

## **How Can We Use Natural Variation in Disease Resistance to Understand Host Pathogen Interactions and Devise New Therapies?**

### **WORKING GROUP DESCRIPTION**

#### **Background**

The genetic variation in the genomes of pathogenic microbes and the organisms they infect provides a DNA sequence record of the evolutionary "arms race" between host and pathogen. Specific pathogens are increasingly recognized as powerful selective forces in the evolution of all organisms and similarly the need for the pathogen to adapt to the host is a major force driving pathogen evolution. Dramatic recent progress in genetics and genomics provides numerous exciting insights into this process, which may identify previously unrecognized host defense pathways, as well as new opportunities for therapeutic intervention.

Polymorphic susceptibility and/or resistance alleles at multiple genetic loci have been identified in human populations, as illustrated by the classic example of the sickle cell hemoglobin mutation, which confers resistance to malaria. The spectacular resources now available with the completion of the genome sequences for numerous mammalian hosts, as well as their specific pathogens, provide unprecedented opportunities to dissect these complex pathways of interaction and to identify new targets for therapeutic intervention.

#### **The Problem**

- Consider the numerous examples of genetic variation that contribute to the host response to infectious pathogens in terms of resistance, increased susceptibility, or varying response. Are there any general themes that can be derived from the growing number of examples of such genetic variants and are there specific approaches that can be taken at the genome level to identify large numbers of clinically important variants?

- As such specific resistance and susceptibility alleles are identified, often with widely different prevalences among human populations, what specific social or policy issues does this raise when approaching these populations?
- What approaches should be taken to increase the interaction between infectious disease experts and geneticists in harvesting this enormous dataset? Are new database structures and novel bioinformatic approaches necessary to effectively analyze this sequence variation information, including the interaction between the separate but ultimately related genomes of host and pathogen?

### **Initial References**

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## WORKING GROUP SUMMARY

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## Summary

Two people catch the same common cold. One suffers from a raging sore throat, weeks of sniffing and sneezing, and a nasty cough. The other breezes through it, barely noticing a sniffle or two.

Why? Is sufferer number 2 blessed with genetic differences that confer natural resistance? How can we use this natural variation to illuminate host-pathogen interactions and pave the way for new therapies?

Asking these questions may seem silly when talking about the common cold, but when dealing with diseases such as malaria, TB, or HIV, it could mean life or death.

At the end of four intense discussion sessions spread over three days, focus group 14.1—which included some of the leading scientists in genetics, medicine, immunology, cell biology, and engineering—had outlined an ambitious strategy for tackling the problem. But first they had to redefine it.

“We can’t leave the pathogen out,” one group member said. The group decided their assigned question, “How can we use natural variation in disease resistance to understand host-pathogen interactions and devise new therapies?” implied restricting the discussion to genomic variation in the host. The group felt that in elucidating host-pathogen interactions the pathogen could not be ignored, so the group decided to broaden the topic to include natural variation in the pathogen as well. Then, going one step further, the group decided to throw environmental variation into the mix, because environmental factors are sure to play a significant role in disease resistance.

Examples of natural resistance abound. There’s the famous relationship between the allele for sickle cell anemia and malaria resistance. Another example was provided by a group member who described a village in Africa where two tribes live together. Members of one tribe are completely resistant to monkey pox while members of the other tribe die from it. Another group member mentioned hepatitis B. Eight percent of people in China are infected with the virus, but while some die, others are fine. Finding the

underlying cause of this variability in disease resistance and using that knowledge to combat disease is becoming increasingly possible, given the advances in genomic science.

The group decided to focus on humans, a marked contrast to the other focus group dealing with this question, which decided to start with mouse models. Every member of the group agreed that sequencing the genomes of all humans would be ideal, however, that being unrealistic, the group thought it sensible to begin with large-scale association studies, most likely conducted in Africa, where the most variation exists and the burden of disease is profound.

The interdisciplinary studies would involve sequencing all host and pathogen genomes to identify the mechanisms of interaction and pinpoint therapeutic or vaccine targets. The ethical and legal issues would be staggering, but the group felt the potential benefits to society of controlling or eradicating deadly diseases would make the endeavor worthwhile.

Of course, the cost of sequencing a human genome (currently around \$20 million, though that price tag will soon drop to around \$100,000, according to scientists at the conference) will have to come down significantly before such studies are feasible. But technologies are constantly improving and the \$1,000 genome is not far off, according to another group at the conference.

*Large cohort studies: It's all about the phenotype*

One of the key problems that arise when carrying out large-scale association studies is the issue of phenotypic characterization. Diagnosing diseases accurately is difficult in developing countries like Africa, where many people are infected with more than one pathogen, as well as multiple strains of the same pathogen, and environmental conditions are extremely variable.

The best approach is an integrative analysis, in which the host genome and the pathogen genome are evaluated together, in an environmental context, to determine the effects on the phenotype. This would require people who view things from the

perspective of the host to work closely with people who analyze the behavior of pathogens, an important development resulting from these types of studies.

“In most medical schools, for example, there’s a department of infectious disease and there are people who work in human genetics and they rarely talk to each other,” the group spokesperson said at the final presentation. This has slowed progress in genomic research in regard to infectious disease, according to the group. The studies the group proposed would get the two disciplines talking, which is one of the goals of the National Academies Keck *Futures Initiative* Conference.

The studies would also require tools for detecting and analyzing multiple infections, and multiple strains of the same infectious agent—quickly and cheaply. An ideal device would be handheld, would run on batteries, and be able to separate and sequence the host genome and the genomes of all the microbes in a single drop of blood.

Assuming that sequencing becomes affordable, and appropriate technologies become available, another challenge associated with these studies is finding large, diverse study populations. “To really pull this thing off you may need study samples on the size of 10,000 humans,” the spokesperson said.

With projects of this scale, the ELSI—or ethical, legal, and social issues—would require serious time and attention. For instance, there would be an obligation to follow up with medical treatment for all the participants. “If you’re going to screen for something, you’re obligated to tell them about it and treat them,” a group member pointed out. Cross-cultural communication issues would also arise. The group felt that to alleviate some of these problems, partnerships should be cultivated with local scientists and public health officials. This would help researchers get a feel for the local ethical and political attitudes.

These partnerships would be part of a broader infrastructure needed to appropriately integrate local data collection with large-scale genomic science. To carry out what the group called “big science,” consortia would be needed involving partnerships between public and private institutions, to help address multiple diseases and to advance funding opportunities, and between scientists and legal professionals, to aid in obtaining informed consent and addressing privacy issues.

*Finding pathways and selecting targets: Quite an obstacle course*

Inferring pathways of host-pathogen interaction from the data on genomic variation would be a daunting task. The group decided protein-protein interactions would be the place to start and called for a systems biology approach, in which many complex interactions are integrated in order to produce a model of the whole system. They also acknowledged the need for computational tools to make inferences about interactions. Statistically speaking, dealing with three sources of variation—in the host, the pathogen, and the environment—would be a challenge.

Once the pathways are found, possible therapeutic or vaccine targets would have to be identified. This is a challenge in drug or vaccine development because target selection has been notoriously poor in the past, leading to failed product development. "Knowing the variation of the host and pathogen allows us to select targets that are less likely to fail," one member assured the group. Once the candidate gene is identified through genome sequencing, the key would be to select multiple targets, looking at other genes found near the candidate gene that may influence its function. With the targets in hand, the next step would be to carry out standard methods of drug development, including target validation in animal models, functional assay development, and high-throughput screening to identify promising leads. The group decided the main obstacle for this phase of the project would be developing appropriate assays, which are expensive and time consuming. One solution would be to bring in additional funding from private companies at this stage. The group said these funding sources usually come in at a later stage when there is less risk, but involving them earlier would be crucial for this project.

*Societal benefits: Where health goes, money follows*

"If you improve health in general in a population, you get what's called a demographic transition," a group member said. After an initial boom in population, people start choosing to have smaller families, which helps lead to economic

development. In addition to the obvious benefits of improving health and economics, these studies would increase research and development capacity in developing countries by building facilities and forming partnerships between local scientists and large institutions.

From a scientific standpoint, the group felt the project would increase basic understanding of how humans and pathogens interact, and provide a model for interdisciplinary science.

There was some discussion of the possible advances in personalized medicine that could come from these studies. The group agreed that a “one size fits all” approach is the norm right now in drug development and that this approach has serious limitations. One group member described the process of prescribing medicine as a game of trial and error. The doctor says, “Try this, it usually works.”

The studies that the group proposed could be geared toward improving the “one size fits all” method by looking for a “magic bullet” that would really fit all. But the group members agreed that finding magic bullet cures for diseases is very unlikely and decided the studies should be designed to encourage development of more precise personalized medicine, where the right therapy is selected for the right person based on the person’s genotype.

By the end of the four sessions most of the group members were satisfied with the plan they had proposed. They called for science at its grandest: large cohort studies built on complex infrastructures and partnerships with the goal of finding therapies for the world’s deadliest diseases, using natural genomic variation as a guide. Some thought the strategy should involve more population biology, and others weren’t sure whether the question was answered as fully as it could have been, but most were content.

“It was kind of nerve wracking at first, but it came together,” one group member mused. As the group got up to leave at the end of the last session, another member said, “So we’re done. It’s kind of sad. It’s like the end of summer camp.”