COLUMBIA | Zuckerman Institute

MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

Finding the Brainy Genes That Make Us Human

~ A Q&A with Franck Polleux, PhD, and James Noonan, PhD ~

What does it mean to be human? The answer to this question often starts with the brain: with language, creativity, abstract thought and problem solving. When and how these abilities arose in our evolutionary history has long been the subject of debate. Scientists knew that the origins of our enhanced cognitive powers are in large part guided by our genes and our DNA. The challenge was to find them.

Enter Franck Polleux, PhD, of Columbia University's Zuckerman Institute and James Noonan, PhD, of the Yale School of Medicine. Armed with advanced genetics, stem-cell technology and neuroscience, these two scientists are mapping the genetic factors that make the human brain unique.

We spoke with Drs. Polleux and Noonan as they embark upon their journey into the human genome. The researchers' ambitious project was made possible by the generous support of the NOMIS Foundation, an organization that funds high-risk, high-impact basic research aimed at tackling humanity's biggest questions.

What is the central question you plan to investigate?
Franck Polleux: We want to understand how the human brain evolved to become unique. That starts with our genome. Our goal is to investigate the genetic changes that have contributed significantly to the evolution of our complex brains.

James Noonan: This is an extraordinarily challenging task. The human genome is a big place. But we have a number of factors working in our favor.

In a worldwide scientific effort, researchers have mapped the human genome, as well as the genomes of many primate species closely related to us. By comparing these genomes, we can identify sequences in the human genetic code that differ from these other species. The question for us now is: Which of these genetic differences are important for understanding human brain evolution?

How will you identify the genetic changes that drove human brain evolution?
JN: We will each take complementary paths of investigation. In my lab, we study regions in the genome that control where, when and at what level genes are active during development.

We want to know how uniquely human genetic changes in these regions influenced the evolution of the human brain. We will focus our efforts on the role of a particularly relevant class of genome sequences called human accelerated regions, or HARs. HARs are regions of the genome that have been conserved over long periods of evolutionary time, meaning they can be found in the genomes of many species, largely unchanged. But in our genomes, HARs look different; they have evolved many uniquely human changes to their genetic sequence.

HARs largely serve to regulate the activity of other genes, including those that guide brain development. It is therefore likely that the sequence changes we see in HARs may have altered gene activity in ways that contributed to the evolution of the brain.

FP: In my lab, we study how the evolution of *new* genes may have driven brain evolution. In particular, I study a type of genetic change called gene duplication. As the name implies, gene duplication occurs when a region of DNA is copied and then inserted elsewhere in the genome. So far, dozens of these human-specific gene duplications have been mapped, and my lab was among the first to ask how these gene duplications influence brain development.

JN: Our first task is to identify promising HARs and human-specific gene duplications for further study.

Once you have identified the most promising candidates, how will you pinpoint their role in human brain evolution?

FP: We will first develop a mouse model to study the most promising human-specific gene duplications and HARs. By using CRISPR and other advanced genome engineering tools, we can introduce these changes into the genome of a mouse. We will then examine any differences in individual brain cells, or neurons. We can also monitor both structural and functional changes to groups of interconnected neurons, or neuronal circuits, and ultimately observe any large-scale differences in the animals' behavior.

JN: We will also observe human brain development in action, but there is no way to do so in a living brain at the level of detail that we require. Instead, we use induced pluripotent stem cells, or iPS cells, to build brain organoids, or "minibrains," in the lab.

iPS cells are a type of stem cell derived from mature adult cells. By giving these adult cells a special chemical mix, we can convert these cells back into their pluripotent, or stem cell, state. We can then direct them to develop into many different brain-cell types.

Working in close partnership with In-Hyun Park, PhD, of the Yale School of Medicine, we will use iPS cells from humans and closely related species to generate minibrains. By studying

how these minibrains develop, we can identify key aspects of brain development that are unique to humans and then link those differences to individual genetic changes.

How will your investigations provide insight into human diseases and disorders?
FP: One of the areas in which we hope to gain new insight is autism spectrum disorder, a socially devastating collection of neurodevelopmental disorders that have a strong but complex genetic basis.

A large fraction of genes implicated in autism affect the development of connections in the brain, called synapses. To understand the significance of this, we modified the brains of mice to be more similar to those of humans; to form these synapses in a manner more similar to the developing human brain.

We use a gene called SRGAP2 to do this. Several years ago, we discovered that SRGAP2 is duplicated in humans. We and others found that, in humans, SRGAP2 gene duplications drastically boost the number of synapses in the brain. By introducing the human-specific version of SRGAP2 into a mouse model, we can stimulate the growth of synapses.

We anticipate that this and other, similarly developed mouse models to be a more accurate and effective way to study how genetic mutations associated with autism affect normal brain development.

As you look to the future, what do you hope to achieve with this research?
JM: As a geneticist, I am captivated by the mechanisms that guide biology. Deciphering those mechanisms is the work of a lifetime. As we move forward with this project, I hope we develop a concrete, detailed understanding of uniquely human traits, of how and when those traits arose in our evolutionary history. If we can discover that, we are much closer to defining what “humanness” actually means.

FP: I also hope we make unexpected discoveries. It is often tempting in science to see the light under the lamppost, to search for answers in the easiest places to find them. But this project requires a leap into the unknown — a deep dive into regions of our genome that have yet to be explored and might reveal previously unknown features of human brain development. This collaborative project is ambitious, and we don’t yet know what we’ll uncover, which makes it so exciting.

###

COLUMBIA | Zuckerman Institute

MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

Grant Title: “Deciphering the evolutionary origins of human uniqueness”

Duration: Five years – 2020-2024

Columbia University’s Mortimer B. Zuckerman Mind Brain Behavior Institute *brings together a group of world-class scientists and scholars to pursue the most urgent and exciting challenge of our time: understanding the brain and mind. A deeper understanding of the brain promises to transform human health and society. From effective treatments for disorders like Alzheimer’s, Parkinson’s, depression and autism to advances in fields as fundamental as computer science, economics, law, the arts and social policy, the potential for humanity is staggering. To learn more, visit: zuckermaninstitute.columbia.edu.*

The NOMIS Foundation *supports and enables insight-driven science across all disciplines, focusing on researchers who put forth bold new ideas, exhibit a pioneering spirit and seek to inspire the world around them. NOMIS’ vision is to “create a spark” in the world of science by enabling pioneering research in the natural sciences, social sciences and the humanities that benefits humankind and our planet.*