

To give a perspective on the genetics of cardiovascular disease, it occurred to me that we might look back at a lecture that I gave in 1963, published in 1964, and look at what has happened since that time. The lecture was a Louis A. Conner memorial lecture given at the American Heart Association meeting in October 1963 and was entitled, "A Genetical View of Cardiovascular Disease." I pointed out at the beginning that, whenever one looks at genetic disease of a particular system, one finds that there are three categories. First, chromosomal aberrations; second, single gene disorders — that is, Mendelian disorders; and, in the third place, multifactorial disorders or, as they are called these days, complex traits.

In the article, I used the law of illustrative material from our own experience. For chromosomal aberrations, I used the XO Turner Syndrome and Down's Syndrome. These have been described, as far as the chromosomal aberrations, or only shortly before, in 1959. This is a patient with the XO Turner Syndrome who'd had the coarctation of the aorta operated on. One can see the scar on the lower left thoracic area, as well as the characteristic somatic features with the web neck, and so on. Ah, look at the chromosomes and how crude they were at that stage, yet sufficiently clear that one can see that there's one X chromosome, one sex chromosome which, in this orientation, is placed in the northeast corner of the layout. This was a patient from an experience with, what was then called mongolism which, soon thereafter, mercifully became known as Down's Syndrome, with an extra chromosome 21 as one sees at the bottom.

In the case of the single gene disorders, we listed a table here illustrating a number of the particular ones. One of them was Marfan syndrome, shown here with the various manifestations in the eye, in the aorta, and in the skeletal system of that pleiotropic disorder. X-linked muscular dystrophy, pseudohypertrophic or Duchenne-type muscular dystrophy, as shown here with the striking hypertrophy of the calf muscles and a characteristic X-linked pedigree pattern; involvement of the myocardium is a feature. Here is a case of a syndrome with pheochromocytoma. This is from von Hippel-Lindau Syndrome with a characteristic retinal angioma and pheochromocytoma of the right adrenal. This is a patient with tuberous sclerosis showing the characteristic cutaneous adenoma sebaceum of the face. And here, the brain and heart involvement in that disorder and multiple small tumors of the brain and rhabdomyomata of the myocardium. There is a histology section there showing the characteristic spider cells of the heart tumors, the cells being laden with glycogen and the strands of cytoplasm crossing the glycogen collection results in a spider type of appearance.

These are the lip telangiectasia, the lip telangiectases, and tongue telangiectases of heredity hemorrhagic telangiectasia. This is a telltale sign where one can often pick up the lesions in the patient, for example, with pulmonary AV fistula. The diagnosis can be made by detecting these telangiectases at the site. Here, one sees a supravalvar aortic stenosis at the top an experience we had with a 70-year-old patient with isolated supravalvar aortic stenosis. At the bottom, a sporadic case of supravalvar aortic stenosis which was associated with a typical facies which are better looked at than described, also with hypercalcemia in the early stages of the disorder.

This is the mother of a mother-daughter combination with Holt-Oram Syndrome. Holt and Oram in London described their syndrome of radial abnormalities in the hands and atrial septal defect about 1960, and we reported the second family and suggested the designation Holt-Oram Syndrome. That family had a mother with anomalous thumbs on each side, these being triphalangeal and with atrial septal defect, and the daughter had an absent thumb on one hand and a triphalangeal thumb on the other hand. In our studies of the Amish in the early 1960's, we found a very large number of cases of the Ellis-Van Creveld syndrome, sometimes known as 6-finger dwarfism in the Lancaster County Amish, and this is an EVC child with a single atrium. This is a patient with neurofibromatosis with pheochromocytoma, a well-known, although unusual complication of Type I neurofibromatosis.

As far as multifactorial disorders are concerned we, in the Connor lecture, made reference to the fact that one can take various approaches for evaluating genetic factors in common diseases, and most of the multifactorial traits, including those in the cardiovascular system, such as hypertension, atherosclerosis, and so on, are multifactorial, and here are six approaches that were used at that time — familial aggregation; the second, twin studies, comparing monozygotic and dizygotic twins; interracial comparisons; looking at the genetics of pathogenetic components, such as cholesterol, in the case of atherosclerosis; blood group and disease association; and, finally, animal homologies .

I would like next to go to a discussion of the origin and evolution of a focus on medical genetics between 1947 and 1964, and then proceed with what has happened in cardiovascular genetics in the 40 years since 1964. I can tell you that I have been at Johns Hopkins uninterruptedly for more than 60 years, starting with my medical school experience here. I graduated from medical school in 1946 and have pursued four successive partially overlapping careers since that time — first as a cardiologist, 1948-1960; second as director of a pioneer medical genetics unit, 1957-1973; thirdly as Chairman of the Department of Medicine and Physician in Chief from 1973 until 1985; and since 1985 as promoter, advisor and kibitzer, I would say, of the human genome project, and keeper of OMIM.

This is a patient that was very determinative as far as my interest in genetics are concerned whom I saw in June of 1947 as I was finishing my internship. He has melanin spots on his lips, also inside the mouth and on his fingers, and had a horrendous history of intussusceptions due to polyps in the jejunum shown here. Soon thereafter, four other patients came along — three of them in the same family — indicating an autosomal dominant inheritance of this apparent syndrome of polyps and spots, and I heard by the grapevine that Harold Jeghers in Boston had five cases and, together, we wrote these patients up. Harold Jeghers came to Washington as a first full-time professor of medicine at Georgetown in 1948, and I would trundle over to Washington to write up the cases with him. And this paper, in two successive issues of *The New England Journal of Medicine* appeared in December of 1949 entitled, "Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits". We were aware of the publication by Peutz in Holland in the 1920's and in 1953 in a series from the Mayo Clinic. The designation Peutz-Jeghers Syndrome was applied to this disorder.

I was responsible for the genetic interpretation that accompanied this paper, having mentoring from Dr. Bentley Glass at Johns Hopkins University, and he dissuaded me from any idea that I might have that this association of polyps and spots was due to linkage of separate genes for the two traits on the same chromosome. He said, “No, it’s much more likely Victor, that this is a case of pleiotropism, that this represents multiple clinical effects of a single mutant gene, even though you may not be able to understand that connection.” And we still don’t know today precisely how the two hook together, even though the basic defect has been identified. I was a cardiologist at that time. Of course, there was no such thing as medical genetic training, and I was studying cardiovascular sound, heart sounds and murmurs, by modification of a method for studying speech sound that had been developed at the Bell Telephone Laboratories. We referred to this method as spectrophonocardiography in its application to heart sounds and murmurs because the frequency spectrum was demonstrated and published in a big fat book, *Cardiovascular Sounds and Health and Disease*, on the basis of that work. But, in parallel, I had come up against the Marfan syndrome in my cardiological experience and was off on a study of that disorder. And having been tutored in the principle of pleiotropism, it was easy to interpret this disorder as a defect in one element of connective tissue wherever that connective tissue was in the organism. And so that one could construct a so-called pedigree of causes relating all of the manifestations back to a unitary defect.

I first published on Marfan syndrome in March of 1955, “Cardiovascular Aspects of Marfan Syndrome”, and this is the first time that I used the term, “heritable disorder of connective tissue,” choosing, I could have said genetic disorder of connective tissue or inherited disorder. Heritable seemed like a good term because, in the individual case, although capable of being inherited thereafter, the case might be a new mutation. I looked around for other disorders that might be interpreted in the same light as heritable disorders of connective tissue and fell on Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and Hurler syndrome, the prototype of the mucopolysaccharidoses, and these were the five chapters, major chapters, in my monograph, “Heritable Disorders of Connective Tissue,” which was first published in 1956. It went through three more editions which I did alone, and the fourth one in 1974.

Medical genetics was institutionalized here at Hopkins in 1957 when my boss, Dr. AM Harvey, asked me to take over the operation of a multi-faceted chronic disease clinic, which had been initiated by Dr. J. Earl Moore, and the deal I made with him was that I be committed to develop a Division of Medical Genetics within the Department of Medicine arguing that heredity disease represents the ultimate in chronic disease. And because of fortunate circumstances of funding, of position, and of a large general hospital drawing departments in many areas, and so on, and with the opportunity to draw fellows from all over the world for training, we were able to develop a very active program.

The genetic nosology, that is, the clinical delineation of birth defects, of course in the area of heritable disorders of connective tissue and in the skeletal dysplasias, was an important part. I should say that cardiovascular genetics was also very important because I came from a

cardiology background. Also, much of our funding in the early stages came from the National Heart Institute which was interested in fostering that development.

Clinical population genetics of the Amish was a big area, and gene mapping, about which I'll have much more to say, was also a big area. This is our studies of the Amish, and this is a picture I refer to as the Amish Madonna, an Amish mother with an Ellis-Van Creveld child, which you see with the extra fingers. It turned out that there are a very large number of cases of this disorder in Lancaster County, Pennsylvania, which traced back to a single founding couple, and we had, in our first publication in 1964, 50 cases of the Ellis-Van Creveld. Many of them had died because about a third of the patients died before the age of 6 months because of the cardiac defect, and yet we had identified 50 cases and, at that time, there were about 50 cases reported in the world of literature. So, at one fell swoop, we doubled the number of cases.

We organized a series of conferences for five years running, 1968-1972 entitled, "Clinical Delineation of Birth Defects" covering all areas of medicine with the patients drawn for presentation from many departments here and with involvement of workers all over the world interested in syndromology and dysmorphology. And the three principles of clinical genetics that I have referred to already were very important:

- pleiotropism: recognizing single gene disorders because of multiple clinical effects
- variability: difference in clinical picture produced by the identical gene, of which one can have several examples
- and, finally, genetic heterogeneity: several different genetic causes of the same or clinically very similar disorder.

Nosologists tend to be divided into lumpers or splitters as indicated here. Geneticists, clinical geneticists, have to be splitters, in particular, because if the disorder is due to mutation in a different gene, even though there's considerable or even complete overlap of phenotype, they have to be considered fundamentally different disorders. This picture using Abe Lincoln as the splitter and Senator Douglas as the lumper indicates that splitting is harder work. It's easier to lump everything together. This is a cartoon that was produced by a friend of mine, Gene Jackson, showing that oftentimes one ends up being a fence straddler; it's hard to determine whether one is dealing with more than one disorder.

In those very exciting conferences which were held in Hurd Hall, we would have a large number of living eponyms in attendance over those five years as shown here — the Bartter syndrome, of course, has cardiovascular implications; the Char syndrome is a patent ductus arteriosus syndrome, and there are others here that one can point to as cardiovascular.

Also, during that period, Mendelian Inheritance in Man was initiated, and I will say more about that later. The first edition, first book edition being in 1966. These were catalogs of autosomal dominant, autosomal recessive, and X-linked phenotypes. These were conferences in syndromology and dysmorphology, and the conferences helped make syndromology and dysmorphology academically respectable, one might say. Many of these

things have individually rare syndromes have been elucidated at the molecular genetics level now, and I often think how useful it was that the groundwork was laid back then as far as the description of the disorder and the delineation from related disorders.

And, finally, let's look at what has happened in cardiovascular genetics in the forty years since 1964. This is the title page from the *Anatomy of Vesalius*, which was published in 1543. This is Vesalius. Medical historians tell us that the *Anatomy of Vesalius* and his contemporaries was powerfully important in determining the course of modern medicine. It provided the basis, for example, of Harvey's description of the circulation of the blood in 1628 and Morgagni's *morbid anatomy* in 1761. And I would like to propose that we have been provided an anatomy of the human genome which serves as a neo-Vesalian basis for medicine in the 21<sup>st</sup> Century. And we have been provided with this anatomy by clinical cytogenetics after 1956. This is obviously anatomy of which is important to clinical medicine. We have been provided by gene mapping beginning for the autosomes in 1968. The orientation of genes on our chromosomes is part of our micro-anatomy. And, finally, we have been given the complete sequence of the human genome, which is the ultimate anatomy. This is a picture of the famous mermaid in the Copenhagen Harbor, which I took in 1956 on the occasion of the First World Congress of Human Genetics. At that Congress, Dr. Tjio had an exhibit showing that the correct chromosome number in man is 46 diploid and not 48 diploid as it previously had been held. It's rather remarkable that this was three years before the correct chromosome number in the human was determined, three years after Watson and Crick had deduced the structure of DNA, reported in April 25, 1953, about 50 years ago and more. This was one of Tjio's preparations. As you see, the trick of his success was using hypotonic solution to spread the chromosomes apart and to swell the nucleus, so that he could count them. This, of course, was before the days of banding. Jerome Lejeune in Paris in 1959 was able to spot the extra chromosome in mongolism, as he called it.

Banding of chromosomes came along in about 1970, and banding of extended chromosomes was the standard practice by 1977 as you see here, which permitted unique identification of every chromosome by its stripes.

Gene mapping began in 1968 for the autosomes, and the first gene locus that was assigned to a specific autosome was that for the Duffy Blood Group assigned to Chromosome 1 by one of our graduate students, Roger Donahue, in 1968. And you can see there that, in 1968, there were (you can't see the number, but I will tell you) that when the first chromosome, first gene, was put on an autosome, there were 68 genes that we knew were on the X chromosome because of the characteristic X-linked pedigree pattern. The reason I know the number 68 with fair confidence is that, in the 1968 second edition of *Mendelian Inheritance in Man*, there were 68 X-linked traits listed in that catalog, listed on the basis of X-linked pedigree pattern. Donahue mapped the Duffy Blood Group by linkage method to an unusually shaped heteromorphism of Chromosome 1 by linkage methods. In the 1970's, the field took off, particularly because of the use of somatic cell hybridization, as I'll tell you presently.

Frank Ruddle and I organized a series of human gene mapping workshops, first in 1973, at which the information that was collected by workers all over the world was collated, and the diagram you see here represents the data collected in those successive conferences. In the 1970's, the field took off particularly because of somatic cell hybridization in which one fused human and mouse cells, for example, and looked at what came out of the cells derived from the hybrid. The hybrid cells hung on assiduously to the complete complement of most chromosomes but tossed out the human chromosomes rather prolifically. And so one could correlate the presence of a particular human cell trait with a particular chromosome to show that that trait was determined by that chromosome or one could do a synteny test by determining whether two different human cell traits were on the same chromosome.

Restriction enzymes were introduced in about 1970, and Ham Smith and Dan Nathans were involved in that from this institution, and shared with Werner Arber from Switzerland, the Nobel Prize for that discovery in 1978. The restriction enzymes were essentially a scale bell with which to dissect the anatomy of the human genome. This is the Southern blot introduced by Ed Southern in 1975 in which one could display restriction fragments in a particular pattern.

Molecular genetics contributed to gene mapping in the 1980's, first by providing probes which could be used for identification of the human genes in the rodent human somatic cell hybrid. You did not have to have expression of the gene; you could go directly for the gene without it necessarily being expressed. In the second place, it provided probes for in situ hybridization to chromosomes. It was 1981 before single copy genes were reliably mapped by the in situ hybridization method. And, in the third place, it provided a plethora of DNA markers beginning with the famous RFLP's, Restriction Fragment Length Polymorphisms, or RFLP's, which were determined by Southern blot.

Previously, linkage studies had been terribly hamstrung by the pitifully small handful of markers with which we had to work, a few blood groups and serum protein types, and so on, but the number of DNA markers that could be used in family linkage studies was very large, of course.

This diagram illustrates the clinical application of gene mapping defined as location of genes to specific chromosome sites and/or identification of their near neighbors. If one has linkage, one can use it for diagnosis by the linkage principle — prenatal diagnosis, pre-clinical diagnosis, carrier detection. And this was the case with Huntington's Disease, which was one of the first mystery diseases to be mapped using DNA markers in 1983. But even more important, it gave one the possibility of determining the nature of the gene defect, either by positional cloning, which involved walking in on the gene from flanking markers, let us say, or determining the gene defect by the candidate gene approach, looking around in the area where the disease phenotype had been mapped, looking for genes that had been mapped by other means that plausibly could be considered the site of the mutation, then identifying, by either way, mutations in the gene. Once you determine what the anatomical lesion, that is what the mutation is, one can design specific DNA diagnostic tests. Also important, it improves your

chance of determining what the steps are, what the pathogenetic steps are, between a gene and “phene” and, if you know that, you may be able to improve management through a better understanding of mechanisms.

And, very shortly, map-based gene discovery became a major paradigm in biomedical research, beginning in 1986. The way this works is you first map the disorder to a particular chromosome site. This shows Chromosome 4 and, on the short arm Chromosome 4, you see Huntington’s Disease up there at the tip of the short arm. Distal to it is achondroplasia and its mild allelic form, hypochondroplasia, and distal to that is Type I mucopolysaccharidosis. This is the way it works. You admit, by linkage, you map the particular disorder to a particular chromosome site, ideally finding markers that flank it on each side and then you create a contig of overlapping segments of a chromosome and identify genes within those segments and look for a mutation in a gene which means that you’re home when you find a mutation.

This is a list of selected disorders that were mapped through positional cloning, the Duchene Muscular Dystrophy in 1986 and so on down to this year, congenital pernicious anemia being the one selected for this year. One can see that Huntington’s Disease was not, the gene was not cloned until 1993, even though the mapping had been achieved in 1983 and was used for prenatal diagnosis, and so on, already back at that time. The Huntington’s Disease gene was a tough one because it was in a gene dense area at the tip of the short arm of chromosome 4, and it was an unusual mutation, an expanded repeat that people were not hitherto familiar with.

All specialties of medicine use, have used, the gene mapping strategy to study the most puzzling diseases, and I’ve listed Long QT syndrome and hypertrophic cardiomyopathy as two cardinal examples. I would note parenthetically that both of these were mentioned in the table in the 1964 paper as single gene disorders, but they were not given very much play. We had no sense whatever of the large amount of genetic heterogeneity within these two categories and had, of course, no idea about the nature of the basic defect.

Finally, the complete sequencing of the human genome, which was achieved about 2003. The human genome project was first proposed formally, as a project to sequence completely the genome. We talked for 15 years or more about the exciting prospect of mapping all the genes, how we thought we could achieve it, precisely why this would be very useful for medicine, I don’t know, but the human genome project was proposed as a project to sequence the whole thing. This was debated, discussed and planned over a five-year period and had its official start at the NIH, October 1, 1990, and the National Academy of Sciences Committee had suggested that it could be completed in 15 years. This was a committee on mapping and sequencing the human genome, suggested that the project should be done, that it should be done with add-on funding, and it could be done for 200 million dollars a year over a period of 10 to 15 years. It was suggested by the committee of which, incidentally, was commissioned in late 1986, reported out in February of 1988, that map now, sequence later, was a way to go. This was because the sequencing technology was not felt to be up to what

was needed to do it in an efficient way and, furthermore, the map was necessary to do the sequencing in a most efficient and knowledgeable way. So, technology should be pushed at the beginning and, most importantly, it was emphasized that model organisms should be studied in parallel.

I'd like to digress for some definitions. The term genome was first used by Winkler in Germany in 1920, and he apparently created the term by combining the word genes and chromosomes and, of course, that is what the word means, a complete set of chromosomes and the genes they contain. The word genomics, meaning the structural and functional study of genomes, has a newer vintage and was suggested by Tom Roderick at the Jackson Laboratory in Bar Harbor in 1986 when we were casting around for the title of a journal we were going to start on mapping and sequencing the genome. We couldn't use that as the title, but he said, "Why not call it genomics." So that we did, and the inaugural editorial in the first issue in 1987 was entitled, "A New Discipline, A New Name, A New Journal." And nine years later, the editorial was entitled, "An Established Discipline, A Commonly Used Name, A Mature Journal." And one year after that, genomics was defined as structural and functional studies of genomes. The project did get off, as I said, in 1990, the NIH program being headed up by Jim Watson, shown here with his appropriately spiraled staircase at Coldspring Harbor in 1993. Francis Collins took over as director of the program.

The NIH program was, in a way, following the recommendation of the National Academy of Science Committee a top-down project starting with a genetic map, starting with a physical map of overlapping YACs, for example, and ending up with the sequencing of each of those contigs. In my way of thinking, one of the most, perhaps the most exciting aspect of the human genome project has been the non-human genome projects and, arguably, the most contributory, and all of these organisms of these classes, and many others, have now been fully sequenced with very useful information. The first free-living organism that was completely sequenced was *Haemophilus influenzae* which was sequenced by Ham Smith and Craig Ventner in 1995, and they used a bottom-up approach rather than a top-down approach. They sheared the single chromosome of the bacterium into multiple pieces, sequenced the pieces, and then reassembled them through overlapping ends. This is a picture of Craig Ventner on the front and Ham Smith on the back. This work was done at TIGR, a private institute, which stands for The Genomic Research Institute, TIGR.

In 2000, many other bacteria and other organisms, including yeast, were completely sequenced. The complete sequence of *Drosophila* was announced, this being, of course, the pet of the geneticist with a great deal of genetic and other information available. The reason why the study of model organisms is important was known to William Blake, the English painter and poet, when he said, "Am not I a fly like thee or art not thou a man like me", it's the same story of comparative anatomy, or comparative genomics in this case and, of course, it's turned out that the similarities are more striking than one might have guessed, and the similarities have been very useful in determining function and other matters about the human genome.

This is June 26 of 2000 in the East Room of the White House when the preliminary drafts derived by Craig Ventner and his group at Celera and by Francis Collins and his consortium of investigators have come to the White House to announce their findings. They've just come into the East Room and, apparently, the President has asked Francis if Jim Watson is in the room because he wanted to make note of the fact that he was there, and Collins says he's right over there, as indeed he was, because I took this picture.

And in the following February, the Celera sequence was reported in *Science* and the consortium sequence in *Nature*. There's a saying of uncertain derivation that "as the radius of knowledge gets longer, the circumference of the unknown expands" and, of course, with the complete sequence, the fun and work really just begins. And there have been a number of paradigm shifts that have come along, a shift from structural genomics to functional genomics, from map-based gene discovery to sequence-based gene discovery, from single gene disorders to complex traits related to that, a shift from genetic disease diagnosis to common disease prediction, that is, susceptibility, and down at the bottom, genomics to proteomics. The shift, proteomics, of course, refers to, in the case of the proteome, there is the complete set of proteins in a particular tissue, or a particular organism, a particular tissue at a stage of development, and so on, and the study thereof. One of the reasons why proteomics became so important was this paradox, that there are so many more proteins than there are genes, perhaps, by a factor of ten; that there are many ways in which, through different kinds of splicing, or different kinds of processing, the protein product that results from a single gene may be quite different.

Multifactorial traits have come in from more satisfactory analysis with the availability of the genome with which to work and, although I will not go into this in great detail, would point to this quote, for example, from Olson and his colleagues, saying "it's becoming increasingly clear that many cardiac anomalies once thought to have multifactorial etiologies are attributable to mutations in developmental control of genes", and I will make reference to some of those in just a moment.

Go back to *Mendelian Inheritance in Man*, these successive editions of the book which represent the serial cross-sections as it were of the development of medical genetics from the 1960's to the present, it's been on the computer from the beginning and was a pioneer in computer-based publication. It went online at first in 1987; it became generally available since 1995; it's been distributed from the National Library of Medicine at Bethesda. I think that Dr. Hamosh will tell you more about this and other genetics databases, but the title up until 1992, the subtitle was "Catalogs of Autosomal Dominant, Autosomal Recessive and X-linked Phenotypes". Since that time, the subtitle has been "A Catalog of Human Genes and Genetic Disorders". The online version is known as OMIM, "Online Mendelian Inheritance in Man." I like to refer to it as a genetics knowledge base rather than database. Knowledge base implies more intellectual input, and it has obvious advantages over MIM because of its searchability and, because of its timeliness, it's kept right up to date. On the other hand, the book has archival value and value of accessibility in the non-electronic setting.

This is the growth of entries in MIM. This is the growth of our knowledge of molecular defects in Mendelian disorders. There are 1,552 genes that have at least one known point mutation causing a disorder or neoplasm. The total number of mapped disorders for which a causative mutation has been identified is 2,418. This is bigger than the number of genes with at least one point mutation because, of course, many genes have multiple disorders due to allelic mutations in the same gene, and the total number of mutations catalogued in OMIM (we don't catalog all of them) are shown there.

I will end up by saying something about syndromology and dysmorphology and meeting in Molecular Genetics. The von Hippel-Lindau Syndrome gene identified by positional cloning is located on the short arm chromosome 3. Two forms of tuberous sclerosis have turned up to be the case as shown here, genetic heterogeneity. Two forms of hereditary hemorrhagic telangiectasia, as shown here, and the interesting story of supravalvar aortic stenosis in the isolated case due to point mutations in elastin on the long arm of chromosome 7, but the sporadic SVAS with typical facies, now known as the William Syndrome, turned out to be a contiguous gene deletion syndrome involving not only the elastin gene but other neighboring genes, which gives it the syndrome with facies and other features, and the Holt-Oram Syndrome proves to be mutation in a transcription factor, the Ellis-van Creveld Syndrome, a gene has been isolated, a novel gene producing that abnormality and, of course, neurofibromatosis due to mutations in the NF1 gene on Chromosome 17. And with that, I will stop.