Genome Institute of Singapore
GIS

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NEW LEADS IN RESEARCH INTO THE ORIGIN OF IDENTICAL TWINS
Identical twins have unique epigenetic profile

SINGAPORE – An international group of researchers led by Jenny van Dongen and Dorret Boomsma of the Vrije Universiteit, Amsterdam, the Netherlands has made a groundbreaking discovery that could lead to new insights into the blueprint of identical twins. The researchers found a unique epigenetic profile in identical twins. The article "Identical twins carry a persistent epigenetic signature of early genome programming" appeared 28 September 2021 in "*Nature Communications".* The findings represent a huge step forward in understanding identical twins.

The mystery of identical twins

Identical (monozygotic – MZ) twins cause much confusion to their parents and friends and make very cute cover photos for magazines, but despite a century of amazing progress in most areas of science we still have no idea how they arise. As MZ twins appear to crop up randomly in families at a rate of about 4 per 1000 births all around the world, neither analyses of possible genetic predisposition nor studies of putative environmental exposures have cast much light on the origins of MZ twinning. In contrast we are making fast progress on understanding the biological origins of nonidentical (dizygotic – DZ) twins, which run strongly in families, pointing to genetic influences. Not surprisingly, genomic studies are proving useful in finding the genes behind DZ twinning.

The processes leading to these 2 types of twins are very different. Dizygotic twins arise after double ovulation, in which the genetic predisposition of the mother plays a major role. Identical twins arise from a single embryo that splits into two in the very early stages of pregnancy and retain the same base-pair sequence of their genes. To date, it is unknown why this happens.

The main finding

Now, researchers have made an important discovery: epigenetic information in the chromosomes differs between identical twins and others. These epigenetic differences are not in the DNA code itself, but in the small chemical marks associated with it. Twin registries from the Netherlands, Great Britain, Finland, and Australia participated in the study. The researchers measured the level of methylation at more than 400,000 sites in the DNA of more than 6,000 twins. The researchers found 834 locations in the DNA where the methylation level was different in identical twins than in non-twins.

Professor Dorret Boomsma of the Netherlands Twin Register specializes in genetics and twin studies and spent most of her career working with twins and their relatives. Boomsma: "This is a very big discovery. The origin and birth of identical twins have always been a complete mystery. It is one of the few traits in which genetics plays no or very modest role. This is the first time that we have found a biological marker of this phenomenon in humans. The explanation appears not to lie in the genome, but in its epigenome".

Professor Bruno Reversade, Senior Group Leader of the Laboratory of Human Genetics and Therapeutics at A*STAR's Genome Institute of Singapore (GIS), said: "This amazing finding is diagnostic, it brings hitherto unknown insights into the fabrics of MZ twinning. The epigenome-wide association study (EWAS) findings amounted to being able to retrospectively diagnose MZ twinning based on the persistence of epigenetic marks in their soma. The next step will be to find out why MZ twinnings occur. We are now actively pursuing a genome-wide association study (GWAS) approach to decipher common genetic variants that predispose to identical twinning."

The epigenome

Around the building blocks of DNA (the DNA code) are control elements that determine how genes are tuned and how strongly they are expressed. This is the so-called epigenome. A

useful analogy is how holding the shift key on a keyboard, can make the letter “a” become capitalized “A”. This allows another level of regulation on how each letter or number on the keyboard can be displayed. Likewise, DNA methylation (like pressing the shift key) controls which genes are “on” and which genes are “off” in each cell of the body. The field that studies this tuning of genes is called epigenetics.

Important breakthrough

Dr. Jenny van Dongen, who leads the study is a researcher at the Netherlands Twin Register at the Vrije Universiteit, Amsterdam, who specializes in epigenetics: “These locations in the DNA are involved in the functions of early embryonic development. In addition to insights into the fabrics of monozygotic twins, our results may lead to a better understanding of congenital abnormalities that occur more often in monozygotic twins in the future. A particularly surprising finding in this study is that we can determine from the epigenetic profile of a person whether he/she is an identical twin or has lost a monozygotic twin sibling early in pregnancy, also known as vanishing twin syndrome”.

Professor Nick Martin of the Queensland Institute of Medical Research, Brisbane, Australia, adds: “This study could only have been done by an international collaboration of twin researchers. It provides an exciting new breakthrough. Instead of focusing on genomics, an epigenome wide association study was done, comparing methylation levels at over 400,000 sites across the entire human genome in Dutch MZ twins and controls. Jenny van Dongen found to her surprise large numbers of very strong signals, in non-random clusters, for example near the ends of chromosomes. Thinking the large number of findings might be some artefact she then sought replication data from 3 other twin cohorts in Australia, UK and Finland, and saw almost identical patterns in those. This was replicated when she repeated the experiment in a different tissue than blood. Meta-analysis of these results points to unusual methylation patterns in genes involved in cell adhesion which might explain why there is spontaneous fission of an early developing embryo into two identical halves. This finding may also provide important clues to the origin of numerous birth defects known to be strongly associated with MZ twinning.

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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.

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ANNEX A – NOTES TO EDITOR

Paper published in *Nature Communications*

Identical twins carry a persistent epigenetic signature of early genome programming:

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Abstract
Monozygotic (MZ) twins and higher-order multiples arise when a zygote splits during pre-implantation stages of development. The mechanisms underpinning this event have remained a mystery. Because MZ twinning rarely runs in families, the leading hypothesis is that it occurs at random. Here, we show that MZ twinning is strongly associated with a stable DNA methylation signature in adult somatic tissues. This signature spans regions near telomeres and centromeres, Polycomb-repressed regions and heterochromatin, genes involved in cell-adhesion, WNT signaling, cell fate, and putative human metastable epialleles. Our study also demonstrates a never-anticipated corollary: because identical twins keep a lifelong molecular signature, we can retrospectively diagnose if a person was conceived as monozygotic twin.