Karen Helene Ørstavik

interviewed by Trine Prescott

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Biography

Karen Helene Ørstavik, nee Jakhelln, was born June 12th, 1937 in Oslo, Norway. After having done mathematics and chemistry at the University of Oslo, she received her medical degree in 1964. She defended her PhD thesis *(Immunological studies of human coagulation factor IX)* in 1979 and became a specialist in Medical Genetics in 1981. From 1981, she worked as a consultant in medical genetics at Oslo University Hospital. In 2002, she was appointed the first professor of clinical genetics in Norway at the University of Oslo. She retired in 2007. Her main interests have been in clinical genetics, dysmorphology and X chromosome inactivation.

Interview

*TP: Let’s introduce ourselves.*

KHØ: I am a retired clinical geneticist and professor emerita at the Institute of Clinical Medicine, University of Oslo.

*TP: And I am a clinical geneticist in the Department of Medical Genetics at Oslo University Hospital.*

*TP: Tell me a bit about yourself. What did you do when you finished school at age18? How did you end up studying medicine?*

KHØ: After having finished school in 1955, I spent one year in London, part of the time as an au pair in a family with a three year old. The parents told me he was a “mongol”. He got leukemia and died: and this made a great impression on an 18 year old with no experience with severe disorders. Back in Oslo, I studied mathematics and chemistry at the University of Oslo. There I met the medical student who was to become my husband. He and his fellow students were constantly talking medicine, so I decided I would not listen to this for the rest of my life, I would rather join the discussions. Instead of probably ending my life as a math teacher, I did medicine, a very happy choice for me.

*TP: Did you go into genetics directly after obtaining your medical degree?*

KHØ: No, I didn’t. I had four young children and did part-time work at well-child clinics.

*TP: Why did you choose medical genetics? How old were you when you started?*

KHØ: After six years of part-time work, I was 35 years old and had to make the difficult choice of a career. Fortunately, I had read an article in the Journal of the Norwegian Medical Association in 1969 on genetic counseling by the founding father of Medical Genetics in Norway, Kåre Berg. At that time, genetic counseling was hardly a topic. With my background in mathematics and chemistry, I thought that genetics might be interesting.

*TP: Tell me about the road to becoming a medical geneticist in the 1970’s in Norway and say a little about your PhD.*

KHØ: The access to Medical Genetics in the beginning of the seventies in Norway was by doing a PhD. There were no training positions. So I started as a “scientific assistant” at the University of Oslo in order to do a PhD – though I didn’t know on what. Many PhDs at that time were performed on genetic polymorphisms, protein variants. Probably due to the discovery of coagulation factor V by the Norwegian doctor Paul Owren in 1947, research on coagulation had a strong position in Norway: and coagulation factor IX, the factor deficient in hemophilia B, had just been purified at the University of Tromsø in Norway. We could therefore produce rabbit antibodies to factor IX, and I did my PhD on the study of variants in the factor IX protein in patients with hemophilia B. At that time, there were new immunological techniques that made this possible. We were happy to find many variants in the 13 patients registered in Norway with this very rare disease – and this is not surprising, given that more than 1000 mutations have now been described in the small factor IX gene.

I started in genetics because it seemed interesting and I’m convinced that I chose the ideal specialty for me. Lots of challenging theory, combined with seeing patients and families and being allowed to spend sufficient time to try to solve complicated cases. I knew that emergencies were not for me. However, there was also the practical side; I had four young children and was glad to avoid night duties and very fixed working hours.

*TP: Who were the people who were important for you at work when you were doing your PhD in the 1970s?*

KHØ: The Institute of Medical Genetics at the University of Oslo in those days was an exciting place to work -- few, but good colleagues, such as Carl Birger van der Hagen, Arvid Heiberg and Helge Boman. Highly intellectual environment, great discussions. Chromosomes were interesting, prenatal diagnosis had just started, and it was a time of great progress in immunology.

And then we had the head of the Institute, Kåre Berg, who had spent three years at Rockefeller, and had a large network of interesting people that came to visit in Oslo; such as Alec Bearn, who was a pioneer in genetic disease – I’ll just mention Wilson’s disease. He was a very enthusiastic man. Any time anyone had an interesting idea, he suggested the possibility of a ticket to Stockholm.

*TP: The Nobel Prize?*

KHØ: Yes

*TP: There weren’t many women in Norway with PhDs in medicine at that point. Did you feel you were treated differently because you were a woman?*

KHØ: Well, of course there were few females in medicine and therefore few doing PhDs in medicine. I didn’t really feel serious discrimination, but some skepticism about how I would manage to take care of four children and do scientific work at the same time -- as if I didn’t have a husband. To me research is often easier to combine with family life than clinical work. At that time I had not met Judith Hall, but I did what I later heard her advise female colleagues to do: choose the right husband, and buy help.

*TP: Norway was, I think, one of the first countries that acknowledged Medical Genetics as a specialty.*

KHØ: Yes, you are quite right -- as early as 1971. Norway was one of the first countries in the world to establish Medical Genetics as a specialty.

*TP: So, when did you complete your training and become a consultant?*

KHØ: I was allowed to train while I was doing my PhD, and I qualified as a specialist in Medical Genetics in 1981. At that time, a position for a consultant was established, so I was happy to get a position the same year.

*TP: So that may be coming back. Some places people may be doing combined PhDs with their specialty training.*

KHØ: I think that the reason it was possible to do both was that there was no other way to get the training. In these days, when you have three years to do a PhD, it is of course not possible to train as a specialist at the same time.

*TP: When it comes to recruitment – that is to say, who goes into Medical Genetics today -- do you see any difference in who is being recruited now and who was being recruited when you started in genetics in the 1970s?*

KHØ: Yes, of course, there is a big difference. In the seventies, the males did medicine and the males did scientific work. Today it’s the opposite. I think that now when we have training positions, Medical Genetics naturally becomes a female specialty – and this is worldwide, which is unfortunate. Females are of course taking over most of the specialties; because there is such a large majority of female medical students.

*TP: Okay, but you could have continued on and only done research, why did you decide to do clinical work as well?*

KHØ: At that time, it wasn’t as difficult to get a full-time position as a university professor as it is today. Actually, it was easier to get a full-time than a part-time position. I was very happy to get a position as a consultant. I really enjoyed my clinical work: I liked being part of Oslo University Hospital services, and collaborating with the many different departments. I think that the combination I had was quite ideal for me.

*TP: If you were forced to limit yourself to a list of only three things that you have found especially rewarding about clinical work…*

KHØ: I think that trying to solve a puzzle was really what I enjoyed – for the family’s benefit, maybe also sometimes for the benefit of science, such as contributing to the identification of a new gene. But for me it was also a special joy, I think, simply to solve a puzzle. And I always enjoyed meeting parents -- for instance at the neonatal unit where the parents had just experienced a shock, the birth of a malformed child. I thought that being there was a great challenge and a job I really enjoyed.

*TP: So you’ve mentioned two things, there’s the puzzle and there’s trying to help people in a difficult situation, genetics being about people and about meeting people. You can add one more point to your list of three things that you found rewarding.*

KHØ; Since I started in genetics in 1972 of course many new concepts have been introduced in genetics. I particularly enjoyed when imprinting was coming up. We had a family with three sibs with Prader-Willi syndrome, and this family contributed to solving the puzzle of the inheritance of this syndrome. Again, I think that it was a privilege to have patients with a rare disorder -- a new concept comes along and you are part of solving the puzzle.

*TP: If we switch back and talk some more about your research career. After you completed your PhD what did you become interested in and why? Which people, places and events were important?*

KHØ: After my PhD I continued doing work in coagulation. We could characterize antibodies to factor IX that can develop in hemophilia B patients, a very serious clinical problem. I also studied the heritability of the plasma level of coagulation factor VIII since I had access to large twin populations. These studies brought me to John B. Graham, a pioneer in hemophilia research at the University of North Carolina at Chapel Hill, and to Walter Nance and the twin research group in Richmond, Virginia. So this work allowed me to get out and see some important places in the US.

*TP: So when would that have been?*

KHØ: Early 80’s.

*TP: I think that if there is one research topic people in Norway connect with your name it’s perhaps X chromosome inactivation.*

KHØ: Yes, as is often the case, you meet a patient and you become curious. My interest in X chromosome inactivation started when I early in my career met a female patient with hemophilia B. One of her problems was that when admitted to hospital, the doctors didn’t believe that she had hemophilia. What they remembered about genetics was that hemophilia is an X-linked disorder and therefore only occurs in boys. Of course, the most likely explanation for her hemophilia was that she had skewed X chromosome inactivation. And we could prove that 14 years later, when the factor IX gene was known and a PCR method for the analysis of X chromosome inactivation had been established: her hemophilia was due to extremely skewed X inactivation. However, one of her non-carrier daughters also had extremely skewed X inactivation. So maybe the skewed X inactivation in this family was due to selection against a lethal mutation in another X-linked gene. I got interested in the genetics of X chromosome inactivation. We were able to study the heritability of X chromosome inactivation in a large Danish twin population. Whereas monozygotic twins had a very similar pattern, the dizygotic twins did not. We found a heritability of about 0.60, but there are problems here that have not been solved.

*TP: And you have been interested in X chromosome inactivation and age.*

KHØ: Yes. The effect of age on the X inactivation pattern in peripheral blood cells is quite striking. In a population of centenarians, we found that 70% had skewed X inactivation compared to 5% in a younger population. The increase in skewing with advancing age is not well understood. Is it of any significance at all? Is it related to why females live longer than males? However, we did find that skewed X inactivation was associated with lower mortality in a population of elderly females.

*TP: And you were interested in X chromosome inactivation as it relates to disease in heterozygous females. Are there things that still fascinate you? What issues about X chromosome inactivation in addition to those you have already mentioned remain?*

KHØ: I think that there will be lots of interesting research in the future. Little attention has been given to the phenomenon of female mosaicism: all females are a mixture of cells with the paternal X as the active X, and cells with the maternal X as the active X. We know of course, that not all genes on the X chromosome are inactivated. Some escape inactivation, and to make it more complicated, some genes are partially inactivated – and this varies between females and between tissues in the same individual. So I think that future interest in X chromosome inactivation will focus on the significance of the mosaicism and how it relates to diversity between females. With new technology it has been possible to visualize the X chromosome inactivation pattern *in situ* in individual cells. Studies of mice brains have revealed a huge diversity between individuals. For example, in some brains, the mother’s X dominated the left side, and father’s X the right side -- the whole brain might be dominated by the X of one parent. It will be interesting to see if humans have the same diversity, and the significance of this for the differences between females, and between males and females.

Another interesting field of research is the X chromosome and autoimmune disorders, which are much more common in females than in males. Having two X chromosomes is an advantage; however the price for this may be the increased risk of autoimmune disorders. We studied X chromosome inactivation in autoimmune thyroid disorders and found a significantly increased frequency of skewed X inactivation in the patients compared to healthy females.

*TP: I’m thinking about the trajectory of your scientific career. Most of your scientific publications were published after you turned 60, weren’t they?*

KHØ: Yes. When I started in genetics doing a PhD at the age of 35 years, one of my colleagues said it was too late to do research. This did make an impression on me because, I already felt quite old. Most of the people at the Institute were younger than me. However, the majority of my work was published after age 60, and I became a professor at age 64.

*TP: Our paths crossed about 15 years ago because we both have an interest in rare disorders. Tell me about your interest in this field and about becoming Norway’s first professor of Clinical Genetics.*

KHØ: My interest in rare disorders came quite naturally as a consequence of all the patients without a diagnosis, including many non-ethnic Norwegian patients, I met in my daily work as a consultant in a hospital with a large pediatric department in the early 80’s and 90’s. My colleague Arvid Heiberg had managed to establish a very close collaboration with many of the clinical departments at our hospital. So, I visited the pediatric department regularly, and always felt welcome.

*TP: There was only one professor in Medical Genetics at the University of Oslo, from 1967 until 2002. So establishing a professor II position, a part time professorship in Clinical Genetics, was really overdue in 2002.*

KHØ: Yes, that’s right.

*TP: Now we’re in an era of quite amazing technological advances. Do you think single patients and families ”still matter” scientifically?*

KHØ: Yes, of course. There must be a lot of unidentified genes out there. A good example is the publication by Stray-Pedersen et al in the American Journal of Human Genetics in 2016. A single Norwegian family was the beginning of the process that identified mutations in *UNC80* as a cause of severe intellectual disability.

*TP: You got out into the world. How did you manage that? Why did you think it was so important to do so?*

KHØ: Well again, I feel very privileged. Of course, I knew that I had to get out and meet colleagues. I was mostly supported by quite generous funding, both for my own travelling and for inviting people to Oslo for lectures. Not only was I able to go to important meetings abroad, I also had the privilege of, for example, meeting Mary Lyon in person. She was a great scientist at a time when a career in science was very difficult for females in the United Kingdom. I would also like to mention the privilege it was to meet colleagues from Eastern Europe in the early 80’s: to gain some insight into how difficult it was to do science in East Germany at that time.

*TP: Whom else did you meet?*

KHØ: I met many people who today may be history for our younger colleagues – at that time they were stars, such as John Edwards, Michael Baraitser, Marcus Pembrey, Robin Winter, Andrew Wilkie, Arnold Munnich, Dian Donnai, Han Brunner, Gabrielle Gillessen, John Burn and Judith Hall. All these people came to Oslo because we had funding that enabled us to invite them.

*TP: Well, you did. You were the person that secured the funding.*

*TP: You visited Johns Hopkins, too, didn’t you?*

KHØ: Yes, I did. Victor McKusick was a friend of the head of the pediatric department in Oslo and he visited Oslo many times. I was allowed to attend his clinics at the Johns Hopkins Hospital, and attend the demonstrations of live patients for an audience. This was very rewarding for me, but I believe that this type of patient demonstrations is no longer done, fortunately.

*TP: I remember when I started in genetics you told me to make sure and go to the ESHG meetings. You have been to most of them, haven’t you? Why were they so important to you?*

KHØ: Since Medical Genetics is such a small specialty you have to get out and meet colleagues. The ESHG meeting which was quite small in the old days is now a good and important meeting. There used to be a Nordic meeting, but there are large distances in Scandinavia and travelling expenses were the same as for going to Europe. And because of the Finns the language at meetings had to be English. So we ended up in Europe, of course and the Nordic meeting sort of died out.

*TP: Can you remember when your first ESHG meeting was?*

KHØ: I really do. It was in Amsterdam in 1972. I was so excited. I had basically been a housewife for six years and I was going to a conference in an exotic place like Amsterdam. It was quite a small meeting so we were all assembled in the town hall. We were received by the mayor who in his speech assumed that all the men were participating in the meeting and that all the women were accompanying spouses! In 1977 the ESHG meeting was in Oslo; a small meeting, about 200 people attended, and we did all the practical work ourselves. So times are changing. I have been to all but a couple of the annual ESHG meetings.

*TP: Dian Donnai has meant a lot to you and to Clinical Genetics in Norway. Talk a bit about how you met her and about having her come every year to the dysmorphology meeting in Norway.*

KHØ: Doing dysmorphology in a small country like Norway in the 80’s was a lonely business. Looking up diagnoses in the David Smith book and searching the literature was what everybody did. I understood that I needed to get out and meet colleagues. By chance, I heard of the London Dysmorphology Club and was generously allowed to attend and to present my own unknown cases. It was overwhelming. I was scared, but was treated very politely when I presented my first unknown, which of course was not an unknown for the sophisticated audience in London. I also discovered the joy of describing and recognizing faces. I still like to describe faces when I see people on the metro. I was also permitted to follow Michael Baraitser on some of his rounds in the neurology department. It was like being a student again; I still remember some of the cases. Later it was the Manchester Dysmorphology Conference, a meeting that is extraordinary of its kind, based on active contribution by all attendees.

*TP: For many years you were the only Norwegian who was invited to apply to attend the biannual meeting in Manchester. But now, how did the Norwegian dysmorphology meeting start?*

KHØ: In 1990 I attended a British Council Course in Clinical Genetics in Cardiff. This was my first meeting with Dian Donnai who was to become such an important person for dysmorphology in Norway. She gave an excellent talk on dysmorphology. This talk was an eye-opener, and I knew that she would have a lot to teach me and my Norwegian colleagues in genetics and in pediatrics. So I invited her to come to Norway, and her first talk in Oslo was in 1992. And she has come to Norway every year but one since! I was lucky and was able to get ample funding for an annual dysmorphology meeting in Oslo with talks by the best qualified speakers in Europe. This meeting has now more than 100 attendees from many specialties, and we are very proud that people come to this meeting also from other countries.

*TP: The meeting was renamed in your honour several years ago, Karen Helene Ørstavik’s Dysmorphology Meeting. To what do you attribute its success?*

KHØ: Money was important, at least in the beginning. Ample funding allowed us to avoid a registration fee and to invite excellent speakers. We only invite speakers that we have heard ourselves. Dian Donnai has been the major contributor for almost 25 years. Another major contributor was Michael Baraitser, and later Han Brunner. All three are gifted speakers.

A friendly, non-competitive atmosphere has been essential. This has been due to Dian Donnai’s friendly and inclusive personality. At the beginning, nervous young speakers who had never presented in English before were taken care of. Participants were made to feel comfortable in presenting unknown cases and to feel that they were contributing to the dysmorphology community.

Once the meeting was up and running regularly, rumor spread that it was a meeting where you could learn something

*TP: You are interested in communication, oral and written. Any advice to younger colleagues about giving oral presentations and about how to learn to write?*

KHØ: Well, I have heard too many bad oral presentations. I would advise anyone, young or old, beginner or established speaker, never to give a talk without having practiced it in front of an honest audience. You always need to think: Who is it that I am talking to. As for writing, I would remind people that it is very hard work and very time consuming. Barbara Migeon, one of the great minds in X chromosome inactivation, in her book on the subject, thanks a Nature editor for having taught her to cut a paper by half.

*TP: Murder your darlings?*

KHØ: Yes.

*TP: What teaching have you enjoyed most and why?*

KHØ: I have had many teaching experiences, some not so enjoyable. Bayesian statistics at the blackboard with young bright medical students in the audience was a challenge even with my background in mathematics. I inherited a lecture for medical students called “races” -- quite a topic in the seventies. The lecture was removed from the curriculum of course. All in all, I have enjoyed teaching. A special joy has been teaching genetics to midwives in training. They are adult nurses who are specializing by taking a two year program in midwifery. They have a lot of experience and are eager to learn. I have taught this group for 44 years, and will continue as long as I am wanted.

*TP: What qualities do you think a good clinical geneticist should have today?*

KHØ: Maybe the same as what makes you a good doctor. In addition: perseverance, patience. You must have the desire to solve a puzzle and be willing to spend a lot of time on the same patient. Without the necessary resources, sufficient time for each patient and family, I don’t think this is possible. That may be a problem these days when so much is about “production”.

*TP: Given the recent technological advances in laboratory genetics do you see Clinical Genetics fading away as a medical specialty? Will clinical geneticists be replaced by a combination of genetic counselors, other medical specialists and technology?*

KHØ: I certainly hope not. But this is a difficult question. The answer will probably have to do with money and the policy of the hospital. The clinical geneticist must be good at making her- or himself useful for other clinicians. That is what my colleague Arvid Heiberg did in the 70s when he started doing clinical genetics in Norway. He tried to be helpful by answering the clinicians’ questions. In the old days, we used to say that a good clinical geneticist could prevent the use of unnecessary expensive tests, but new technology may be changing this. Fortunately, for us, genetics is quite complicated; you need considerable training both to understand and to be able to explain some issues to patients and families. As for genetic counselors, some patients need a doctor; the doctor cannot be replaced easily.

*TP: You retired in 2007, almost 10 years ago. Are you still interested in genetics? Is it still a part of your life? If so, how do you make that happen?*

KHØ: Yes, I am still interested, of course, and I feel lucky to be able to follow –if not always understand-- the rapid developments. Since I am a professor emerita I still have access to the journals and I have my university email which makes it easier for me to be connected to people. After I retired, I have accepted almost any invitation to odd jobs, such as talks, peer reviews, committee work, anything that forces me to update myself. I was a member of our Regional Ethical Committee for six years, which was a way of following what is happening in research in Norway. In addition, I am happy occasionally to meet the many clever younger colleagues that have taken over.

*TP: And lastly, a question I heard you answer at a national meeting in Trondheim a few years ago, ”Does technology – especially as it pertains to human genetics, ie. all the new tools – frighten you?”*

KHØ: I am tempted to answer the way somebody recently did when asked to comment on technology at a meeting in Oslo. He said, “I do not fear new technology, I fear old technology.” So the answer is: No. There are so many other things to fear these days.