Jean-Louis Mandel

Personal Details	
Name	Jean-Louis Mandel
Dates	Born February 1946
Place of Birth	Strasbourg
Main work places	Strasbourg
Principal field of work	Human molecular genetics

Short biography	Born and educated in Strasbourg, Jean-Louis Mandel studied under Pierre Chambon and after time in Toronto returned to Strasbourg to establish human molecular genetics there. His main contributions have been in the isolation of a number of human disease genes, notably that for fragile X syndrome.

Interview	
Recorded interview made	Yes

Interviewer	Peter Harper
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Edited transcript available	See Below

INTERVIEW WITH PROF JEAN-LOUIS MANDEL, 08/05/2008

PH = Interviewer (Peter Harper)

JL = Jean-Louis Mandel

PH Today is 8 May 2008 and I am talking with Professor Jean-Louis Mandel from Strasbourg but the interview is being made in Canakkale, Turkey.
Jean-Louis to start things off, tell me please, when and where were you born?

JL So, I was born in Strasbourg in February '46, just after the war and apart from a post -doc in Toronto all my school and career were in Strasbourg, so I didn't move much.

PH Am I right that your family had a very prominent university role in Strasbourg?

JL Yes my father was both an MD and scientist and was one of the early founders of neurochemistry, so he was director of a big research lab.

PH Do you think this was a conscious or unconscious influence on you going into science?

JL Sure. I saw that my father was so excited and enthusiastic about science and about the possibility to apply it also to medically relevant disease, that indeed, although I had at one point some hesitation to go to music, soon I saw that actually I was not talented enough to go to music, and then it was obvious that I wanted to go into research, and I would say that it was my father who said that it would still be nice to have the dual MD, PhD thing, rather than just doing a PhD. So this is the beginning.

PH How about on your mother's side? Any particular science?

JL So, my mother was also an MD and she worked with my father but she was less, let's say, science oriented really. On that aspect it was really my father who was the driving force I would say.

PH Have you brothers and sisters?

JL I have one brother, who has not been in science at all.

PH You were born just after the war, but may I ask did your family have very special problems and difficulties, thinking of France and the Second World War?

JL Actually they were both Jewish Poles born in Lodz, and because of the numerous clauses against Jews, actually they went to France to do university studies; although initially I think my father wanted to do mathematics, he very soon went in doing medical studies, and my mother too. So they arrived, I think, in Strasbourg probably in 1928, 1930 and then stayed up to the war, did their medical study, my father was already kind of resident, and then of course they had to leave Strasbourg and hide in various disguise. They stayed in France, in either central France or south of France and managed to be unharmed but living under false names etc.

PH Many people I have spoken with have told me of these experiences, which I think are very important to recognise.

JL Yes, absolutely,

PH So was your schooling what you might call conducive to going into science or was it rather traditional?

JL It was not too much traditional because, OK it was traditional at the beginning but I was also playing violin and at one point I was rather good, so the last three years of my secondary studies I went to

Paris, to the music conservatory, and doing the secondary school by mail etc. But then, as I said, when I saw that compared to some of my fellows my talents were not as great as those of some others, I understood that if I can enjoy music I had better not do it as my profession and so, as I told you, I wanted to go into science and my father convinced me that having the dual thing would be good, so I started actually doing both MD, but also to do science studies and more chemistry and physics. Not at a very high level but still, you know, the first years of the faculty of science in chemistry and physics. Then, when I was in the 4th year of medical studies, I was not that much interested in going into wards. My father actually suggested that I could start in the lab with one of his pupils, who was Pierre Chambon. You know Pierre Chambon became very famous of course.

PH Was he one of his students?

JL Was one of his students, but at that time he was already established and had just come back from a sabbatical in Arthur Kornberg's lab in Stanford and my father suggested that I could start working with Pierre Chambon and indeed I started working with Pierre. I did my PhD with him, then I went for a postdoc in Toronto, where I was exposed for the first time to human genetics. I was doing somatic cell genetics there and human genetics. I went back to Strasbourg, still working with Pierre and worked with him cloning the ovalbumin gene, finding the exon structure which was an important thing. Then after a few years I thought that the work on ovalbumin gene had gone as far as I wanted, and I wanted something else, and there were two things that orientated me to human genetics. One is, I was actually first, I don't know how you call it, Reader in biochemistry at the Faculty of Medicine and then nominated Assistant Professor in Biochemistry and I was teaching biochemistry to medical students, and obviously I don't know how it is in UK, but the fundamentals of science are not always of great interest to prospective medical students and one way to try to interest them is to tell them about diseases, and I was doing, for instance, teaching purine and nucleotide metabolism and I was using actually the Lesch Nyhan and immune deficiency and showing how you can relate this to disease and I was also teaching haemoglobinopathies and I thought this was absolutely extraordinarily beautiful, also teaching amino acid biochemistry, phenylketonuria, so really started to be interested in human genetics.

PH May I just ask you Jean-Louis, before we come into that in more detail, did you actually finish your medical degree?

JL I finished my medical degree, but the basic thing, that means in French we have La Concorde Internate, the resident competition, which is really what you need for clinical career and I didn't do this, because instead of doing this competition I started working in the lab. So I had the basic MD diploma but without any specialisation. I did very little ward work, so it was really the basic thing.

PH And all this was initially at the University of Strasbourg?

JL Yes.

PH But you mentioned then you went to Canada.

JL To Toronto.

PH So who were you with to give you the exposure to human genetics?

JL Actually this was really total chance. At that time I had also to do my military duties. This was still mandatory, but you had a way in France to do your military duty as what was called co-operation, cooperation with foreign countries. Usually it was former French colonies like Algeria or going to Africa, etc, teaching or whatever, being a doctor there for two years under military duty. But actually there was also the possibility, because at that time they did not need so many people in the Army any more, but to go even to the US or Canada etc. So I tried for this and the only thing that I had to promise, there were two things. First that the French would not pay for me to go to Canada. I had to find somebody who would pay me as a post doc. Secondly they had to say that I would teach molecular biology in

French. And so we used this, Canada being, you know, both French speaking, and English speaking and indeed the PhD students had to pass a French exam. So we took this as, I would teach molecular biology in French, which I never did, but this was the excuse to go there. And then Pierre Chambon, when he was on sabbatical in Kornberg's had met a young guy, who knew I had gone to Toronto and seemed very energetic and nice etc called Mark Pearson and he told me, maybe you could contact him and maybe there are places. So Mark Pearson was willing to take me as a post doc and he was working in the Department of Lou Siminovitch and actually I was interviewed in Paris, Lou was going to Paris so I was interviewed by him. He was a very special person so I was a little bit destabilised by his kind of interview but nevertheless I went to Lou Siminovitch's department to work with Mark Pearson. At that time Lou Siminovitch was extremely interested in somatic cell genetics and Mark Pearson was part of this thing, he was doing somatic cell genetics and trying to create cell mutants but this was actually the medical genetics department, working in the medical research building but part of the department for instance; there was Ron Worton at Sick Kids. And so they organised a graduate course in medical genetics and I actually, at the Faculty of Medicine at Strasbourg, I think I had two lectures on genetics, one on haemophilia and Queen Victoria etc and one I think on sex determination and there was Turner I think, but very little.

PH Because France has traditionally until recently never been very receptive to the science of genetics.

JL So really in Strasbourg there was nothing. Apart from these two lectures I knew nothing about human genetics. But you know, since I was in this department and there was this graduate course then I started to attend some of the courses or some of the lectures etc and I thought this was very interesting. I may as well tell you, when I went back I started teaching biochemistry and using genetic disease as an example of what happens when biochemistry goes wrong. And then started working on the ovalbumen gene cloning with Pierre Chambon.

PH What year are we in now?

JL So this was when I went back from Canada. It was 1975. During one year I tried, because I wanted to have an independent project, to do some somatic cell genetics in Strasbourg but I was working alone and didn't go very far and Pierre proposed me, he was starting so this was now '76. He had this project of cloning the ovalbumen gene because this was a gene that responded to oestrogen stimulation and he was interested in understanding how hormones controlled gene expression and so proposed me to start working with this. So I started working and another guy, actually who went after that in human genetics in Ireland, Peter Humphries.

PH I know him well.

JL Actually cloned the ovalbumen CDNA.

PH I had forgotten that.

JL Yes, he was a post doc in Pierre Chambon's lab and he cloned the ovalbumen CDNA and so we had

this ovalbumen CDNA and Pierre had the idea that maybe there would be change in gene structure between oviduct, where there was very high expression of the ovalbumen gene, and between blood where it was not expressed. So my task was to actually compare by Southern blot the structure of the ovalbumen gene between oviduct. I was actually co-operating with, who did the major part of the work was another British post doc, Richard Breathnach. His father I think was professor in St Mary's of Dermatology or something like that.

PH I don't know the name.

JL I think his father was kind of professor in some medical specialty in London but I'm not too sure. Nevertheless there were two things that we found. One was that the structure was the same in oviduct as in blood, but that the enzyme where we expected only one fragment, we had several fragments and this didn't fit, and this led actually to the discovery of the split structure in exon introns of the ovalbumen gene, which was found at the same time as the globin genes. This was an important finding. Then for some reason, I think because I had heard once a talk on DNA methylation and that it could be linked to gene expression, I wanted to actually compare the methylation pattern and just as the methylation sensitive restriction enzyme started to be found and I started to compare using two of these enzymes, HHA1 HPA2; the globin gene in oviduct and blood, and I had one problem because I was analysing from several different chickens and different chickens gave me different patterns of bands, and it took me a little bit of time and cloning the variant bands to find that I was looking at a restriction fragment polymorphism. And as I was using this HHA and HPA2 which are CG enzymes, actually I was finding a lot of variation. In 1979 I actually published this paper in Nucleic Acid Research on the fact that indeed, you find difference in methylation between oviduct where the gene is expressed and a lot of it where it is not expressed. But I mentioned also in the article with HHA and HPA2, you are finding a lot of polymorphism in the chicken and as there had been a paper showing that methylated C were a hotspot of mutation in bacteria, I suggested in the paper that this could be useful to find polymorphism in humans and it was just time for the publication showing the first polymorphism in the beta globin gene and how you could use it. I put in the paper that this could be used for human genetic purposes and for following disease genes in families etc. Then I made this one mistake, which I always told my students then, though this was in the paper, it was not in the title and barely in the abstract. I think there was maybe one sentence in the abstract about this polymorphism. Although this paper was highly cited for the methylation linked to expression, nobody really noticed that actually it was about one of the first RFLP. I think just after the Y W Kan it was probably the first RFLP, although in chicken, paper.

PH Before both Botstein and Solomon.

JL Yes. This was a 1979 paper. What I had found was CPG enzymes We were finding a lot of these compared to ECORI. So this was a time I thought, I am fed up with ovalbumen gene and I thought methylation, I had heard that maybe this is linked to X inactivation, this is nice. Then I wanted to work on disease, and indeed also reading the Botstein paper about possibility to map genes, I thought a good idea was actually to work on the X chromosome, for the reason that may be methylation has to do with inactivation, which it has but I didn't actually follow-up on this. And for disease I thought at least I know already on which chromosome it is, because as you mentioned yesterday, CF, you know, the prospect of doing the whole genome, seemed you know, just totally crazy. So I thought at least on the X I will know where to go. So I set up trying to have human probes, trying to find polymorphisms, using mostly CPG enzymes, because I was convinced that you get more polymorphism using these.

There is one funny story about this which I always tell when we have these site visits which judge every, the only time in my whole career when I had a very negative comment was when the site visit for Chambon's lab came in, probably it was '82, late '82 and I tried to present my work that we wanted to clone haemophilia A gene and Duchenne muscular dystrophy etc, and at the end of the site visit they were saying general comments and saying how great was Chambon's lab, all this science is really great. There's just one new team there which was problematic, Jean Louis Mandel. We don't really understand what he wants to do. It's fuzzy and of course I didn't really know where it would all go.

I must say that also from the French, actually Frézal for instance, asking for families, because you need families and clinical genetics was extremely non existent and in a poor state in Strasbourg, Frézal asking, never had an answer. Nobody in this field, not linked to medical genetics etc, but I was very lucky because very soon I could establish things. Actually there was one biotech company in Strasbourg who was set up, and one of their first projects was to try to clone the Factor 9 gene, because they wanted to produce Factor 9 for their purposes, and they succeeded in cloning the Factor 9 and I told them, you know I'm starting to look for polymorphism on the X chromosome and Factor 9 is on the X, so maybe I can use it just for finding polymorphism and use it as a marker, and this is something you are not interested in.

At first they were a little bit reluctant, because you know it was a company and they were doing this, but they let me use the CDNA. We found a very nice taq 1 polymorphism and as I tell my students and with this taq 1 polymorphism, we did a Nature paper, JCI, the Lancet and PNAS, which was not bad. And actually what we did, we found the taq 1 polymorphism, which was very informative, and we could show that we could follow and determine carrier status on a haemophilia family, this was a JCI paper; that we could use this for prenatal diagnosis, and this was a Lancet letter, I think one of the first molecular prenatal diagnoses. And then I had mapped the CDNA clone using, we co-operated with people who had established, you are talking about the gene mapping community and of course there were people in Jean Frézal's lab doing somatic cell genetics and hybrids and we had different hybrids, different region of the X chromosome so I asked them can I have these hybrids so I can make a mapping panel. And with this mapping panel I could map Factor 9 CDNA to Xq26. This was the PNAS paper at that time you know. I had read actually one New England Journal of Medicine paper about this curious disease Fragile X, that seemed very frequent. I had never heard about it but it seemed very frequent, and actually after that I had gone to my first European Human Genetics Meeting in Madrid and Jean Pierre Fryns had talked about this disease, really interesting. So I thought, I need to have families for that, because you know this is distal X and the factor 9 polymorphism is on Xq26, Xq27, so it looks about the same. So I do all the literature and then I see that there is just a French group who has published something about 15 Fragile X families, a certain Mattei. I didn't know him at all, so I found out who is this Mattei and at first he seemed a little bit reluctant. I said I would like to study the families etc and part of his reluctance was because Kay Davies had asked him two weeks before. But he

said OK, actually why not, but with one condition, that my wife comes and learn the techniques in your lab, Southern blot, as part of the study.

PH This was Mattei from Marseille?

JL This was Mattei from Marseille, who later became Minister of Health in France. So his wife, who was an excellent cytogeneticist, Marie Jeanette Mattei, came to our lab. She was very efficient, charming and a very nice woman. I had a post doc, Giovanna Camarino, working on this, and she brought this huge family, Fragile X family, with a smaller one, but especially this huge family, with the third generation there were 17 children and probably about half of them affected. So it was really ..... So we put our Factor 9 RFLP on this Southern blot and then we developed and start. It was very clear and then we start to see all the affected had the same allele, all the unaffected, the other. This was really great you know, bingo. Then we had one problem, that the affected allele comes from the normal grandfather and Mattei had put of course, that the grandmother was the carrier, because you know she had several obligate carrier daughters and lots of, you know, so she was the carrier, but we had 17 meioses. It would mean 17 recombinants out of 17. And then I remembered Jean Pierre Fryns talk in Madrid where he had said that sometimes with these families you find pedigrees that really suggest that it was the grandfather had passed it. He had shown even pictures of old grandfathers, all nicely dressed who had succeeded in life, but who apparently were the transmitters because you had two brothers. So I think that maybe this is just another case and of course that would be 17 non recombinants. So at that time I calculated the lod score by hand. You know I had had no human genetics training at all apart from maybe in Toronto. But the lod score, I learned this in the Emery book, the little Emery book and also blood groups by

PH Sanger, Race and Sanger?

JL Yes. Race and Sanger. So there was one chapter which was very simple and I could understand, not too mathematical. You know there was no recombinant, so it was not too difficult to calculate the lod score and we had this published in Nature, both because it seemed to be very close and this was when Mattei thought we were just on the gene because no recombinant, in the smaller family also there were no recombinants. This is perfect. We are just on it. And of course because it helped to show in this family where you didn't have pedigree data showing that it came from the father, but the molecular data were really saying that it has to come from the grandfather not the grandmother.

PH What year, remind me, was that first Fragile X?

JL So this paper was in 1983. At the time, Marcello Siniscalco also published his paper in Journal of Medical Genetics showing linkage with G6PD. I think this was linkage with G6PD variant, not with molecular, with family from southern Italy.

PH I remember that paper very well and I think like most of us, we all thought it's impossible that the grandfathers can carry it. It was something completely unexpected.

JL Sure sure. So nevertheless, this established me because these four papers was published in '83/'84 while I started the human genetics work in '82 so things had gone pretty well and then I negotiated with Kay Davies to give me her X library so that I could search more efficiently for polymorphism and we set rather efficient search for polymorphism on the X mapping them by somatic hybrids. I became one of the first participants in CEPH because I was part of a small polymorphism group that Lalouel was, informal meetings occurring in Paris and I participated in these groups.

And I remember actually, this is a funny story. In these groups I met Frézal and then I said, you know it is very important to collect families and have blood so that one can do linkage study. I was nobody in Human Genetics and he said, this doesn't serve any purpose. We have our fridge full of samples that

have never been used by anybody and it is not interesting. Who was I to tell Frézal what to do. So actually it took me several years before I started to get things from Paris. But having started to publish this I contacted the Boués and started to have Fragile X families from Boué, and also I looked at muscular dystrophy, which was another story, and then I had seen that there was this person, I must say, I didn't know, because without any training in medical genetics I didn't know about the history of cytogenetics, this person in Hawaii named Pat Jacobs, who had just published that she had several families. So I wrote to Pat Jacobs in Hawaii and we started a collaboration, I think in '83 she started sending me families and I actually saw her for the first time I think in 1988, so for several years it was a very nice co-operation entirely by mail, not e-mail, by mail and she was sending us the samples. I found that once you have put the blood pellet in SDS it is very stable at room temperature so she was sending me big tubes with SDS treated nuclear pellets and so we started co-operating with the Boués, and working not only with Fragile X but also starting mapping other genes, also Duchenne and being very involved in the mapping community for the X chromosome, in the CEPH community for the whole linkage mapping etc. So this is the beginning.

PH Can I ask at this point, remind me when did the CEPH collaboration really begin and who were the initial people involved?

JL I think Jean Dausset had the idea, in the HLA type of things, that the large families he knew and used for HLA typing could be used for, maybe for the community, but he was thinking of association studies and when I met him and discussed linkage studies this was not in his mind. But he had this young medical student with him, Daniel Cohen, and Daniel Cohen and I were participating in this polymorphism group that Lalouel had formed, an informal group in Paris, and I think it was probably Lalouel that made the contact between Dausset and Ray White, pushing to unite because Ray White had started his large families there, Mormon families and then there was one meeting in Paris where I was, which was a founding meeting, I think in 1983, because I remember I was on the collaborators list, I was number three. Each co-writer had a number so it was one of the very early members, and Marc Lathrop was also very active in this. So I think it was really through Lalouel and the meeting between Ray and Daniel actually rather than Lalouel. Dausset was the grand old man but I think it was Daniel who was willing to move fast.

PH And was Howard Cann already involved at this point?

JL He was involved early on. I don't really remember whether he was there at the very first meeting but he was certainly involved very early on. But I must say I don't remember exactly from this first meeting.

PH And Jean Weissenbach?

JL Jean Weissenbach not, he was a bit later because Jean Weissenbach had started on the Y chromosome, and on the Y chromosome of course linkage was not interesting, and actually Jean Weissenbach became interested in these aspects when he went to do a kind of sabbatical in the CEPH and started working on microsatellites. This was a time where Daniel was having talks with the French AFM, with Barateau, about setting up a big lab and then Jean, I don't know whether he proposed or he was proposed, or he saw the opportunity to actually do this microsatellite mapping on a grand scale, so he actually quit his Pasteur lab and his Y chromosome, a very successful project, to join a newly created Généthon. But Jean Weissenbach was not from the initial thing at that time, he was really working on the Y chromosome.

PH So coming back to Fragile X, until 1983 I suppose it had mainly been mapping but when did you begin, and how did you begin efforts to actually clone the gene itself?

JL The mapping started in '83, OK, because I think probably our first lot was in early '83 and I think that right away we wanted to have more probes, one started to see recombinants actually; I remember

Steve Warren's first paper was showing that Factor 9 is not that close because of recombinants, and so we started to have more informative probes and they are actually from Kay's library. We actually identified an X linked minisatellite in Xq28. That was very useful because it was on the outside of the Fragile X which was then very useful for haemophilia A testing, so we named ST14 because the ST stripes were probed. And when you are talking about the importance for a carrier, we did really a very extensive analysis of many haemophilia A families in co-operation with an Italian guy, Manucci, because Giovanna Camerino, the post doc, was from Italy and she knew, because from Paris I tried to recruit a haemophiliac family. I tried to tell them, I need the family, not the patients. I need the family. So I had put a design what I was needing, even the normal etc and after several months I go to Cochin and they say yes yes I have samples for you. Only patients. I said OK, I can do nothing with this. So Manucci had families and we showed that ST14 was very close and we could know who was the carrier and who was not the carrier etc and I said, we will send this to New England, Journal of Medicine, and we had this review from an old man in the haemophilia A field, I think Ratner or something like that. He signed this saying this was all nonsense because he had published that by doing very careful measurement of Factor 8 activity in plasma in families and by doing elaborate statistical analyses, you could know with great certainty who was the carrier and who was not. I asked my colleagues, do you use this? And they said no, you have probably to analyse the level in one lab in the very - so I insisted and finally it was published in the New England Journal of Medicine, because I said, maybe this one reviewer thinks it's not useful but most of the people we talk with think that if you can have something else for carrier diagnosis.

So we started to find and see that actually Factor 9 and ST14 were not that close, so we wanted to have closer probes. So in fact you know it was obvious that we wanted to have the mutation, but in order for that you needed to have closer probes We didn't have a really definite idea of how we would do it but certainly having closer probes was a good thing. And then technology started to evolve, and for instance there was jumping technology and at that time our co-operation with Mattei split because there was one microbiologist in Marseille, Bertrand Jordan, who started co-operating with them and he wanted to do it. And at first we said we would collaborate in it but he was doing it by himself. He used the jumping technology and we were trying to find closer probes, to map them and we had very extensive panels of translocation hybrids to map and then we co-operated, I had a very good, she was more than a student, although she never did her PhD and she was sent to Peter Goodfellow to try to map a radiation hybrid and select probes that would be in the Fragile X region and then we started to have probes that seemed to be very close.

There is one funny story also that I like to tell students. We had these probes that we selected first from this radiation hybrid, that were polymorphic and seemed to be really close, but we still had recombinants. And so when we went to write the paper about these probes I noticed that the two recombinants were female with 2 per cent fragile site and because they had 2 per cent they were put as carriers. Then I thought if they are not a carrier, and this is just background, there is no recombinant at all and so these are the closest probes and we started to do pulse field and then came the YAC. We found that actually one of the probes was extremely close to the YAC and in the pulse field as well as this probe we started to notice that there were abnormal fragments in males that we didn't see in premutations etc. We used CPG probes and I recognised immediately that actually, we probably would have seen a methylation problem, so actually when we found the Fragile X site we were looking for a site with abnormal methylation and this was the way we actually found exactly, because we knew there was some abnormal methylation site in this region in affected males.

PH Do you think you would have recognised it if you had not had previous experience with working on methylation.

JL It's difficult to know, because at that time there were quite a number of people using methylation sensitive enzymes to map, but I think, indeed I had always had this interest in DNA methylation. I was very quick to recognise that obviously what we were seeing was probably a methylation problem than some kind of rearrangement. This was on the pulsed field study and we published this in Nature, and then things went very rapidly because we knew there was something at this methylation centre next to this site, and when we isolated probes next to this site and put this on our families on the bloods we were using for mapping, we started to see these bizarre things and we had fuzzy bands and they were not the same in the family and they moved. At one point I must say I thought maybe this is under replicated DNA, because there was the thing that maybe because of the Fragile site I thought, maybe this is DNA that has not replicated and so it's fuzzy because it moves in a different way, until we directly found out that this was the repeat that was expanding.

PH Am I right that that first paper then was the one where it was Oberlé was the first author?

JL Yes.

PH She died very young?

JL Yes, she died the same year at the age of 35 from breast cancer. This was very tragic and actually there was this kind of funny story on the first author of the Science paper because she knew she was very sick. Even when she had gone, it was her who went to Peter Goodfellow, she already had her first chemotherapy and she had started to have pain in the back so she knew that things were not very good. And then we found this really exciting thing and we started writing the paper, and it was obvious to me that she should be the first author because she had done really the major part of the work, and she started saying that it would be useless for her purpose as she didn't expect to be there very long. And I said you have done most of the work. You need to be on it. And then we wrote the paper. It was sent to Science and there was a good review, they were asking for a few things, and I was going to the Cold Spring Harbor meeting where actually I was presenting this. It was in May I think and the proofs had gone back while I was at Cold Spring Harbor, and Isabel had changed the order to put a Quebec post-doc as first author I think. And when I came from Cold Spring I saw she has changed and put somebody else as first author. I phoned Science asking them to re-put Isabel Oberlé as first author, which they did. She then persevered in writing a paper in the New England Journal and diagnostic applications. I think she was correcting the proofs in the hospital and she died within a few days. It was really very very sad, as she was a very energetic and bright young woman. Her first attack was when she

was thirty. I guess it was probably a BRCA1 or BRCA2. This was indeed very sad. So this is the all the history on Fragile X. Details maybe, but there were lots of collaborations of course.

PH May I ask about Grant Sutherland. Did you have links with him at all over these years?

JL Yes, we actually collaborated on the exchange of probes so that actually I was even a minor co-author on the patent he had on Fragile X because I think the YAC they used was identified using a probe that we had sent them. So we had good collaboration. Of course at the very end, you know, each one found his own thing, but we had very regular mail exchanges and it was very nice co-operation. Yes we exchanged probes with a lot of people in the field.

PH And with Kay's lab also, or was that more separate?

JL With Kay's lab there were some exchange of probes, but after that I think it was more separate.

PH Before we leave Fragile X, are there any other major points you feel you want to make about this history, because the cloning of the Fragile X gene was a very historic event.

JL I think, like a few other people, we thought because of the normal transmitter males there would be

some kind of funny mutation and in fact you have actually we thought more of unequal recombination type of things etc, but this didn't fit because there was no recombination in the family. So from the premutation to the full mutation there was no male recombination that we could recognise etc. But I must say the thing that we observed we never dreamed that such a thing was actually made so clear. And I remember writing to Pat Jacobs suddenly explaining our families and it was so clear, because you can then understand and explain everything, why somebody was a non-affected transmitter etc. So what I think is that there was indeed a lot of collaboration- competition because of course each one tried to do his own thing, but on the other hand exchanging a lot of probes and material was both stimulating and . . . But of course it was the evolution of the technology, the pulse field and of the YAC. The jumping didn't really hold much because [---]started to jump with probes too far so even making a 50 KV or 100 KV jump didn't leave him anywhere. And the radiation hybrid for instance was very useful for us. So it was really trying to use the progressing technology as it was evolving and having this collaboration with many clinicians, because we needed more and more families. Also the importance of having the right diagnosis, at least this was actually probably pushing the interpretation, a biological test which was the fragile site test, which had of course some background and so this was kind of . . . but it was eight years, it took eight years.

PH Just to spend a little time on other diseases, after you had been successful with Fragile X, which was the next disease that really you focussed on?

JL Actually, we had during the mapping time, we were continuing with several other diseases, so this was in parallel, because I was doing general mapping of the X trying to find probes on all the X and then, so for instance at one point we started our co-operation, this was actually our first co-operation with Claude Glissaley who was the head of paediatric immunology and he had of course all these X-linked immunodeficiencies and we mapped Bruton, we mapped X linked SCID, we mapped, also we did some mapping on Wiskott Aldrich, not the first one but we did quite a bit of mapping. But I must say at this point I thought this immunology is very complicated and probably should leave it to immunologists and we considered more neurological diseases etc. We were still having, from the early times also, trying to have the Duchenne gene, so we co-operated and tried actually from the translocation of Hélène Vermoulin to find the gene but didn't succeed in time, compared to Ron Worton. So we were pushing the Duchenne and actually doing also with Philip Abner, comparative mapping of mouse and human X chromosome, and I must say this was a thing where we were doing things in parallel with Kay. I remember once we had actually mapped the MDX mutation and with markers close to Duchenne in humans, what I was doing was actually some zoo blot you know. We didn't publish the name or recognise it, when you have conserved probes they indicated the corresponding locus on both, so we had linkage analysis on mouse suggesting that indeed the MDX mutation was a homologue of

Duchenne and Kay had similar. I thought maybe we could do a small paper and she suggested me, maybe we can try Nature back-to-back and indeed we succeeded, because I would never have dreamed to send this to Nature, because I thought this was not of Nature, but I guess some people have better openings than others. This was the one Nature paper that I got thanks to competition. Certainly I would never have actually sent it to Nature like this. So we were doing this comparative mouse/human analysis. So Duchenne we pursued, but then dropped soon after the gene was found.

Adrenoleukodystrophy, actually I think we had a linkage paper with this SD14 probe already in 1984 and then started co-operating with Patrick O'Boure with the families, and this was progressing in parallel to the Fragile X and we got the gene in 1993.

This was also a very nice story because it was from a false hypothesis that we ended in the right gene. The false hypothesis, Patrick O'Boure had been in Hugo Moser's lab for a year. In France he was already the specialist of adrenoleukodystrophy. Did one year in Hugo Moser's lab, used our probe ST14

to show that it was linked, there was no recombinants or seemed to be very close and there was one guy in Johns Hopkins who had done colour blindness or colour vision studies in patients with adrenoleukodystrophy, and he had noticed abnormality in colour vision in most patients with adrenoleukodystrophy. And so we thought this must mean the ALD gene is adjacent to the colour vision genes. And so as Patrick was going back from Johns Hopkins he asked Hugo Moser whether we could study this set of patients that had been studied also for colour vision anomalies, phenotypic vision anomalies and Hugo Moser said yes, and when we started cosmid walking there was a very talented student, cosmid walking from the colour vision genes, and we started walking and testing the panel of patients, assuming that if they had both adrenoleukodystrophy and an abnormality in colour vision maybe we were in kind of contiguous gene syndrome. This was it. And also doing pulse field on these patients etc. All the patients looked normal but one. There was one that looks abnormal. But all the other ones, even though they had these colour vision anomalies, they were desperately normal with all probes, either 5 prime or 3 prime from the colour vision genes and there was this exception. So getting back to what was the guy having. He had a totally different colour vision problem, he was what is called a blue monochromat. He had no expression of green and red and he had actually a deletion taking part of all of the red gene, plus the region upstream which controls the expression of the red and green genes. So he was blue monochromat because he had the deletion and the red gene in upstream region. So we thought OK, we will travel, we'll walk on the deletion and we will find the ALD gene in the deletion. So we do all the deletion and we don't find anything, but we wanted to actually walk on the deletion and clone on the breakpoint. I think this will be easier and by walking to the end of the deletion and cloning the breakpoint, we arrived at two different places. Actually this guy had an inversion with two deletions at either end of the deletion. One deletion was in the red gene the other end of the inversion in the other deletion was affecting the ALD gene. So by walking and by jumping we ended in two different places, because by walking we ended at one end, but by jumping we found the other end and so we found the second deletion. And then we started looking for conserved probes and looking on a large panel of patients for deletion etc, and then we found one probe which was conserved and detected a deletion in a few patients and cloned the gene etc.

There was this other funny story. So we have the gene. First we went to publish this in Cell. Cell goes very quickly and says we don't think adrenoleukodystrophy as such is an interesting disease thank you and goes back. This is the kind of thing you cannot fight. So we say, OK, we will try Nature, and we had shown, you know, we didn't have point mutations but we had several deletions which were internal deletions, removing a few of the exons. Only in the minority of patients. So we sent this to Nature and we wait and finally we get a review back and especially one referee is extremely negative because this can't be an adrenoleukodystrophy gene, because also we had done some expression study and it was poorly expressed in liver, and it was known that adrenoleukodystrophy was a peroxisomal disease and peroxisomes are active in liver in the ALD gene and it had nothing to do with fatty acid biosynthesis, which was also well known, you should have something that is related to fatty acid biosynthesis. So the guy said, you know this is not convincing. And I remember at the time I said this is the kind of guy, probably more a biochemist, who doesn't understand the power of genetics. Even if this gene is only expressed in the big toe you have to find an explanation why this gene is causing adrenoleukodystrophy. The mutations say it is a gene. But you know, Nature said, we have had it reviewed but it is negative. We can't take this paper. I was very upset. I did two things. One was phoning Peter Goodfellow who is a good friend, and I knew that he was probably closer to Nature and I told him, Peter you know, we have this paper and we've sent it and they don't want it, because they say it is not sure that this is an ALD gene. There is no other possibility. It is sure. Then in positional cloning you want to have your thing published fast, and so finally there was this new journal created by Nature, Nature Genetics. So we had a few days and decided we would send it to Nature Genetics and

then within two days we get this letter of acceptance saying, oh this is great, because actually it's very well timed because there is this Hollywood movie on ALD just getting out and this is perfect timing. So they are pretty happy, although Nature Genetics was just beginning so it was not as famous etc. Then two days later we receive a phone call from Nature and they say actually we referred back, we asked some of our, I'm pretty sure Peter phoned them. We have thought back and actually we will accept your paper. And then they asked us to put in the title 'putative gene for adrenoleukodystrophy'. I said this is not a putative gene, this is the gene. Still was not convinced. You should put putative. So we wanted the paper and we put putative gene in the paper. They got out the paper with the cover of Nature the day the movie was out in London and the title on the cover of Nature 'Lorenzo's Oil gene cloned', without any putative, although the title was still putative you know and with two news and views, one on the science, one on the movie.

PH Oh my!

JL So the adrenoleukodystrophy story had been going in parallel with this since it was published in '93. We had the gene in '92 but by the time, all these rejections etc it was '93. So this was the end and it was totally unexpected gene function and this was the second one and some of the others also decided Simone Gilgenkrantz and when we started to do the map of the X, she passed one medium sized family but for that disease it was a large family for Coffin Lowry syndrome and it was enough for us to map Coffin Lowry and one of the people and the lab continued in Coffin Lowry and so this led to identified Coffin Lowry in '96, but the initial mapping had been done in '88 so this was also a long story.

PH If we took every disease, we would be here for a very long time, but I must just ask you to say a few words about the Friedreich's gene isolation, because that was always to me something very unexpected.

JL Yes totally. I can tell you also. First, why did we start on Friedreich's? Again, not having any training in clinical genetics, I actually knew very little about many diseases. And one day, I think it was in '86, there was one neurologist from Lyon which had asked to see me and comes to Strasbourg and he tells me he wanted to see me because he is the scientific adviser for a patient's association for Friedreich's ataxia. I didn't really know what was Friedreich's ataxia. I thought that maybe things could be done with these families and the history was actually that he had been contacted by Bob Williamson to have French families and this guy was a very chauvinistic guy. He had never thought that one can do anything with Friedreich's ataxia families. He was just a kind of an adviser for what that kind of treatment one could try on the families etc. But the idea that there maybe something interesting but sending it to British.....was too much for him, so he contacted François Gros saying maybe there are some people who can do things with this, and François wrote to him, go to Jean Louis Mandel, maybe he would be interested. So this guy describes the disease and the association and the number of the families he has. I thought, oh this looks an interesting disease. It's not on the X but things have improved now and so I said why not? So we started a campaign to draw blood from Friedreich's ataxia. Just at this time, there Bob Williamson's lab published the first linkage, so we didn't have to scan the whole genome and we could start from there and look at chromosome 9 and we could have found closer probes etc, and

actually we were always looking for this conserved region, there was a kind of zoo blot because if you have genes it is always more interesting, and in order to verify these were genes we were sequencing, I had just been to Cold Spring Harbor where I heard Michael Litt describing microsatellites. And I came back and there was just some sequencing of the probe in Friedreich's ataxia region and I saw this repeat thing. I said this is great. We should use this. See if this can be a marker and I think this was probably the second paper on microsatellites published. We published it. It could be used for mapping, although this was again not in the title, for linkage disequilibrium study because we had linkage

disequilibrium this marker on Friedreich's ataxia, and so we map and we do even some homozygosity mapping, really association study, to map and then we are very close to the gene. We had this one gene and the only mutation that was found in a family, I think it was mis-sense, we found the heterozygote state on one family out of eighty or a hundred in an Italian family and that's it. And then Michel Koenig was leading the project and we started to show, Michel Koenig, that there have been genes where you can find from time to time nonsense mutations that are not really pathologic, especially for a recessive disease; we found out of eighty patients we found one heterozygote mutation. It doesn't look like the gene. At that time, Michel was co-operating with Massimo Pandolfo in Houston. This was actually something where we knew Massimo Pandolfo was also trying in Houston to clone the gene and I'd been in Houston and met him and then I went to see Michel and I said I think we should rather co-operate with him than try, I think it is better to be one of the two who found the gene together rather than being maybe the one who didn't find the gene. If we are sure to find it, fine. So I said we should cooperate with Massimo. Massimo had some idea maybe there could be some methylation problems etc. So we sent in the probes from this gene and did a Southern blot and then he phoned Michel and said there is something funny on the Southern blot. So we sequenced the region and we see a repeat. And this was not at all envisaged because of course there was no anticipation of any sort. And we found 80% of the alleles. But this was totally, it was actually, we had looked at point mutation and we sent the probe for Massimo to do a Southern blot. So he saw something funny.

PH That's interesting. Jean-Louis we must finish soon, but in terms of looking at the field of positional cloning from the perspective of somebody who has been in it from an early stage, have you any general observations or thoughts about this rather extraordinary period of science where this has all happened?

JL What can I say. I must say that obviously at the beginning and looking actually at some history on CF etc, or on retinoblastoma, I think that very few people thought that this was something that would lead anywhere, so this is one of the things which explains probably why people like Lap Chee Tsui or Ted Dryja, who were told it would not go anywhere. But I think when the first success started, which was Duchenne and then, Ted Dryja, really showed that more and more people started to be interested. The other thing and this is really, as you said we had of course overlooked totally the difficulties of doing it. I'm sure that Jim Gusella didn't expect that it would take 10 years for Huntington and

PH Ten years for myotonic dystrophy.

JL Eight years for the Fragile X and so this is something that we were totally naïve about We thought we would saturate with probes and find something. So I think it is also the evolving technology and using findings like the microsatelites for instance. They were very important. The second thing that was important and I think there the AFM for instance, the CEPH and AFM played a very important role, the CEPH in allowing to have one linkage map rather than everybody doing his little linkage with his own probes and not being really able to interconnect. This was one important thing. The second very important thing was when CEPH and AFM started genome-wide strategies both for the YACs, and I must say you may see actually in this interview, when I was a counsellor of AFM, I was one of a few people with Jean Claude Kaplan who was asked, is it worthwhile to give this large amount of money to Daniel Cohen and set this huge lab to do mapping with also Jean Weissenbach. At first it was only Daniel Cohen I think and Daniel Cohen had not published much in the past few years because he was trying to do this YAC library, and I had been in Daniel's lab and I knew that this was difficult and that this would be important, so I was very much in favour. So having this YAC library, genome-wide YAC library and having a way to screen them, was immensely important. And having Jean devising this microsatellite was also immensely important, though I think this was really the important thing in tackling the things genome wide and making tools and the data available for everybody, really

revolutionised completely the approach. I think this was really showing that you need both to be bold, at least to have some bold projects, or the people need to be involved in this genome-wide thing. But this was really important, and then the sharing of information and the sharing of the tools, of YACS, of probes, of microsatellite sequences, this was extremely important. So it was great fun, but chance played, almost for every disease that we cloned we have a funny story to tell about how we started in this and how sometimes there was one patient, like in this ALD patient. We could have walked if we had not had this one patient, I think the ALD gene was 600 Kb from the colour vision genes, so if we had not had this special patient that made the jump for us we wouldn't have had the gene. Luck has to play but also interpretation of this funny data you know. It was very exciting.

PH Just to finish, there have been two questions I have been asking everyone that I have talked with and one of these is, has there been any particular person, or maybe more than one person who you would say has been a special influence on your scientific development.

JL Yes, certainly Pierre Chambon because he was my mentor. More than that, he was my mentor and also put in place, in Strasbourg, an extraordinary institute where you could do really everything in an extremely good environment, plus although he was not really interested in human genetics and wanted me rather to go into Drosophila genetics, he actually, even when I had this bad review, he was behind me. So he taught me also the importance of technology. That you have to use up-to-date technology and to change technology, and not to stay in one thing. So this was the one mentor who really counted. In human genetics, I learned human genetics 'sur la taille' in France and rather than mentors it was collaborators. I learned from interacting with the Boués, with Pat, with lots of people. I gradually learned my way in this field and of course, as it was exploding, in a way you didn't have to know too much from the distant past, at least this was what I wanted. Only later that I actually started to be interested in what had been in the distant past. But it was more through collaboration that I learned bits and pieces, and from reading of course.

PH And then the final question which I have been asking everyone is, is there one particular piece of work, paper or project that you feel particularly stands out in importance in what you have done, or at least you feel a particular affinity to?

JL Yes, I would say it's obviously the Fragile X thing with the unstable mutations and methylation, which probably stands out as the one thing which, also the excitement of seeing, this was what was great with Southern blots. You had images that suddenly told you something, you were seeing a result that was extraordinary. I think this is probably the most exciting thing. It's just an autorad and then you see the things that you never, you can't explain but obviously you are on something which is totally new and totally exciting. So I think probably this is the one thing.

PH Jean-Louis, thank you very much. I will turn the machine off. Many thanks.