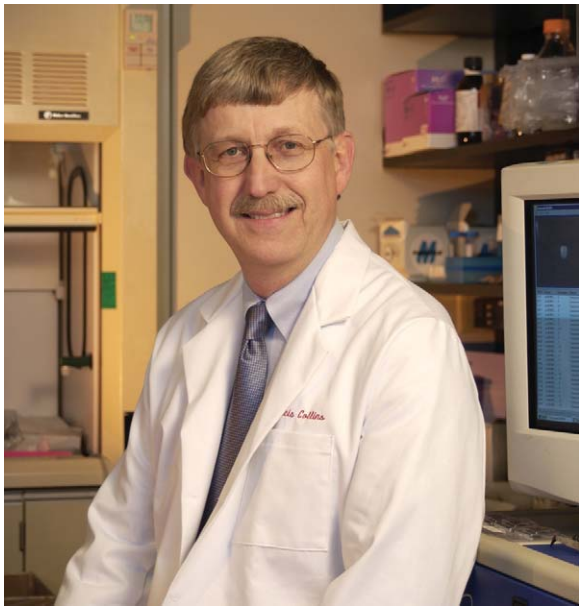
No Longer Just Looking under the Lamppost*

Francis S. Collins



Francis S. Collins

It is an honor to be receiving this award from a Society for which I have the greatest affection and admiration. There are many friends, former students, post-docs, and colleagues whom I would love to acknowledge, but I won't be able to in these brief remarks. I would, however, like to recognize and thank one person, and that's my wife, Diane Baker, a long-term member of this Society. Her stalwart support over the many bumps in the road the last few years has never wavered and is deeply appreciated.

This Society has meant a great deal to me in the course of the last 27 years. I started out as a physical chemist, did a right turn into medicine, and then discovered genetics as a promising area of medicine that was appealing to somebody with a quantitative sense. But there weren't a lot of role models for me to observe, because, in those days, medical genetics was not a field that was widely represented, particularly in internal medicine, which was my clinical choice. So, I came to the meeting of the American Society of Human Genetics (ASHG) for the first time in Vancouver in 1978. (At that time, I was a junior resident in internal medicine in North Carolina.) I will always treasure that experience—and I hope that those of you attending this meeting for the first time will feel the same excitement and exhilaration that I experienced on that amazing trip 27 years ago.

It was a little different then: there were only ~500 people at the meeting. The first afternoon, Y. W. Kan stood up and described how he and Andrée Dozy had identified a particular restriction fragment–length polymorphism (RFLP) that was associated with the presence of the sickle mutation. They essentially described human linkage disequilibrium and how it could be used for diagnostics. Wow, that was exciting! In that same session, Mark Skolnick talked about how the use of RFLPs might be generalized. Of course, that concept then emerged later on in a famous paper[1] that laid the groundwork for mapping human disease genes by linkage, even when you didn't know what the function of the gene was. That became the first step in positional cloning.

Then Uta Francke, later to be one of my most significant mentors when I was a fellow in genetics at Yale, described how she had been able to stretch chromosomes out, to look at extended, high-resolution banding patterns to detect small deletions and inversions that otherwise had escaped detection. Pretty impressive stuff, all in one afternoon!

More than that, there were role models in great abundance at the ASHG meeting, including Lee Rosenberg and many others. And some of them were even internists, which gave me confidence that this pathway was viable. That really clinched my decision to become a medical geneticist—and the ASHG meeting has reinforced that decision every year that I attend. I've only missed one meeting in 28 years.

I went on to become a genetics fellow at Yale, under the able mentorship of Lee Rosenberg, as the department chair, and Sherm Weissman, as my research supervisor. From the perspective of a genetics fellow in 1981, there were a lot of exciting things going on, but there were also some stiff challenges that lay ahead. Recombinant DNA had come along, making it possible to clone and study human genes. DNA sequencing was possible, although, in those days, we did it with radioactive isotopes. It was not for the faint-hearted to be involved in a laboratory that did a lot of this stuff, because your Geiger counter was always going off when it wasn't supposed to—especially in Sherm's lab!

We also had lots of clinical information in 1981 about

From the National Human Genome Research Institute, National Institutes of Health, Bethesda

Address for correspondence and reprints: Dr. Francis S. Collins, National Human Genome Research Institute, National Institutes of Health, Building 31, Room 4B09, 31 Center Drive, Bethesda, MD 20892-6050. E-mail: fc23a@nih.gov

* Previously presented at the annual meeting of The American Society of Human Genetics, in Salt Lake City, on October 28, 2005.

Am. J. Hum. Genet. 2006;79:421–426. 0002-9297/2006/7903-0003$15.00

medical genetic conditions that Victor McKusick had catalogued. But, for most of those conditions, the specific gene mutation remained unknown. A few disease genes, such as that for hemophilia, were being cloned because something was known about the functional consequence of the gene mutation—allowing one to work backward from the protein to the gene. But that knowledge wasn't available for most genetic disorders. And to be forced to take a candidate-gene approach for these thousands of disorders was generally not very rewarding. That brings me to my metaphor for today's presentation.

The metaphor relates to the story of a person who realizes he has lost his keys after spending a few too many hours at the bar. Looking up and down the dark street, he decides to focus his search under the single lamppost. His friends come along and inquire, "So, what's the problem?" He responds, "I've lost my keys." And they say, "Well, why are you just looking in this one place?" And he says, "It's where the light is."

That's the same situation we faced in the mid-1980s when trying to find the genes for most Mendelian conditions. We really desperately wanted to understand them, but we lacked enough biological or biochemical information to be able to know where to look. That challenge inspired a host of people to develop a new strategy, which we now call "positional cloning."

As a fellow at Yale, I developed a method called "chromosome jumping" that allowed one to cross chromosomal regions in jumps of 100 kb or so. When I became an assistant professor at the University of Michigan in 1984, I looked for a place to apply this to a human genetic disease. Several conditions seemed particularly appealing: cystic fibrosis (CF), Huntington disease, and neurofibromatosis. But, at that point in 1984, only one of those, Huntington disease, had been mapped.[2] This was the first success of RFLP mapping; later, of course, there were many hundreds more.

The focus of my own small laboratory was to try to jump from a linked marker to the actual disease gene. Ultimately, CF, which I first encountered as a clinical disorder while serving as an internal medicine resident, became a very appealing target. Here was a disease that was particularly common and that caused a great deal of suffering and early death. Despite the advances that had occurred in management of CF over the course of the preceding decades, there was still little known about its molecular basis. Without knowing the nature of the gene that was responsible, it was hard to know how research could move forward. As a first step, the CF gene needed to be mapped. That breakthrough was announced, exactly 20 years ago, at the 1985 ASHG meeting, also in Salt Lake City.[3]

In short order, the candidate interval was reduced by linkage analysis to ~2 million base pairs on chromosome 7, between two flanking markers. But there were no additional clues to help narrow that daunting interval.

Tackling a problem of this difficulty in the 1980s was a high-risk undertaking. I found myself trying to defend why my own small laboratory was foolish enough to take on such a hard problem. Months passed with little progress. I tried to come up with metaphors about how hard this was, in order to explain to colleagues why we hadn't succeeded yet. I even went to a local farm in Ann Arbor to have my picture taken holding a sewing needle while sitting in a haystack.

But what finally led to success was meeting up with Lap-Chee Tsui's group in Toronto and deciding, at the 1987 ASHG meeting, that our two groups would work together. The energy generated by the complementary nature of our approaches ultimately allowed the crossing of an unprecedented amount of genomic territory.

Jumping and walking across 400 kb, we encountered a large gene with 24 exons. Defining the anatomy of this gene now seems trivial, but, in those days, it was quite a challenge. Ultimately, we became convinced that the deletion of just three base pairs—CTT—is responsible for ~70% of the causative alleles for CF. This is the ΔF508 mutation.[4] Jack Riordan, Lap-Chee, and I celebrated by sipping on Canadian whiskey in coffee cups in Lap-Chee's office that summer of 1989.

Although the search for the CF gene was ultimately successful, it was enormously frustrating along the way. It took years of effort and a lot of resources, both in terms of intellectual capital and financial capital, to find this one gene. If we were going to extrapolate such efforts to the hundreds or thousands of disease-gene targets that one would like to see successfully identified, we had to have better tools. In this way, I think the CF gene discovery served as an additional impetus for the genome project to get under way. Finding the CF gene proved that positional cloning could work but also demonstrated that more-efficient methods would be needed if we were going to see these discoveries occur on a larger scale.

I was a strong supporter of the Human Genome Project, but I never expected to lead it. It was with some trepidation, therefore, that I came to the National Institutes of Health (NIH) to direct the U.S. genome effort, beginning in 1993. I will not dwell on that experience, because you've heard much of that before. But I will have to say what a marvelous group of scientists I had the privilege of working with. We produced a draft sequence of the human genome in 2000, published an analysis of that draft in 2001,[5] and went on to finish the sequence in April of 2003,[6] 2 years ahead of schedule.

The genome sequence lit up the whole street—no more just looking under the lamppost. This provided the opportunity for people chasing down Mendelian-disease genes to be able to search through the whole genome swiftly and efficiently. What we labored for years to do with CF could now be essentially accomplished by a single graduate student in a matter of a few days. The results were spectacular: today, genes have been identified for >2,000 Mendelian conditions.

But that is not the end of the story. There still are plenty of rare Mendelian traits for which we do not have answers.

Linkage may have mapped the gene, but the interval is still too large, and the candidate genes have not panned out. What then?

To respond to this, the National Human Genome Research Institute (NHGRI) has mounted a new program. We will devote a significant component of our prodigious sequencing capacity (roughly 150 billion bp per year) to medical applications. We are seeking your advice about interesting targets—including both Mendelian and non-Mendelian conditions—where large-scale sequencing could push the field forward.

But what about the genetics of common disease? Despite all the tools produced in 2003 by the Genome Project, Joel Hirschhorn, who has kept track of the reporting and validation of genetic variants associated with common disease, told me earlier today that he only believes in about a dozen gene variants that cause susceptibility to common disease like diabetes. While that number is a lot better than 5 years ago, we want to make this list grow faster. The problem is difficult, however, because linkage, which has been such a successful workhorse for Mendelian conditions, is woefully underpowered when it comes to polygenic conditions. Risch and Merikangas showed us almost 10 years ago that association would be a more powerful approach.[7] The problem, of course, is that comprehensive association studies for complex diseases, such as diabetes, have not really been possible in the past—you were forced to pick candidate genes, and you were usually wrong.

Does this sound familiar? We're back in that same "searching under the lamppost" scenario. Clearly, we need a more systematic way of approaching this complex disease–gene search that doesn't force you to know the answer before you start.

That's what the International HapMap Project has been all about. This is an organized production effort that has been carried out by a wonderfully dedicated group of scientists from six countries. By February 2005, we had completed a Phase 1 map of >1 million SNPs, genotyped across 270 DNA samples from four different populations. Phase 2, including 4 million SNPs, was completed last summer, and the analysis of Phase 1 was published in October 2005 in *Nature*.[8] Using the HapMap resource, you can effectively survey the entire genome for evidence of association with ~300,000 SNPs for European or Asian samples and ~500,000 for African samples.

Some of the early successes with HapMap have already been reported in publications or at this meeting. Perhaps none is more impressive than the discovery that a polymorphism in the complement factor H gene contributes approximately half of the attributable risk for age-related macular degeneration.[9]

As another example, type 2 diabetes (T2DM) is one of those conditions that all of us hope will greatly benefit from the availability of HapMap. Working with my colleague Mike Boehnke and several other collaborators around the world, we have been trying for 10 years to track down susceptibility variants for this common disorder, and it is a challenging problem, to be sure.

The Finland-U.S. Investigation of noninsulin dependent diabetes mellitus (FUSION) study has managed to collect thousands of DNA samples from affected and unaffected individuals in Finland. We have applied the strategy of linkage analysis to >700 affected sib pairs across the genome. There have been a few interesting linkage signals, particularly on chromosomes 6, 11, 14, and 20. With the availability of high-density SNP maps, we were recently able to follow up the chromosome 20 signal, and were able to identify associated variants that are near the P2 promoter of the HNF-4α gene.[10] Loss-of-function mutations in this gene cause maturity-onset diabetes of the young, but we had previously excluded its role in T2DM. Now, we know that our original conclusion was incorrect because we were just looking at the coding region, and the associated variants lie far upstream. Another group led by Alan Permutt in St. Louis independently came up with the same finding in a group of Ashkenazi Jews,[11] and several other teams have also now confirmed this same association.

While this was a gratifying outcome, we are certain that other important susceptibility genes were missed in our first phase of linkage analysis. So the next step of whole-genome association studies for T2DM is anticipated with great excitement. In fact, several groups around the world that are studying T2DM recently agreed that this would be a great time to collaborate and pool their data as we move into this new phase.

How successful will this strategy be? We don't really know. But I've recently made a wager with my former chairman, Tom Gelehrter. Tom is a professional cynic; I'm an incorrigible optimist. So, we're going to see who's right this time. I'm betting that, by the time of the ASHG meeting in 2008, whole-genome association studies will have led to the discovery of at least four *validated*—not just guessed at—susceptibility variants for at least five common polygenic diseases. I've asked Joel Hirschhorn to be the referee. And, of course, the wager is substantial: one beer of the winner's choosing.

If I'm even close to right, the Congress had better get busy. That's because we will then be in a circumstance where risk-predicting genotypes will be available for lots of people, initially as part of research and ultimately as part of clinical care. If that information can be used against someone in health insurance or the workplace, then we have not lived up to our social responsibility to prevent that kind of discriminatory misuse. A current bill (S.306/HR.1227) currently under consideration in the United States Congress would solve this. The ASHG has been very effective in supporting that bill, but it will take lots of grassroots support to get it over the finish line.

So genomics holds the promise of revolutionizing understanding of disease and even leading to risk prediction. But what about therapy? Let me tell you a story about a rare-disease research project in my own lab that is leading

toward treatment at a surprising pace. I first encountered this condition when I was a clinical fellow at Yale. During my first week, I was told: "You're pretty lucky, because you're going to be assigned our most famous patient."

That patient was Meg Casey. Meg carried a diagnosis of Hutchinson-Gilford progeria syndrome, the most dramatic form of premature aging—although, at the age of 23, Meg had clearly lived longer than most do with progeria. Most children with this disorder die of cardiovascular complications—usually heart attack or stroke—at about age 12 or 13.

Meg was a feisty advocate for the disabled. She could disarm anybody who took her less than seriously because of her diminutive height and high-pitched voice, by unleashing the most impressive stream of sailor's language that you can imagine. She almost single-handedly worked to make Milford, CT, accessible to the handicapped. Meg was also absolutely charming and spunky. It was a great honor to take care of her for those 3 years.

Because of Meg, I got very interested in progeria and wondered why more wasn't known about this condition. The problem was that the disease never recurs in families. How could a geneticist start chasing after the gene when there were no multiplex pedigrees?

Sadly, Meg died about 3 or 4 years after I left Yale, and I stopped thinking much about progeria. Then, about 5 years ago, I met a boy named Sam who has progeria in the classic form. Sam's parents are both physicians; after learning of their son's diagnosis, they started the Progeria Research Foundation. They came to me asking for advice about how to get scientists interested in working on this problem. After a few conversations, I was hooked! A fearless post-doc in my lab, Maria Eriksson, agreed to take on the task of trying to find the gene for this disorder, even though the tools to do so, lacking pedigrees, were pretty limited.

Through a combination of hard work and serendipity, Maria was able to show that the gene had to be on the long arm of chromosome 1. That achievement was almost a course in human genetics, involving a host of unexpected phenomena, such as somatically acquired uniparental segmental isodisomy. Ultimately, the location of the gene was narrowed to ~6 Mb, within which was located an attractive candidate gene: the gene for lamin A. This gene had already been implicated in six other genetic diseases, with the phenotype apparently depending on where in the coding region the mutation fell. One of those diseases, mandibuloacral dysplasia, had enough similarities to progeria that the two disorders were occasionally confused.

So, the lamin A gene seemed like a very good candidate for sequencing. Maria's efforts were quickly rewarded by finding that 95% of patients with classic progeria had a single-nucleotide substitution of a T instead of a C in the third base of codon 608.[12] We found one other patient with a mutation just 2 bp upstream in the same exon. In every instance in which we had access to parental DNA, the parents were normal, so these were sporadic de novo mutations.

We were puzzled, however, when we looked carefully at the genetic code. The mutation converted a GGC codon to a GGT codon; both code for glycine. By most definitions, this would be called a silent mutation. But from a geneticist's perspective, this recurrent de novo point mutation had to be the cause.

A bit of reflection upon the experience of working on thalassemia with Bernie Forget and Sherm Weissman 20 years earlier, however, helped me realize that there was something else about this sequence that looked familiar: the normal sequences of codons 606–608 look quite a lot like a splice donor, and that similarity increases if either one of these two progeria mutations occurs. So, Maria and I postulated that the mutations created a functional splice-donor sequence in the middle of exon 11, causing skipping over the rest of that exon, leaving out 150 bp and deleting 50 aa. The stop codon for lamin A is located just inside exon 12, so the abnormal splice form would still produce a protein with the correct C terminus.

Fortunately for us, we had fallen into an area of extensive prior investigation by cell biologists. Lamin A is a major structural protein that holds the nucleus in its appropriate shape. It is located just under the nuclear membrane and interacts with a host of other proteins, some of which cause genetic diseases like Emery-Dreifuss muscular dystrophy. In addition, some fraction of lamin A floats around in the nucleoplasm and has been shown to interact with certain transcription factors.

Noting this, we looked closely at the nuclei of cultured skin fibroblasts from children with progeria. Our efforts were rewarded. In early passages, progeria fibroblasts have nuclei that look rather normal. But, as the cells go through later passages, the nucleus becomes quite abnormal. Nuclear blebbing and herniation are eventually observed for the majority of cells, and their morphology can be quite bizarre and dramatic. Eventually, this leads to premature death of the cells, although we are still not quite sure by what mechanism this occurs.

So, how does this protein that is missing 50 aa cause such havoc? Again, we were much benefited by all the work that had been done by biochemists and cell biologists to define the normal processing of this particular protein.[13] Lamin A has a CAAX box at its C terminus, which serves as a recognition site for the farnesyltransferase enzyme. A farnesyl lipid group is added to the cystine, and then an additional enzyme cleaves off the last 3 aa, which happen to be serine, isoleucine, and methionine. Then, there is an additional processing step catalyzed by an enzyme first identified in yeast but that has a homologue in humans called "ZMPSTE24." This enzyme cleaves off 15 aa of the C terminal fragment (including the farnesyl tail), releasing mature lamin A.

Farnesyl groups tend to anchor proteins in cell membranes, so one might guess that pre–lamin A is initially anchored in the nuclear membrane after this hydrophobic

lipid is added. However, to function properly in the scaffold, lamin A needs to be liberated from the membrane so it can float freely and assemble into this multiprotein complex. In progeria, the 50-aa deletion removes the recognition site for that internal proteolytic cleavage by ZMPSTE24. That leaves the protein permanently farnesylated and unable to escape from the membrane, acting like a "tar baby" to drag along with it all of the other components of the lamina.

This mechanistic hypothesis suggests an intervention. If farnesylation is contributing to the progeria phenotype, we might be able to block that pharmacologically. Fortunately, drugs that might inhibit farnesylation have been of great interest for 15 years, since the famous oncoprotein *ras* is also farnesylated. Several drug companies have expended hundreds of millions of dollars in developing farnesyltransferase inhibitors (FTIs) that work well in vitro. In fact, several of those have made it through animal testing, and two of them are now in human phase 3 trials for cancer and have shown a good safety profile, including some studies in children. Both Schering-Plough and Johnson & Johnson, the drug manufacturers, graciously agreed to make their FTIs available.

In initial cell-culture experiments, I did not expect to see an FTI work on progeria cells that already displayed an abnormal nuclear morphology; I assumed these would be irreversibly altered. But, in several different skin fibroblast lines from progeria patients after various doses of an FTI given over just 72 h, the correction of nuclear blebbing was dramatic.[14] This was a very exciting finding.

As a next step, we developed an animal model of progeria by constructing a BAC transgenic mouse carrying the human lamin A gene, with the G608G mutation introduced by recombineering. This mouse has a very interesting phenotype, with much similarity to the human disease.[15] The large arteries of the G608G transgenic show progressive dropout of vascular smooth-muscle cells in the arterial media. This is remarkably similar to the cardiovascular pathology seen in children with progeria. We are now treating these mice with oral FTIs to see whether we can actually prevent these pathologic findings. If all goes well, we could initiate a clinical trial for children with progeria next year.

We've also been interested in other variant forms of progeria, since not every case looks exactly like Sam, who has the classic form. So, we obtained DNA samples from the various repositories and sequenced the lamin A gene to see what we could find. Sure enough, we found a couple of other samples that had different mutations in lamin A. One interesting case with longer survival turned out to have two nonsynonymous coding mutations, essentially a recessive form. When I reviewed the clinical information on this case, I recognized my own words. This was my patient, Meg Casey.

I'd forgotten that, encouraged by my mentors at Yale, I had obtained a blood sample from Meg 20 years earlier and had sent it into the repository, hoping that, some day, somebody might discover why this wonderful young woman had this terrible disease. I never dreamed this would come full circle.

In closing, I'd like to share a few of the many lessons learned from my 27 years of coming to ASHG meetings and being part of this remarkable and rewarding field of medical genetics.

First, collaboration is critical to making progress. Our most important collaborators will always be our patients. But there are many others, especially students and postdocs. I've had a wonderful opportunity to work with amazingly talented young scientists in this category. They are the real heroes of discovery. They're the ones who are doing the experiments, taking the risks, making incredible observations. But collaborators in other disciplines are also critical, and never more so than now; nobody can know everything we need to know to take advantage of the current opportunities in genetics, genomics, computational biology, physiology, and medicine. Taking collaboration even further, big projects, such as those I've had the privilege of being involved in, need big teams. It's been amazing to see what can happen then—with the sequencing projects, with HapMap, with ENCODE, and with many others. But do not be disheartened if you're not part of one of those big teams. You still have the chance to use all of the data from these big projects, because we'll continue to make sure the data end up in the public domain. And it is the individual scientist with creative ideas, empowered by these new tools, who will continue to make most of the big breakthroughs.

A second lesson: It is very easy in scientific research to stay in your comfort zone. For many of us, our comfort zone has been basic science. But I want to encourage you to go beyond that comfort zone into translational applications if you see an opportunity to do so, as we are now doing in progeria. We could have continued to just study the cell biology and genetics of lamin A, but if we have the chance to bring this knowledge to the clinic and offer a potentially useful treatment to children with this disease, that ought to be our highest priority. The NIH is putting additional support systems in place to make this possible. But it will take determination and risk taking to bring together the cultures of basic and clinical research. This should be a high priority for our field.

A third lesson is the need for all of us to accept a role in social responsibility—whether working to solve the problem of genetic discrimination, taking part in the important debates about what limits there should be on applications of genetics, or dealing with the potentially explosive topic of race and genetics. There may have once been a time when a scientist could go in the lab, close the door, and say "Those issues are somebody else's problem." But that time has passed for genetics.

A final lesson: Don't settle for looking under lampposts anymore. A remarkable and growing list of resources is making it possible to approach research problems with a new and ambitious goal of comprehensiveness. Develop

a "genome attitude!" Now, in our searches for the "lost keys," we have all of the brightness of the "street" laid out in front of us. Let's make the most of that.

Friends and colleagues, we are indeed privileged to work in a field that holds such great promise for medicine—perhaps the greatest since the introduction of antibiotics. Let us resolve together to make good on this historic opportunity, for the benefit of all the world's peoples.

References

1. Botstein D, White RL, Skolnick M, Davis RW (1980) Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet 32:314–331
2. Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, Young AB, Shoulson I, Bonilla E, Martin JB (1983) Polymorphic DNA marker genetically linked to Huntington's disease. Nature 306:234–238
3. Knowlton RG, Cohen-Haguenauer O, Van Cong N, Frezal J, Brown VA, Barker D, Braman JC, Schumm JW, Tsui LC, Buchwald M, Donis-Keller H (1985) A polymorphic DNA marker linked to cystic fibrosis is located on chromosome 7. Nature 318:380–382
4. Rommens JM, Iannuzzi MC, Kerem B, Drumm JL, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui LC, Collins FS (1989) Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 245:1059–1065
5. International Human Genome Sequencing Consortium (2001) A physical map of the human genome. Nature 409:934–941
6. International Human Genome Sequencing Consortium (2004) Finishing the euchromatic sequence of the human genome. Nature 431:931–945
7. Risch N, Merikangas K (1996) The future of genetic studies of complex human diseases. Science 273:1516–1517
8. International HapMap Consortium (2005) A haplotype map of the human genome. Nature 437:1299–1320
9. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389
10. Silander K, Mohlke KL, Scott LJ, Peck EC, Hollstein P, Skol AD, Jackson AU, Deloukas P, Hunt S, Stavrides G, Chines PS, Erdos MR, Narisu N, Conneely KN, Li C, Fingerlin TE, Dhanjal SK, Valle TT, Bergman RN, Tuomilehto J, Watanabe RM, Boehnke M, Collins FS (2004) Genetic variation near the hepatocyte nuclear factor-4 α gene predicts susceptibility to type 2 diabetes. Diabetes 53:1141–1149
11. Love-Gregory LD, Wasson J, Ma J, Jin CH, Glaser B, Suarez BK, Permutt MA (2004) A common polymorphism in the upstream promoter region of the hepatocyte nuclear factor-4 alpha gene on chromosome 20q is associated with type 2 diabetes and appears to contribute to the evidence for linkage in an Ashkenazi Jewish population. Diabetes 53:1134–1140
12. Eriksson M, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS (2003) Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. Nature 423:293–298
13. Goldman RD, Shumaker DK, Erdos MR, Eriksson M, Goldman AE, Gordon LB, Gruenbaum Y, Khuon S, Mendez M, Varga R, Collins FS (2004) Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA 101:8963–8968
14. Capell BC, Erdos MR, Madigan JP, Fiordalisi JJ, Varga R, Conneely KN, Gordon LB, Der CJ, Cox AD, Collins FS (2005) Inhibiting farnesylation of progerin prevents the characteristic nuclear blebbing of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA 102:12879–12884
15. Varga R, Eriksson M, Erdos MR, Olive M, Harten I, Kolodgie F, Capell BC, Cheng J, Faddah D, Perkins S, Avallone H, San H, Qu X, Ganesh S, Gordon LB, Virmani R, Wight TN, Nabel EG, Collins FS (2006) Progressive vascular smooth muscle cell defects in a mouse model of Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci USA 103:3250–3255