genes of an organism.

in humans to non-human primates and mice. Prof Tan is Senior Research Scientist, Stem Cell & Regenerative Biology at GIS, and an Assistant Professor at NTU's School of Chemical and Biomedical Engineering.

Since there are only two catalytically active A-to-I editing enzymes (called ADARs) in humans, which cannot account for the diverse spatiotemporal patterns of editing, Prof Tan's team computationally predicted potential new regulators of editing. They examined one novel regulator, AIMP2, in greater detail and found that it promotes the degradation of the ADAR proteins and plays an important role in controlling editing levels in muscles.

Before the wider adoption of next generation sequencing (NGS) technologies, the earliest discoveries of RNA editing were in the central nervous system or the brain. Hence, for decades, RNA editing was believed to occur predominantly in neuronal cell types. Subsequently, ad hoc studies leveraging on NGS technologies started to reveal that editing may play important roles in other non-brain tissues, although these studies were limited in comprehensiveness. Prof Tan's work represents the most in-depth study of RNA editing in mammals and revealed several surprises.

Firstly, they found that in humans, the highest amount of editing in protein-coding regions occur in the artery, and not the brain. Secondly, from their cross-species analysis, they discovered that RNA editing is largely cis-directed, and not trans-directed. This means that in terms of editing profiles, the human brain is more similar to the human lung than to the mouse brain or even the chimpanzee brain. Thirdly, it was believed that an editing site is either a target of the ADAR1 enzyme or a target of the ADAR2 enzyme and that this dependence is invariable between tissues. However, they found that whether a site is edited by ADAR1 or ADAR2 is context dependent and can vary greatly between tissues.

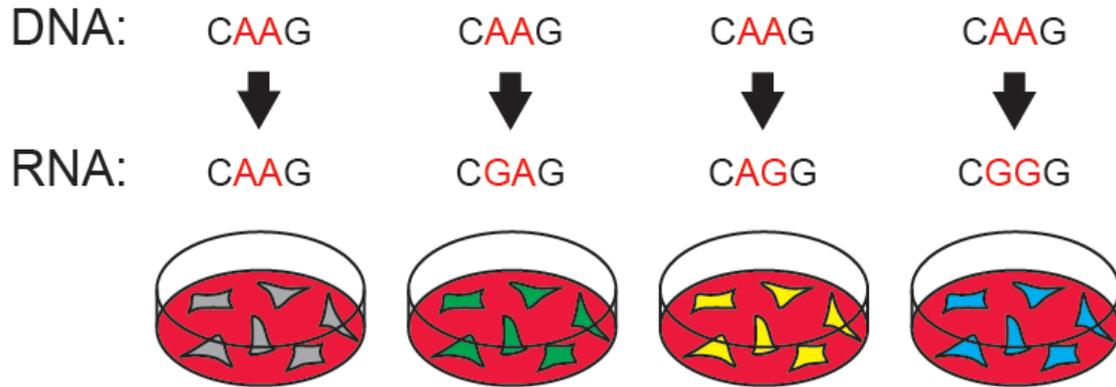
Associate Prof Carl Walkley from St Vincent's Institute and the University of Melbourne said, "Tan Meng How and colleagues' latest work greatly expands our understanding of how RNA editing contributes to the diversification of our genome, across time and age and in different tissues of the body. They have identified important findings about how RNA editing is controlled and defined new regulators of this process. This is a very important study for our understanding of the role that RNA editing plays in different contexts and will provide a foundation for future studies in this field."

"Although there are about a dozen groups working on similar research, our research stands out in that we make effective use of new technologies together with traditional molecular biology, cell biology, genetics, and biochemistry techniques. We also focus on Asia-specific diseases and collaborate with local clinicians," said Prof Tan. "Collectively, our paper serves as a useful resource for the scientific community and lays the foundation for future studies into the functions and regulation of RNA editing."

Executive Director of GIS, Prof Ng Huck Hui added, "This is a truly significant jump in the understanding of RNA editing and functionality. It is an important stepping stone for

scientists to learn more about what makes us human, and from there, how we can look to RNA editing to improve human health.”

IMAGE



Schematic illustrating how RNA editing can increase the number of distinct biomolecules present in the cell beyond what is dictated by the genome. The distinct biomolecules can cause the cells to behave differently.

Notes to Editor

The research findings described in this media release can be found in the scientific journal *Nature*, under the title, “*Dynamic landscape and regulation of RNA editing in mammals*” by Meng How Tan^{1,2,3*}, Qin Li^{1*}, Raghuvaran Shanmugam^{2,3}, Robert Piskol¹, Jennefer Kohler¹, Amy N. Young¹, Kaiwen Ivy Liu³, Rui Zhang¹, Gokul Ramaswami¹, Kentaro Ariyoshi⁴, Ankita Gupte⁵, Liam P. Keegan^{6,7}, Cyril X. George⁸, Avinash Ramu^{9,10}, Ni Huang^{9,10}, Elizabeth A. Pollina¹, Dena Leeman¹, Alessandra Rustighi¹¹, Y. P. Sharon Goh¹², The GTEx Consortium[†], Ajay Chawla¹², Giannino Del Sal¹¹, Gary Peltz¹³, Anne Brunet¹, Donald F. Conrad^{9,10}, Charles E. Samuel⁸, Mary A. O’Connell^{6,7}, Carl R. Walkley^{5,14}, Kazuko Nishikura⁴ & Jin Billy Li¹

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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 will pursue the integration of technology, genetics and biology towards academic, economic and societal impact.

The key research areas at the GIS include Human Genetics, Infectious Diseases, Cancer Therapeutics and Stratified Oncology, Stem Cell and Regenerative Biology,

Cancer Stem Cell Biology, Computational and Systems Biology, and Translational Research.

The genomics infrastructure at the GIS is 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.gis.a-star.edu.sg

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The Agency for Science, Technology and Research (A*STAR) is Singapore's lead public sector agency that spearheads economic oriented research to advance scientific discovery and develop innovative technology. Through open innovation, we collaborate with our partners in both the public and private sectors to benefit 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 contributing to societal benefits such as improving outcomes in healthcare, urban living, and sustainability.

We play a key role in nurturing and developing a diversity of talent and leaders in our Agency and Research Institutes, the wider research community and industry. A*STAR oversees 18 biomedical sciences and physical sciences and engineering research entities primarily located in Biopolis and Fusionopolis.

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About Nanyang Technological University, Singapore

A research-intensive public university, Nanyang Technological University, Singapore (NTU Singapore) has 33,500 undergraduate and postgraduate students in the colleges of Engineering, Business, Science, Humanities, Arts, & Social Sciences, and its Interdisciplinary Graduate School. It also has a medical school, the Lee Kong Chian School of Medicine, set up jointly with Imperial College London.

NTU is also home to world-class autonomous institutes – the National Institute of Education, S Rajaratnam School of International Studies, Earth Observatory of Singapore, and Singapore Centre for Environmental Life Sciences Engineering – and various leading research centres such as the Nanyang Environment & Water Research Institute (NEWRI), Energy Research Institute @ NTU (ERI@N) and the Institute on Asian Consumer Insight (ACI).

Ranked 11th in the world, NTU has also been ranked the world's top young university for the last four years running. The University's main campus has been named one of the Top 15 Most Beautiful in the World. NTU also has a campus in Novena, Singapore's medical district.

For more information, visit www.ntu.edu.sg