

Policy Perspectives from Members of the Scientific Community
Q & A
Gerald R. Fink, Ph.D.

DR. WILLARD: We'll open this up to the committee for questions, I think it would be helpful under the circumstances if you would identify yourself when you're asking the question so that Dr. Fink has something more to go on than just a voice.

Julio?

DR. LICINIO: Dr. Fink, in light of the data that you presented with the complex but not so complex trait in yeast, is there any hope to find anything for human disease? That's my question.

DR. FINK: The short answer is yes, but I believe that the nature of human genetics is such that techniques that have worked for plants and worked marginally for yeast will need to be constantly evaluated. These are questions of statistical significance, as one cannot do breeding studies. I was just at a meeting where scientists reported data on a very measurable human trait, high blood pressure, which they successfully identified in small populations genes that affect high blood pressure in those populations, and these were single Mendelian traits. But the attempt to find the multigenic traits responsible for high blood pressure is still an ongoing research project.

So I think the short answer to your question is that I think these techniques can be refined. The question is whether one will be able to find -- if you get too many genes involved in a trait, and it doesn't matter whether it's yeast or humans, then each gene will have such a small effect that, of course, it questions the use of the study. But if there are a small number of genes that affect a trait, then I think, even given our limitations in providing information to the human geneticist, I think that one will be able to extract these data. But I don't think it's going to be easy.

DR. WILLARD: The next question, Emily Winn-Deen.

DR. WINN-DEEN: Thank you for a really very insightful presentation. My question was about pilot studies. It's been brought up that there actually are potentially some existing studies that could be used as "pilot studies," for example the Framingham Study and the Women's Health Study. Do you think it's necessary to initiate new pilot studies, or would a retrospective analysis of what worked and what didn't work in some of these other longitudinal population studies be sufficient?

DR. FINK: I have some familiarity with the Framingham Study. There's a former student of mine who is now the head of the Human Genetics Department at Boston University and is involved in looking at high blood pressure in the Framingham data.

The reason for initiating a new study -- and I don't have the breadth of information to know all the pilot studies that are going on. My visceral response to that is that the Human Genome Project has added a dimension, a new dimension chronologically that makes some of the earlier studies that didn't collect information in the way that would be important to make statistical differences or don't even have the material, we'd make a new study mandated. Again, I don't know all the pilot studies that are going on, but certainly this is a criticism of some of the earlier studies, that some of the material, either the material or the family histories were not adequate to provide the kind of information that would enable a study like this.

DR. WILLARD: Next question, Robinsue, and Robinsue, you might identify the nature of who you're representing for his benefit.

DR. FROHBOESE: Sure.

Good morning. Robinsue Frohboese with the Office of Civil Rights at HHS.

Dr. Fink, at the conclusion of your remarks, you briefly mentioned the ethical issues of race, gender, age, and I know that some speakers later on today will be addressing these issues in greater depth, but I wondered if you could share with us a little bit more about your insights in this area and the ethical issues that you perceive.

DR. FINK: I have to admit I'm somewhat naive about these ethical issues. I don't mean to sound simpleminded, but I think that scientists are not always in control of the information, and that information clearly can be used by the press and by anyone for their purposes. I remember when there was testing for sickle cell anemia. It was at the time I was at Cornell University. There was testing for sickle cell anemia, and George Foreman, I believe, was on the front page of a newspaper bringing African American children for testing for sickle cell anemia. He was an advocate of it. But the atmosphere quickly changed from being a positive public health measure to a negative one.

I certainly did not anticipate this. So I think it's these unanticipated aspects that you get to anticipate from a pilot study. You can't know them in advance.

DR. WILLARD: I think we have time for two more questions. First, Francis.

DR. COLLINS: Hi, Gerry. This is Francis Collins. I appreciate your thoughtful comments on this. It's certainly true that there are many issues that ought to be considered before undertaking a project on the scale of this, and the reference to the Human Genome Project and all of the planning and specific identification of milestones is well taken.

In terms of your proposal for a pilot project, I think we're blurring a little bit here between two kinds of study designs. There is basically the case/control study design, which is the sort of pilot I think I hear you asking for, where you have affected and unaffected individuals or you have a group on which you've measured a quantitative trait, the kind of study which is going on all over the place now, particularly with the HapMap having come forward now and made it possible for people to do whole-genome association studies as opposed to pedigree-based linkage approaches, which we know have been rather underpowered when it comes to quantitative traits and polygenic conditions, and I would say that kind of pilot not only is getting underway but has even succeeded in some instances, and I would point to the dramatic example of age-related macular degeneration, the most common cause of blindness in the elderly.

Here's a disease which is very late onset where the evidence for heritability was perhaps a little spotty, and yet we now have not one but two loci identified in the course of the last six months. One of them contributes about half of the attributable risk of that disease from a single variant and complement factor H. So at least for that one example, what we thought might be a very complicated situation turns out to be simpler than anyone expected, with a couple of different loci contributing a very significant part of the risk, not to say that that will happen all over the place.

You can look at type 2 diabetes, where a lot of people have been doing case/control studies based upon linkage analysis, but now increasingly on genome-wide association, and I think everybody

would agree that we do have three variants for type 2 diabetes that hold up in multiple studies. They don't contribute a huge amount of the attributable risk, but they do point you towards potential drug targets that could be very valuable to follow up on.

In the quantitative trait arena, I have seen data on long QT syndrome that is probably going to be presented next week at ASHG that suggests that it is possible to prove the principle that you're asking us to look at for a very quantitative kind of trait. This is not people with long QT syndrome. This is just people who are normal in the population who have had EKGs where the QT interval has been measured, and that's been assessed by looking across the genome, again with a HapMap-based approach and association studies, and identified what appeared to be quite impressive evidence of loci involved.

So taking all of your points about how hard this has been in yeast, maybe this time the proper study of humans will turn out to be humans, and we're a better model organism for ourselves than we realized, and the advantages of working with a newly arrived population like Homo sapiens, because we are so much alike, will make this kind of study more tractable than expected.

Again, I just wanted to challenge a little bit this argument that we need to carry out this sort of pilot project on case/control studies as if it wasn't happening, because it is happening all over the place, and I think you can see already signs of pretty good evidence of success. But what the population cohort study has is a really different kind of idea in mind. It is, frankly, not so much designed to do discovery of variants that are involved in quantitative traits for diseases. I think a lot of that will come out of case/control studies. It's really designed to quantitate exactly what does a variant contribute to risk, because case/control studies will always be a little biased in that regard, and most especially to assess gene/environment interactions, which are very difficult to do with case/control studies because you often have a recall bias problem.

So maybe several of these issues could be talked about during the course of today, because I think they're important to keep somewhat separate in our minds. Again, I guess I think maybe it's a little optimistic, but I think we can assume that in the course of the next couple of years, because of the tools that are available and the decreased costs of being able to do really prodigious amounts of genotyping, that the case/control arena is going to provide the kind of pilots that you're interested in. To undertake a U.S. population cohort study is going to take at least a year or two of planning. So don't worry, that pilot data I think will undoubtedly be in hand in considerable amounts long before one would consider enrolling the first subject in a prospective cohort kind of design.

DR. WILLARD: I don't hear a response, so I'm going to move to the next question, the last question. Muin Khoury.

DR. KHOURY: Yes, Dr. Fink, this is Muin Khoury from the Centers for Disease Control and Prevention. I heard you mention in passing CDC, and I wanted to pick up on a couple of threads about the major differences between the Human Genome Project and the large population cohort.

It's obvious from your discussion and from what has happened in science that the Human Genome Project was designed with very specific endpoints that were met, under budget, and in shorter amounts of time. Here we are embarking on something more open-ended that is not clear how long and how costly it will be, regardless of what the scientific merits are.

You mentioned an early yardstick of success, benchmarks of success in such an endeavor, and I wanted to ask you what you might think as we plan ahead or plow ahead in this regard, what

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could be some benchmarks in this endeavor. Before you answer, I just wanted to insert my public health perspective because there is a lot of data collection that public health agencies do, like birth defect surveillance systems and cancer surveillance systems and population surveys like NHANES, that are open-ended, and we collect information on large amounts of people, and nobody says at the end of the day you've succeeded or you've failed, because the endpoint is a bit different. We're not trying to test a scientific hypothesis but we're trying to develop a resource by which we can quantify how many people are affected with a certain disease and what's the relationship between different parameters in the general population.

So I don't know if that kind of feeds into your idea when you mentioned CDC or not. But anyway, can you elaborate on what you think are parameters of early success? With the Human Genome Project, when things moved forward, they were under-budget, there were some benchmarks. What could be some benchmarks in this endeavor that could galvanize the scientific community and get them to buy in rather than be scared by such an endeavor?

DR. FINK: I think that's a question for Francis. I mean, I could think of some, but I don't know what he would consider a benchmark for success.

DR. WILLARD: I think we're asking you, Gerry.

DR. FINK: I see.

DR. KHOURY: What do you think Francis should think?

(Laughter.)

DR. FINK: I could imagine some. I mean, it seems to me that in the case of spina bifida, for example, if it turned out that one found that there were in the population people who were particularly deficient in folic acid, it would be very useful to have the kind of information (inaudible) people to a vitamin deficiency, for example, just to take off on your CDC study, which in some ways is open-ended because you can't really identify subpopulations who are specifically at risk, but with these data you could.

DR. WILLARD: Well, with that, and in the interest of time, Dr. Fink, I want to thank you for your time this morning and for sharing your insights with us, and particularly appreciate your doing it as you're marching off to teach a class of MIT students. But thank you very much.

DR. FINK: Thank you all.