

Albert de la Chapelle



Personal Details

Name	Albert de la Chapelle
Dates	Born 1933
Place of Birth	Helsinki, Finland
Main work places	Helsinki; Ohio, US
Principal field of work	Cytogenetics; human molecular genetics; cancer genetics

Short biography

After training in Medicine in Helsinki, he worked on the cytogenetics of human sex determination and its disorders, followed by the molecular analysis of the 'Finnish Heritage' disorders. His more recent work, in Finland and USA, has been on the molecular basis of familial cancers.

Interview

Recorded interview made	Yes
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INTERVIEW WITH PROFESSOR ALBERT DE LA CHAPELLE, 12/10/2011

I = Interviewer (Peter Harper)

C = de la Chapelle

I It's Wednesday, October 12th 2011 and I'm talking with Professor Albert de la Chapelle at the International Human Genetics Congress in Montreal, Canada. Albert, can I just ask, when were you born and where?

C So, I was born 11th February 1933 in Helsinki, which is not the place where my parents lived because my parents were farmers and lived about 2 hours west of Helsinki, but my mother came to give birth at the private hospital in Helsinki.

I Was the place where you lived right in the country or was it in a small town or...?

C It's... well, the place is still there and you might call it an estate; you might call it a farm, a large farm. And it is absolutely alone in the wilderness so to speak. Well, to be more precise, it's about 6km from the local church and the little village around the church.

I How many years did you live there before coming more to some town or city?

C There was a tradition in the family that the children were sent to high school in Helsinki so I went to a local school which was about 1km from my house, a local, we would call it primary school, for 2 years. And thereafter I was sent to Helsinki to go to high school. High school in Finland at that time was 9 years, so you entered at the age of about 9 and you came out at the age of 18.

I You said your parents were farmers but that it was a large farm, so they were educated people, your parents?

C Yes. Yes, the family has been educated for many generations and my grandfather was a paediatrician who was hoping to become Chair of Paediatrics at the University of Helsinki but was beaten by somebody to it, so he was the chief paediatrician at the city hospital. And my father had a university degree in agronomy, in agriculture.

I The war must have been a very big interruption to your early life. How did that affect your schooling and your life generally?

C Well, that's a very good point. The war is something you never forget, which was absolutely the major thing that went on in my childhood. So it started in 1939 when the Russians attacked Finland on 30th November. At that time I went to school out there in the country and not so much happened in the country per se but of course the very serious condition that Finland found itself in made an impact on every aspect of life and the one a child could remember from the very first years was that so many people from the city were evacuated to live in the farm with us. There were about 25 people that my mother took care of who were, in part, friends, in part relatives and so on, who moved out, or were evacuated from the city. The city was bombed repeatedly by the Russians.

I And then during the later stages of the war, did that affect your family also very directly?

C Yes, my father was 40 when the war broke out and as a 40 year old he was not called to service but in 1941 when the war continued, he was actually called to active service, or to service in the army, and so he was gone and that of course played a major role in the family's life. My mother was even more than ever in charge of an enormous apparatus including the farm.

I How old were you when the war ended?

C So the war ended in Finland in September of 44 when a separate ceasefire was made with Russia, luckily. And at that time I was 11. So it's a child's memories but they are quite traumatic actually; traumatic. One was afraid; one was always afraid of something terrible happening and people of course, you know this very well. I mean there wasn't a family in which a family member didn't die, or a close relative die, or something like this, so there was a lot of loss of life and loss of property from the bombings.

I When we come to the post war years, it's always seemed to me a major miracle that Finland survived after everything, and how did your secondary schooling progress in those years?

C Well, I think surprisingly well; I think really surprisingly well. Materially of course there was nothing. I mean, the food situation was quite difficult. I think I hear that the food situation was even worse in Britain but it was pretty bad in Finland for several years to come after the end of the war. And of course there was basically nothing. I mean there are things like one remembers when one saw the first banana; and one remembers those sorts of things. But school, as far as I could tell, was not affected; the teachers were there and the teachers were good teachers, and school life was, I guess, more or less as before. The rooms may not, the classrooms may not have been heated, but it worked.

I At what point did you feel that you wanted to undertake a career in medicine or science?

C Well I said before that my grandfather was a paediatrician and as it happens, he died in December of 1932, two months before I was born, and I was named Albert after him. And he remained sort of a half legend in the family and it was kind of absolutely understood that the new Albert was going to be a physician also. It was never questioned.

I And did you question it?

C No, I did not question it.

I At that time, was it medicine that was your goal? Or did you have a feeling also for science as part of medicine?

C When I think about that, and I know people have asked that before, and I think my answer is that I don't really know. I'm not sure I had any clear cut ideas about what I wanted to be, but if it was anything it was more on the clinical side than on the research side, for sure. So for instance, when my classmates, when we came to year 2 or 3, and some of my classmates started working in somebody's lab to do some first research, I didn't do that. I was playing around.

I When you left school did you go direct to university or did you have to do military service first?

C Right, so high school, I was actually a little younger than, I was put in school half a year earlier than most people so I was 17 when I graduated from high school, and then went straight into the medical school, the way things are done in Finland. So I graduated from high school in May, the end of May 1950 and in August of 1950 I already started in medical school. And I just... so we had of course obligatory military service 11 months, but I postponed that and I actually interrupted my medical school in 1954 to do my military service. Interestingly I did that in the company of two or three of my very best friends, who all did the same thing. So between 54 and 55 I spent 11 months in the army.

I And then the year you actually qualified in medicine would have been...

C Then I graduated in December of 57.

I At the time you graduated did you have any clear idea as to which area of medicine you might pursue?

C No, I did not. I definitely did not, but I think that there was a prevailing idea that if you were

sort of intellectually inclined, you were interested in the intellectual part of medicine, internal medicine was probably the most rewarding speciality. So I think that pretty early I started, and it was most prestigious in some way, so I think that at some point I really did start thinking about internal medicine, but before I did that I actually spent 11 months on radiology/radiotherapy of all things, and in the end didn't come to like it. I did a shorter period of gynaecology and liked it but then in the end I ended up in a department of endocrinology and that was, seemed more interesting.

I Was endocrinology the way in, so to speak, to your early work on sex chromosome abnormalities?

C Yes it was most certainly was. As I said, I didn't have any idea about doing research and I was a resident under somebody called Herman Hortling who I consider my main mentor, who was an endocrinologist specialising in thyroid; hypothyroidism in the adults, which is something that he was most interested in and that actually is being much more discussed in the last few years. But he also treated people with any condition that belongs with the field of endocrinology and my interest in research started from a lunchtime discussion with him where he threw a recent issue of The Lancet on the table and that issue had the first paper on the chromosomes in Turner Syndrome. And my boss was quite interested in Turner Syndrome so he threw this issue and this must have been Pat Jacobs' paper, I think.

I Or possibly Paul Polani and Charles Ford?

C On Turner Syndrome?

I 1959

C Yes.

I Pat Jacobs was Klinefelter.

C Right.

I And at the same time came out the paper by Charles Ford and Paul Polani on Turner, and of course, the paper on Down's from Paris.

C Yes, but nobody saw that paper in the English speaking world, I think.

I I think that's quite true.

C To begin with. [laughter] But anyway, so thank you for correcting me. So it was this one issue of Lancet that was thrown on the lunch table by my boss who looked at the karyotype of Turner syndrome and looked at me and said, "Can you do that?" And that's how it all started. I said, "No, I can't but I can try." And from then on I started doing chromosomes.

I Was there some kind of lab attached to the Department of Medicine or Endocrinology that you could use?

C There was a very primitive lab but then there was, very soon thereafter there came a development where a group of research-oriented people from the same department, founded a private little research institute called the Minerva Institute for Medical Research and I was given an opportunity to start my work there.

I Did you do this alongside your clinical work, or did you take, at some point then, time out to do full time research?

C No, I didn't do any full time research at that time at all. I continued my residency in internal medicine all the way to 1966.

I That's quite a long time.

C Yes.

I I mean, looking at your publications, I saw the very long series of papers on the sex chromosomes and one of them actually was jointly with Paul Polani and Ruth Sanger involving the Xg blood group, I think.

C Yes.

I How did that come about?

C Well, I would very much like to give you the full explanation but I'm afraid that my memory fails me a little. Of course the Xg was one of the very first easy markers of the X chromosome, so that whatever you did with the X chromosome, I think especially looking for the origin of the extra chromosome in Klinefelter Syndrome, and the loss of one of the chromosomes in Turner Syndrome, you... we were very happy to have the Xg as a marker. And I started somehow communicating with Sanger and Race, and we became friends and I actually ended up spending a mini sabbatical with them in 1973 at the Lister Institute.

I They were a wonderfully collaborative group, weren't they?

C Yes, and well, they were so good to this unknown little guy from an unknown country. They were really absolutely gorgeous people.

I At what stage was it that you broadened your work from sex chromosome and endocrine type disorders to more general aspects of medical genetics?

C Well, the major thing with the sex chromosomes of course, was the XX male. And it was actually my boss, Herman Hortling, who had the patient who turned out to be the first XX male. He actually had these typical Klinefelter's small testes, pea sized testes, and he was consulting with my boss and at that time we took it for granted that he had Klinefelter's Syndrome and we did a chromosome study and it was XX. And this was probably, well I'm not going to tell you the year because I don't remember, but from then on I actually devoted much of my time and my energy to the question of the male sex determination. And that meant that while I was still a cytogeneticist and I collaborated mostly with David Page and Jean Weissenbach; the three of us together were doing all sorts of things we could think of in search of the elusive male determining gene. And that meant that various techniques and strategies and ideas that were not strictly cytogenetic started to be on the agenda. So it was sort of a gradual process through the male sex determination that led me to more, less chromosomes and more other things. Now I forget to tell you the crucial thing of course was, that in 1966 - 1968 I was a post doc with somebody called Paul Marks at Columbia University in New York, and that was a lab, basically a biochemistry lab where we did fetal haemoglobin research. And that of course set the stage for me to actually leave the chromosomes, which I then did totally, and get interested in something, in these different other things.

I Was there anybody in Helsinki at that time who was doing what we would know as human genetics? Apart from yourself.

C Well, from my horizon I would say that in the early days human genetics was cytogenetics because there wasn't anything else. I mean, you may disagree, you may say, "Well, there was Penrose and there were many others" but really the field of genetics was pretty dominated by cytogenetics up until about 1970, I would say.

I But there was nobody else who had come in from, say, the basic sciences: cytology, botany, or anything like that, who had an interest in the human genetics side of things?

C No, there wasn't. In the faculty or in the school of biological sciences, there was a department of genetics that had been there a long time with a number of well known people. None of them actually ever veered into human genetics. I had very good relations with them and went to all their meetings and vice versa, but we were sort of apart. And was there anybody else? Well, there was somebody called Pertti Aula who was also a cytogeneticist who worked with

children, and he and I were probably the only ones in something more human than *Drosophila*.

I So can I ask, when was it that human genetics in Helsinki and with yourself in particular, when did it become a definite field rather than just part of something else?

C Well, that's not a difficult question. I should say, I should mention one person: his name is Harri Nevanlinna. He was actually a paediatrician by training but his lifetime accomplishment was related to the fact that he was head of the Finnish Red Cross blood transfusion service. And he was a geneticist, but he was sort of medical and very much a population geneticist, he was a mathematically oriented person, as you might perhaps imagine from somebody who is head of a blood bank. And I think that most people, let's say in 1970, felt that Harri Nevanlinna was our big human geneticist; however and as a result of the fact that I had been doing all this cytogenetics and there was also somebody called Aldur Eriksson who you may know, who was a population geneticist who had also worked on aspects of the genetics of the Aland Islands; Aland Islanders, from which he is. And the fact that there was Nevanlinna and there was Eriksson, there was me, the school began to think that maybe genetics is something that we should have; maybe we should even have a department and a professor. At that time there was enough money so they could really expand if they wanted to and medical genetics was chosen as an area to develop and a chair was announced that it was, how do you call it, that you could apply for the chair and everybody expected Nevanlinna to get it, and in the end it turned out that I got it. And that started in 1974 and immediately I started working on having a department, which we got in 1975 or 76 and with that department came positions, younger researcher positions and technicians, and space and money. And that's how it then started.

I Right.

C So that was Finland's first department of medical genetics and first chair in medical genetics. It soon spread to other university towns in Finland, actually.

I That's interesting.

C Yes.

I Can I ask at what point had you developed your interest in genetics and leukaemias? Because I see looking at your papers, that comes really quite early on.

C Yes, I think it has to do in part with Caspersson. In other words, well, first of all the Philadelphia chromosome was found early on, and second, more and more chromosomal abnormalities were seen in the bone marrow cells of people with acute leukaemia. And we were asked to study those and got quite interested but there was no... it was so utterly uninformative and descriptive because there was no banding of the chromosomes. So you could see there were three chromosomes of the so called C group, but you didn't know what chromosome it was and whether it was the same chromosome in all cases or all different chromosomes etc. So I think that a big change came in 1969 with the banding and we immediately, we actually collaborated with Caspersson. One of my graduate students went to spend time with him and brought back the banding technology and we had a couple of papers together even with Caspersson. And with the banding, studying the chromosomes of leukaemia became much more meaningful. So yes, we did a lot of that in the 1970s.

I At that time did you also have any contact with Albert Levan in Lund, in terms of cancer and genetics?

C My contact with Albert Levan was earlier; much, much earlier. It was, as soon as I started doing chromosomes in Finland, I think in 1959 or 60, I managed to get invited by Levan to spend a week, I should have spent a year but of course, he invited me to spend a week in his lab. So that of course was highly memorable and I learned the techniques of Tjio, to process

human chromosomes. But speaking about how to process human chromosomes, one of the most important events in the early cytogenetics part was this little course organised by Court Brown and Pat Jacobs in Edinburgh, I think in 1960.

I It could have been.

C Right. Where they were able to invite I think there were 8 of us, something, people from various parts of the world to have a practical course in human cytogenetics. And the point was, of course, that first of all that Court Brown and Pat Jacobs were so good and nice people, and taught us so much; but secondly while we were there this rumour about the phytohaemagglutinin spread, and so we all went home saying that we should try that phytohaemagglutinin on blood cells, and that of course revolutionised cytogenetics absolutely. So that was quite memorable.

I When did you first get interested in gene mapping?

C So this is easier again to say because here there really was some thinking behind it, so we're now talking about the period when we had lost the race for the SRY gene; I guess I'm not stepping on anybody's toes if I say that there were two camps. There was the camp led by Peter Goodfellow and Robin Lovell-Badge, looking for it. And there was the group of David Page, Jean Weissenbach and myself, and we lost the race. The British found the SRY and at that time my interest in that whole field disappeared. And at the same time of course, in 1978 or something, the Nobel Prizes, to people whose names I forget now, but the restriction enzymes were given the Nobel Prize and things were beginning to happen in molecular genetics. And at that time, so now to answer your question, at that time I said, "Forget about chromosomes; forget about sex determination: now we shall look for the Finnish genes." And that was a very, sort of determined decision with a clear goal and a clear way of going about it. And the way I went about it was to get a sabbatical which I spent in 1981 with somebody called Jean-Claude Kaplan in Paris to learn molecular genetics, which I did. And then I came back and little by little was able to start a lab in molecular genetics, and in part with the help of Kay Davies. Because one of my students went to Kay Davies and learned some tricks from her and came back and we could start doing things.

I Did you start with X-linked conditions or were you from the beginning looking at some of the autosomal Finnish diseases?

C Well, we were quite interested in Duchenne and in the X chromosome, yes. We were quite interested in the X chromosome but the main goal was to find those genes underlying those 25 or so recessive disorders that are so common in Finland and rare elsewhere. I understand there are now 37 of them.

I Had those already been looked at clinically...

C And they had been very, very well studied clinically. That was the whole basis. The paediatric hospital in Helsinki specialised in that and especially Reijo Norio, who you know and may have interviewed.

I No, I haven't actually. I should.

C I mean, he wrote his thesis on congenital nephrosis showing that it was a recessive disease, very highly enriched in Finland and not occurring really much elsewhere except in Minnesota, as it happens. [laughs] And many, many other Finnish clinicians had studied one of the, some of the, so called Finnish disorders. So they were pretty well studied and as we all know, that's the basis for anything you want to do, that you have the phenotypes right.

I Did you have young clinical research workers who kind of brought in the family samples and studied the clinical aspects to serve as the basis for the mapping and gene isolation studies?

C No, not quite. The system was usually that there was a graduate student who did all the lab

work and then we collaborated with one of the people at Children's or elsewhere, who were the clinical experts. So it was sort of a group of three: the graduate student, the clinician and myself. That's how this usually occurred.

I Which, out of all this group of diseases, is there one which gives you particular satisfaction to have sorted out?

C Well, I suppose it has to be the first one because it was first.

I Which was that?

C Diastrophic dysplasia.

I It was first. Yes.

C The graduate student was called Johanna Hastbacka. I

C Having said what I said, the graduate students very often were MDs though, or MD students.

I And would they -

C But later on they were often PhD students or PhDs. But the typical thing was that there was only one. I mean they would be pretty jealous of others so that there would be only one per disease and sometimes that could slow down things a good deal because there was not so much manpower.

I I mean that phase of your work, if I'm right, went on really for a very long time.

C Yeah. With a paper we published this year, it's still going on actually. But that's a disease in the Amish. So now that I live in Ohio, the Amish are the substitute Finns and you can do all the tricks we did in the Finns, you can do with the Amish, and even more successfully.

I Coming onto colorectal cancer: what was it that got you involved with that?

C Well, I think that I would say that I'm proud to say that the medical community at the University of Helsinki is very collaborative, and that we were a big family in a certain sense. So somehow I befriended a surgeon for no obvious other reason than that we'd met some places and discussed and sort of liked each other, and his name was Jakka-Pekka Mecklin. And he was a young colorectal surgeon who had done his thesis with someone called Heikki Jarvinen. Heikki Jarvinen is another important name here; more senior... Jarvinen with a J.

C So Jarvinen was a senior gastroenterological surgeon and he had a student called Mecklin, and Mecklin had been told to, like people were at that time, to write a thesis on hereditary colon cancer. So I think he published his paper in, I can't remember when but... probably around 1985 or something, and it was nothing but a description, but a very good description of a large number of families, most of whom actually turned out to have Lynch Syndrome. So he described inheritance, the inheritance and the clinical features of these families, including the other tumours, endometrial tumours and so on. It was, next to Henry Lynch's papers, it was the best description of Lynch Syndrome. And Henry certainly does agree about that. And so Mecklin was telling me about that and I said, "Well, there's a gene; we should map it." And that's how it started. But it was a long... it was very hard because there were no samples available and of course many patients were dead, and the methods of course at that time were what they were. I mean that was, we started basically before the microsatellites really came on; they came in 1987, I think. And they of course made a big, big difference in any linkage. So it was the linkage approach and it was by RFLP which was a tremendous amount of work, so we had, we worked for several years on it before we actually found linkage.

I At what point was it then that you moved your base across mainly from Finland to America? Was that in the middle of this work?

C No, no, no, no, no, no, no. We, the breakthrough in mismatch repair gene mutations was in

1993 and we continued working on Lynch syndrome and mismatch repair deficiency all the way till 1997 when I moved to Ohio.

I And I guess when you got to Ohio you found plenty of opportunity for developing that work further?

C Right, yes. We actually had an NIH grant in Finland that I then got renewed for the US of A. So everything, so there was a smooth transition in terms of funding... yeah.

I And just to bring things up to more recently: the area which you're focusing on these past few years in colorectal cancer, what would you say is the main focus of what you're doing?

C Well, the first thing we did in Ohio was to repeat something we had done in Finland but we did it much better in Ohio because there was more opportunity, there were better methods and strategies. The first thing we did was we took consecutive patients with colorectal cancer and scrutinised them for Lynch syndrome in order to know exactly what the proportion is of all colorectal cancer. The answer is 3%. And that was the highest per cent at that time because we did, if I may say so, the best job of all the various other groups that were doing it because they were all not screening every patient, but rather screening patients with certain characteristics like early onset and the family history. And in that way you lose about 35% at least of the cases. So we did that and that of course led to all sorts of offshoots: we found new mutations, and founder mutations, and that kept us busy for 5 years. And since then we have been preaching that we should screen everybody for colorectal cancer and the idealised numbers are that if you do that in America, and you do cascade, testing of probands' relatives, you should be able to diagnose about 20,000 cases of Lynch syndrome per year. And we think that at present, the way people are looking for Lynch syndrome, at present 5% of Lynch syndrome are detected. Now I'm not saying that we can study every patient in America, that's a total impossibility -

I It's quite a challenge.

C But if we could study half of them we would detect 10,000 new cases per year, which would save a lot of lives.

I It certainly would, yes.

C Right. And that's what we're now hoping to do in Ohio as a model to show people that it can be done.

I Throughout your time in America have you kept a lab or at least a strong link going, back in Helsinki?

C No, very little. When I left there were 6 people who were graduate students mentored by me, and the way we did it was that we found a co-mentor for each one of them so that my role became pretty minor, and so in the early days I had much to do with those 6 people and their projects, but those ended in 2 or 3 or 4 years, and since then I've had very little to do. I mean I'm friends with them all and so on, but I don't have... basically I have no scientific activity in Finland at all. None at all.

I If you look back on the range of things that you've done: is there any one piece of work that you feel most attachment to, or most proud of?

C Well, it has to be, I mean, obviously it has to be, it has to be the finding of the primary, finding of linkage for MSH2 because it led to so much.

I Yes. Yes.

C So that was in the spring of 93.

I Yes.

C And there are two very important names to mention in that context: one is Lauri Aaltonen and one is Paivi Peltomaki. Paivi Peltomaki was a post doc and Lauri Aaltonen was a graduate student in my lab, and the three of us did all the colon cancer work together.

I And Lauri Aaltonen has continued in...

C Yes, and so has Paivi. They are both professors in Helsinki now.

I And looking from the other direction, who would you say has been the greatest influence on your career and work generally? Is there one person who stands out as being a particular mentor?

C Well I cannot but say that Herman Hortling, the endocrinologist who led me to study the chromosomes, he was both a friend and a very positive mentor, so I think I want to mention him first. I think Paul Marks and Jean Claude Kaplan, who were not really well, mentors in a certain sense, but more equal, have been important too.

I Albert, there are a lot of other things I could ask you but before we finish this, is there any particular topic that you'd like to bring up that I've not mentioned?

C Well, I suppose most people would say the same: I cannot imagine a life without genetics. I cannot imagine that I would have been as happy with my work in thyroidology or in gynaecology or something, as I have been in genetics.

I Do you think that as a generation we have been extraordinarily fortunate in the time that all these things have happened, and that so much has developed in one person's professional lifetime?

C Yes, I would say so, and that is pretty, that's absolutely remarkable. I mean when you imagine that I was spending a week with Levan who was, and I had an opportunity, and with all those people we have mentioned here, who are all the pioneers, and we are still active with all these incredible things that are going on now with the new technologies. I mean, at a time when, I mean, I started at a time when, as I said, the Xg blood group was so fantastic; Peter Pearson's first RFLP in the X chromosome was so fantastic because it gave us something to work with. And now we have all of this, all of these things, so I mean, in perspective we have been able to see a development that one could hardly imagine.

I Albert, thank you very much indeed for sparing the time. I shall turn this off now.