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An Invitation: The Most Outlier Humans

Editor

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Photo by Tom Martienssen for Variant

By Josh Wolfe

This is not a traditional funding announcement. This is an invitation: to join in, to help out, to follow one of the most unique endeavors with which Lux has been involved — a company called **Variant.** The company's founders are as special as its mission: to find the outlier traits of outlier individuals (understudied and underrepresented) in outlier parts of the world, with the goal of discovering new therapeutics.

The opportunity at hand is fraught with risk, but if successful, Variant has the chance to be utterly singular and historic. The company was founded at root around a great people-driven human story — the story of survival and adaptation against the odds. If successful, Variant has the potential to unite us across the entire planet, connecting our varied ancestral histories to a shared future. It is based on a foundation of cutting-edge technologies and techniques as diverse in their range (from DNA sequencing to computational genomics to molecular biology to data-science-driven drug discovery) as the outlier populations with which Variant partners.

At Lux, we like to focus on finding and funding the outsiders, the misfits, the rebels of science and technology — people rejected by the crowd or choosing to reject it, confident in charting their own paths. This is because unconventional, unique and rare people and teams tend to achieve unconventional, unique and rare things. This is true with works of art; feats of athleticism; creations of code, architecture and design; scientific or mathematical epiphanies; or products of engineering or manufacturing. And as a result, the most rare things are often the most valuable — whether they are designed or discovered.

While great discoveries await us in outer space and among other planets, there is even more to discover right here on our own planet within ourselves. Variant was founded on the conviction that there are secrets that can unlock the future of human health (allowing researchers and scientists to find treatments and cures for what ails us) already existing in the undiscovered traits and biological code — the phenotypes and genotypes — of outlier humans in understudied and underrepresented regions of the world.

We love to say that the gap between sci-fi and sci-fact is shrinking. In the realm of unserious science fiction, Professor Charles Xavier employs a futuristic headset called Cerebro to help him identify and locate the rare unique outliers in the X-Men universe who have unreal superpowers like the abilities to conjure fire from their fingers, shoot lasers from their eyes or shroud themselves in cloaks of invisibility. But reality can be more surprising than fiction — and the serious science of modern genetics inspires us. With nearly 8 billion people on our planet, a rare unique trait with a miniscule 1-in-1,000,000,000 probability of occurring suggests that there might be 8 people who actually possess that trait.

What kind of traits are we talking about? There exist today humans all over the globe — even its most remote regions — that possess traits such as higher-than-normal metabolic rates that raise body temperature or burn fat while sleeping; very high-visual acuity and eyesight to see in very low-light conditions; bones with density that might withstand accidents that would traditionally break them; adaptations allowing easy respiration at high altitudes or survival at profound depths under water for very long periods of time.

The Variant founding team chastises us when we allude too much to science-fiction — as impressive, respected scientists and entrepreneurs, they rightly approach genetics from a place of ethical responsibility and scientific rigor. Co-Founder and Chief Scientific Officer **Kaja Wasik** earned her PhD in molecular biology from Cold Spring Harbor Laboratory, completed her postdoctoral work at the New York Genome Center and has spent her career developing novel sequencing platforms and bringing them to market. Co-Founder and Chief Technology Officer **Stephane Castel** has deep expertise

analyzing the genome to understand how genetic variation contributes to disease, having also earned his PhD in genetics at Cold Spring Harbor Laboratory and completing his postdoctoral research at Columbia University. Longtime friends and colleagues, they have traveled the world together handling the risky and unknown building partnerships with these outlier populations. They are led by an unusually rare combination of talents in CEO **Andrew Farnum.** A molecular biologist educated at Princeton University and Harvard's Kennedy School, Andrew most recently led the Bill & Melinda Gates Foundation's $2 billion strategic investment program. Prior to a decade with the Gates Foundation, Andrew worked at The Children's Investment Fund Foundation, developing private-sector projects in Africa and India, after working as an investment banker at Goldman Sachs and an investor at TPG focused on investments in the developing world.

They are joined by a growing group of incredible people like **Jay Flatley** (former CEO of Illumina), **Bruce Stillman** (President of Cold Spring Harbor Laboratory), **Rob Hershberg** (former CSO of Celgene), **Julie Sunderland** (venture capitalist and former Director at the Bill & Melinda Gates Foundation), as well as **Rob Scott** (CMO of Abbvie).

The Variant team has anthropologists working alongside molecular biologists, medical doctors and machine learning experts, geneticists, computer scientists and ethicists all embarked on identifying some of the most unique outlier traits (and the underlying genetics) in some of the most unique outlier populations in outlier parts of the world. We were so confident in their approach and vision that Lux invested $16 million in the company's Series A financing.

Variant is creating a global platform to search for phenotypic outliers, sequence their unique genomes, discover new therapeutic pathways, and ultimately treat common and previously intractable diseases. We believe they are amassing the most comprehensive dataset to date of extraordinary individuals and populations from which to make novel scientific discoveries and develop new therapeutics.

Using genomics for drug discovery is already a proven approach; genetically-validated targets are more likely to succeed in clinical trials. There are known targets such as the PCSK9 gene as a target for cholesterol or the CCR5 gene that conferred innate protection against HIV.

Variant's approach goes further. Instead of searching through millions of rows of existing DNA datasets (which are overrepresented by what are predominantly "pale, male, stale" U.S. or Europeans samples), they are starting with outlier populations, who are currently living in and have adapted to extreme environments, genetic isolation, or chance founder events that may have occurred thousands of years ago. Variant has already established partnerships in remote places where population dynamics lead to otherwise rare variants being much more common and where difficult-to-access geography has small populations with the right genetic architecture that have otherwise flown under the radar of the life sciences industry. And they already have the best kind of validation: Mother Nature has already designed the best genetic screen, and it selects for the most adapted individuals across a variety of geographies. That local enrichment means Variant needs many fewer individuals to make the same discoveries compared to those who rely on the databases popularly used. For example, a study of just 3,000 Samoans contributed to a significant finding related to obesity that ordinarily would have required studying tens of millions of Europeans to discover.

The Variant team has trekked to high-altitude Sherpa clinics in Nepal accessible only via foot where these communities thrive with very limited oxygen — their adaptation to low oxygen conditions could hold the key to treating lung disease. The team has evaded herds of sheep on foggy roads that were built by the descendants of Vikings to study unusual autoimmune phenotypes among the Faroese; they have stayed in maraes to learn about conducting genetic research with Indigenous Communities from the Māori.

From the beginning, the Variant team has insisted on a people-first ethos — approaching these communities with empathy and respect for their past and present, prioritizing ethics and careful consideration of individuals, families, ethnic groups, cultures and the cities, states and countries to which they belong. Notably, the very first recruits that the founders insisted on were ethicists and cultural anthropologists — pairing the hard sciences of computational genetics, sequencing and drug-discovery with a committed company culture to get everything right the first time when partnering with diverse cultures.

It was once said, in the context of social justice, that "whatever affects one directly, affects all indirectly." We are convinced those who are a part of the Variant journey will indeed prove that the diversity in our genetic differences — especially in the most different, unique and yet unknown of us — will end up uniting us through breakthroughs in science and global health. We invite you to join us…