Human Functional Genomics Project Begins
Unraveling Links Between Genes, Immune Response

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NEW YORK (GenomeWeb) – Earlier this month, researchers involved in the Human Functional Genomics Project (HFGP) published data on the relationship between genetics and human cytokine response in *Nature Medicine*. The data was derived from a first cohort, the 200 Functional Genomics project, and the researchers plan to publish more data from this cohort in *Nature Medicine* in August.

In addition, the HFGP just finished collecting patient data from a second cohort made up of 500 healthy individuals from Western Europe and aptly named the 500 Functional Genomics project, late last year. The HFGP researchers also recently finished collecting data from their LifeLines-deep cohort, made up of 1,600 healthy individuals from Western Europe.

The researchers are assessing and analyzing the 500 FG and LifeLines-deep data now and hope to publish preliminary results at the end of this year, Mihai Netea, member of the HFGP’s scientific advisory board and professor of the Radboud Center for Infectious Diseases (RCI) in the Netherlands, told GenomeWeb. They also finished recruitment and started data collection for their 300 Functional Genomics project, which is a cohort of 300 obese individuals, he added.

The human immune system is composed of a complex network of organs, tissues, cells, and molecules and has evolved to both protect the host against infections and to play roles in immune surveillance. However, it has previously been unclear what role genetics plays in influencing cytokine responses in health and disease.

The HFGP researchers aim to find out more about the role of genetics in immune response by characterizing and better understanding variation in human response through the use of various omics analyses — genomic, transcriptomic, metabolomic, and microbiomic — and in-depth functional phenotyping.

For each cohort, the researchers used a variety of tools to analyze patient samples, including microbiome analysis with the same tools and procedures used for the Human Microbiome project at the Broad Institute; genome sequencing and analysis with the Illumina HiSeq platform; cytokine profiling using flow cytometry analysis; and transcriptome data analysis of patient blood samples collected in PAXgene tubes and put in cell contact with various bacterial, fungal, and viral stimuli.

The project was founded in 2013 by scientists from RCI in the Netherlands, the Department of Genetics at the University Medical Center Groningen, the Broad Institute of Harvard University/Massachusetts Institute of Technology, and Massachusetts General Hospital.

Since its founding, the project has expanded to include several other collaborators, including the Academic Medical Center Amsterdam, University of Bonn in Germany, the Kilimanjaro Christian
Medical Center, in order to start including cohorts of healthy individuals from Eastern Europe, Africa, and Asia starting in the second half of this year.

Trying to determine the roll genes play in human immune response "is a very old question," Netea said. Previous studies of immune response have been limited by the number of patients involved and the number of variables researchers were able to take into account, he explained.

Researchers at the RCI Nijmegen, Radboud University, and the Broad Institute had been collaborating for some time on several studies. "We thought: 'Let's design a long-term study with several cohorts ... and try to understand the variability in the immune responses [of individual] humans in the populations,'" Netea said.

Research under the project has been funded by various grants awarded to participating institutions by agencies including the European Research Council and the US National Institutes of Health.

While research is ongoing, HFGP has already made some important observations about cytokine response. Netea and his colleagues have found "very clear cut data" that show immune response is modulated towards specific responses against an encountered pathogen rather than the modulation of a particular cytokine expression.

"[This] is evolutionarily very logical," Netea said. "And it has very important consequences. For example, if you respond well to a mycobacterial pathogen [such as E. coli] that's fine, but that says little about the immune response to a fungal pathogen."

They have also observed that polymorphisms found in regulatory regions involved in cytokine production play a much bigger role in genetic variation than polymorphisms in the cytokines themselves do. In addition, they have compared some of their own data with genome-wide association studies that have shown that genetic variation is overrepresented in genes associated with inflammatory cytokines more than genetic variation in genes associated with infections and autoimmune diseases.

The HFGP is not the only project looking into human immune response. Researchers at the Pasteur Institute began a project in 2012 called the Melieu Intérieur that is taking a similar multi-omics approach to differentiate genetic and environmental impact on the immune system. However, they are only looking in a single cohort containing 1,000 men and women of European descent, while the HFGP is expanding its research to people with different ethnic backgrounds, Netea said.

In addition to currently analyzing data from the 500 FG and LifeLines-deep cohorts, Netea and colleagues have also collected data for the 300 FG cohort comprising 300 individuals of Western European descent that have obesity with or without cardiovascular diseases. Future studies will collect similar cohorts of patients with HIV, type 1 diabetes, sepsis, gout, and recurrent vulvovaginal candidiasis. In addition, the project will also recruit cohorts of healthy individuals with different genetic and ethnic backgrounds.
Their aim is to better understand immune response in the context of autoimmune and autoinflammatory diseases and eventually be able to compare those results with the immune response data from the cohorts with healthy individuals.

The researchers also plan to make all of the data available in a public database after the publication of their initial analysis to encourage future research projects. Additionally, they have built a biobank of patient samples from the different cohorts. "In the future if some colleagues would like to collaborate and send us a proposal for a project, we can provide samples," Netea said.

Their hope is that their project and others like it will shed some light on how to treat patients with these autoimmune and autoinflammatory diseases.

"In the end, [we want to] try to understand what is happening in the patients," Netea said, adding that the ultimate goal would be to use this information to improve medical outcomes.