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NEW LEADS IN RESEARCH INTO THE ORIGIN OF IDENTICAL TWINS

An international group of researchers led by Jenny van Dongen and Dorret Boomsma of the Vrije Universiteit, Amsterdam, the Netherlands has made a ground breaking discovery that could lead to new insights into the blueprint of identical twins. The researchers found a unique epigenetic profile in identical twins. The findings represent a huge step forward in understanding identical twins. The article that details the research is titled *Identical twins carry a persistent epigenetic signature of early genome programming* and can be found here: https://www.nature.com/articles/s41467-021-25583-7

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 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 small chemical marks associated with it. Twin registries from the Netherlands, Great Britain, Finland, and Australia participated in the study.

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 has 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 of the Agency for Science, Technology and Research (A*STAR) in Singapore: "This amazing finding is diagnostic, it brings hitherto unknown insights into the fabrics for MZ twinning. The next step will be to find out why this happens".

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 the holding the shift key on a keyboard, can make the letter "a" become capitalized "A" allowing 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.

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."

Professor Jeff Craig, who works in Early Life Epigenetics at Deakin University, Australia is President of ISTS. He kindly wrote the following Question & Answer article about this exciting research finding.

Q & A of the new twin study titled "Identical twins carry a persistent epigenetic signature of early genome programming"

Q: Why was the study done?

A: To find out clues about why, how, and when, a single fertilised egg can split into identical twins within a few days.

Q: How was the study done?

A: The authors were looking for a record of twin splitting events that are 'remembered' by cells present in twins well after they are born. They knew that good candidates are the molecules that stick to our DNA that we call 'epigenetics'. Epigenetics are the molecular dimmer switches that turn our genes up and down as we develop in the womb and beyond. And we know that the experiences a developing baby experiences in pregnancy can sometimes change their epigenetic switches. The authors collected blood from thousands of twins and their parents across multiple twin studies. They then compared the epigenetic switches in the DNA of the blood cells of identical twins with those from fraternal twins and singletons.

Q: What did the study find?

A: The study found that identical twins differed in the levels at which their epigenetic switches were set, at hundreds of locations along their DNA. Many of these differences were located in genes that help different kinds of cells recognise each other and stick together only with those cells that are similar. The authors also found that they could use their data to blindly identify whether a DNA sample comes from an identical twin, albeit with limited accuracy. The authors also say their test could one day identify singletons who started off as identical twins but lost their co-twin very early in pregnancy.

Q: Did the study show what causes twinning?

A: No, the authors admit that they don't know whether their findings reflect the cause or the consequences of twinning.

Q: If the differences they observed were the cause of twinning, what would this tell us?

A: This would tell us that a combination of unknown factors, probably a combination of genetics, environment and pure chance, may be causing cells of the very early embryo to lose their ability to stick together, causing a splitting event.

Q: Tell me more about the implications of these findings for singletons who started life as a twin?

A: The study mentions that it's suspected that in almost nine out of ten identical twin pregnancies, one twin 'vanishes' very early on. And that this increases the chance of birth abnormalities such as cerebral palsy in the surviving twin. Further, it's been suggested that many birth abnormalities can be much more frequent in twins than current knowledge suggests. This study may help resolve this issue.

Q: What does the study mean for identical twins?

A: The study confirms what many identical twins already know – that they are different from same-sex fraternal twins.

Q: What does the study mean for parents of twins?

A: It means that we know a little more about the events that took place inside you and produced the miracles that are your twins.

Q: What does the study mean for singletons and their parents?

A: Some singletons could have started life as an identical twin and lost their co-twin very early on. If there was a test to identify identical twins, singletons could take it. However, they and their parents would need to think about the potential trauma that the knowledge of a loss during early pregnancy could provoke before they chose whether to take such a test.

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Q: Has the study produced a new test that identified identical twins and if so, will this replace zygosity tests?

A: No, the ‘test’ they develop is far from accurate so at the moment it’s not ready for the market. In all probability, zygosity tests will always be cheaper.

Q: Does the study tell us why only humans have identical twins?

A: Actually, only human have identical twins but armadillos can have identical quads and octuplets. However, the study does not answer the question of ;why?’

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