The Almagest

Scientists discover new mechanism that preserves genomic integrity and is abnormal in the rare DiGeorge syndrome

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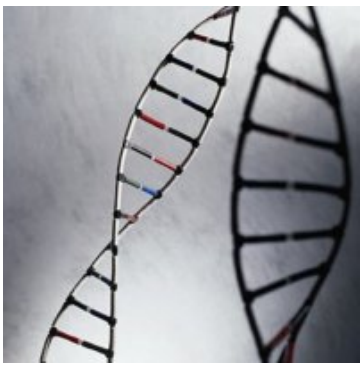

An international team including GENYO centre researchers has described a molecular mechanism that defends human genome integrity against "bombarding" by mobile DNA sequences. Alterations in the mechanism could be responsible for symptoms causing this syndrome

Their research—an important step forward in the field of genetics—is published this week in

the prestigious* Nature Structural and Molecular Biology *journal

This scientific advance could in the future help develop new therapies against the disease, caused by microdeletion of a small part of chromosome 22

An international team of scientists—including researchers at GENYO, the Centre for Genomics and Oncological Research (Pfizer-University of Granada- Andalusian Regional Government)—has described a molecular mechanism that facilitates the defence of the human genome against "bombarding" by mobile DNA sequences. Abnormalities in the mechanism could be responsible for some symptoms of DiGeorge syndrome, a rare disease. The research could in the future help develop new therapies against the disease, which is caused by the microdeletion of a small part of chromosome 22.

The study, published this week in the prestigious *Nature Structural and Molecular Biology*journal, describes a sophisticated mechanism that enables all of our cells to control the uncontrolled movement of mobile DNA in our genomes. In patients with DiGeorge syndrome, the cells present abnormalities in the control mechanism. Currently, the research team are trying to generate stem cells that "suffer" from the disease from cells donated by patients who have it—which would enable them to clarify the molecular base of this complex pathology.

DiGeorge syndrome, also known as deletion 22q11.2, is the most common genetic disease caused by a chromosome microdeletion in humans. It has an estimated prevalence of 1 in 4000 births and symptoms vary greatly. Typically, these affect the heart and immune system, as well as presenting as learning difficulties, mental retardation and psychiatric disorders.

The disease is characterized by absence of the "Microprocessor" protein complex, which means these patients lack a 'vigilante' gene to watch out for repeated sequences and, therefore, are potentially susceptible to being bombarded by these DNA fragments.

"Microprocessor" is the key

Sara R. Heras—co-author of the study and GENYO researcher—explains that all our cells contain "Microprocessor", a protein complex whose known function at the moment is that of generating small regulatory molecules of ribonucleic acid (RNA), known as microRNAs. "Our study has shown that this complex also acts as 'vigilante' and defends the integrity of the human genome. Hence, these proteins are capable of recognizing and fragmenting the repeated DNA sequences that escape previous control mechanisms, thus preventing them from replicating and introducing themselves into the genome".

In *Nature Structural and Molecular Biology*, Sara R. Heras, Sara Macías and their collaborators have described a new mechanism by which most human cells can avoid being bombarded by these DNA fragments. This study has been conducted in the laboratory headed by Dr. José Luis García Pérez in GENYO (Granada) in collaboration with Dr. Javier Cáceres "Medical Research Council-Human Genetic Unit" in Edinburgh (United Kingdom) and Dr. Eduardo Eyras' laboratory at the Universidad Pompeu Fabra, Barcelona.

Embryonic model

In these new studies, the authors are using an embryonic model of induced pluripotent stem cells (iPSCs). That is, from cells donated by patients with DiGeorge syndrome, stem cells with the disease are generated. This is an ideal model to determine the impact of the repeated sequences from which the deletion that causes this pathology are generated: in other words, the embryonic stage. It is foreseen that these studies will clarify the molecular base for this highly complex disease, as well as permit the long-term development of new therapies for its treatment.

The study published in *Nature Structural and Molecular Biology* and current research into DiGeorge syndrome, has been and is today part-financed by the 7th Marie Curie European Framework Program CIG-Grant (PCIG-GA-2011-303812). Moreover, these and other studies in Dr. Garcia-Perez's laboratory in GENYO are financed by the Spanish Ministry of Health (FIS-FEDER-PI11/01489), the Andalusian Regional Government Departments of Innovation and Science (CICE-FEDER-P09-CTS-4980) and Health (PeS-FEDER-PI-002), by the prestigious US "Howard Hughes Medical Institute" (IECS-55007420), and by the European Research Council (ERC-Starting-2012-LS1-EPIPLURIRETRO-339064).

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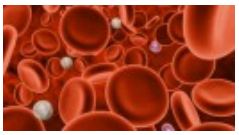

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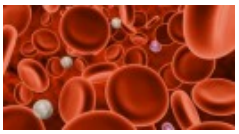

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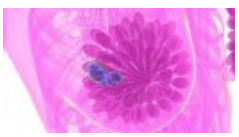

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