Today, it is known that the vast majority of the most severe diseases—including cancer, heart disease, stroke, and neuropsychiatric disorders, among others—involve not just one, but a multitude of genetic components. Called “polygenic diseases,” the human diseases that cause the greatest amount of suffering and highest incidence of mortality, arise from a substantial number of genetic variants dispersed throughout the human genome.

For example, 450 million people around the world suffer from a mental health disorder. Estimates of the heritability of these disorders range anywhere from 40 to 80 percent, with 75 percent of mental illness beginning by the age of 24. And yet, our understanding of the genetic variants of psychiatric disorders remains limited. Neuropsychiatric conditions have complex mechanisms of development and are considered a “biological black box.”

Advancements in our ability to sequence the human genome, with its vast 3.2 billion nucleotide base pairs, have revealed that the DNA variants which give rise to unique traits in individuals also act in combination to mediate the risk of developing complex disease. Billions of dollars have been spent by hundreds of labs around the world over the past 15 years to shed light on the role of genomic variants in disease.

And yet, the translation of biomedical data into new treatments has been slow. That’s because genome-wide association studies (GWAS) identify the larger regions of the genomes that are strongly correlated with disease, but they don’t explain the underlying mechanisms or identify targets for prevention and treatment. To accomplish that, higher-resolution understanding at the single-DNA nucleotide level is required. Identifying the specific-risk nucleotides enables linkage to the medically important target genes that they control, opening the way for new strategies to reduce disease risk and to treat diseases once they arise. The true medical and therapeutic potential of the genomics revolution, therefore, has yet to be realized, because of a need for greater clarity as to how disease risk variants alter the cellular processes in the human body that lead to disease.

Dr. Paul Khavari and his team are opening the proverbial black box; they’re deciphering a language to decode the complexity of polygenic disease. At the frontier of the biomedical revolution, the Khavari Lab combines genomics, epigenetics, proteomics, metabolomics, and the latest artificial intelligence and bioinformatics technologies. By diving down to the level of variation at a single-letter position in a DNA sequence, called a single-nucleotide polymorphism (SNP), the lab is able to map gene pathways and localize exact nucleotides of pathogenic risk. This level of in-depth analysis—a broad and far-reaching effort that has never been attempted before—realizes the dream of precision medicine to unlock new therapeutic strategies with the goal of reducing and possibly even eliminating the risk of disease altogether.

“We have a dream to empower patients and their families to avoid the suffering and loss of loved ones that these diseases have wrought on humanity for millennia,” says Dr. Khavari.
THE ATLAS OF REGULATORY VARIANTS IN DISEASE (ARVID)

In the fall of 2020, the National Human Genome Research Institute of the National Institutes of Health recognized Dr. Khavari’s leadership in the field of genomics and human disease by awarding his research group with funding to initiate the human Atlas of Regulatory Variants in Disease (ARVID). The purpose of the ARVID effort is three-fold:

- Create a single-nucleotide resolution ATLAS of the genetic variants linked to risk of developing the 42 common polygenic diseases responsible for approximately 70 percent of human mortality.

- Generate the capacity for individualized RISK SCORES for each disease to guide early screening and prevention efforts.

- Extend atlas insights to understand disease pathogenesis as a foundation for NEW STRATEGIES for treatment and prevention.

This atlas is focused on diseases causing the majority of human mortality as well as other disease areas:

- The 15 most common types of CANCER, including cancers of the breast, lung, colon, prostate, skin, bladder, esophagus, kidney, thyroid, uterus, pancreas, ovary, and brain as well as melanoma and lymphoma.

- The TOP NON-CANCER CAUSES OF DEATH, including heart disease, stroke, type 2 diabetes, and Alzheimer’s dementia.

- The top NEUROPSYCHIATRIC DISORDERS, including schizophrenia, bipolar disorder, anxiety, major depression, panic disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), attention disorders (ADHD), and borderline personality disorder.

- Common SKIN DISEASES, including psoriasis, atopic dermatitis, acne, rosacea, vitiligo, Behcet’s disease, urticaria, keloids, dermatomyositis, cutaneous lupus, and scleroderma.

Taken together, these diseases afflict 85 percent of the population at enormous economic, emotional, and social cost, while causing more than 1.1 million deaths annually in the United States.

Each of these diseases is heterogeneous and influenced by environmental factors that interact with genetic vari-
A NEW RESOURCE FOR PHYSICIAN-SCIENTISTS

The data uncovered by ARVID will identify the functionally altered regulatory DNA variants linked to human disease risk and their target genes, enabling us to predict individual risk and identify individuals for early disease screening and prevention efforts.

ARVID will increase insight into the pathogenesis of specific diseases and provide new targets for innovative medicines, heightening our understanding of biochemical and biological processes that lead to disease. These efforts will also facilitate the development of new strategies for disease prevention, screening, and risk reduction by targeting the dysregulated pathways identified.

Annotating the human genome with a new layer of information on the functional regulatory variants linked to disease and the genes they modulate will improve and advance human health. The data uncovered by ARVID will identify the functionally altered regulatory DNA variants linked to human disease risk and their dysregulated target genes.

The resulting compendium of new knowledge will increase insight into the pathogenesis of specific diseases and provide new targets for early disease screening and prevention. It will also guide the development of innovative medicines based on a solid understanding of the genetic and biochemical processes that underpin inherited risk for the vast majority of human diseases.

NEXT STEPS

We envision the following path ahead to realize the potential of ARVID to transform medicine:

- First-generation mapping and early discovery
- Second-generation mapping and validation studies
- Dissemination of ARVID findings to the global scientific community
- Development of patient-facing disease prevention strategies
- Development of more precise and targeted interventions

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Support is needed to expand and accelerate the ARVID effort. When complete, ARVID will become an open platform for scientists around the world, providing more precise targets to test new therapeutics in clinical trials and develop treatments with greater potential for real and lasting healing.

Dr. Khavari’s work will also directly inform efforts at Stanford’s new Innovative Medicines Accelerator (IMA), a university-wide initiative designed to accelerate the translation of Stanford research discoveries into new medicines, while expanding our knowledge of human biology. The IMA will make it easier to create new therapies for rare diseases and those that primarily affect the developing world (and hence have less market potential). By pursuing innovative ideas and encouraging the development of cures, instead of more profitable long-term treatments, the IMA will help researchers across Stanford turn their best ideas into new ways to help patients.

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