Russell Snell

Personal Details

Name	Russell Snell
Dates	Born 29th March 1960
Place of Birth	Fielding, New Zealand
Main work places	
Principal field of work	

Short biography

Write a little bio in this cell

Interview

Recorded interview made	Yes
Interviewer	Peter Harper
Date of Interview	13/09/2011
Edited transcript available	See Below

INTERVIEW WITH RUSSELL SNELL, 13/09/2011

I = Interviewer (Peter Harper)

S = Russell Snell

I **It's Tuesday, September 13th 2011 and I'm at the International Huntington's conference talking with Russell Snell about the isolation of the Huntington's gene and the work that led up to it, and about a few other things as well. Russell, can I start at the beginning? Where were you born and when?**

S I was born in Fielding in New Zealand which is a small town on the North Island, on 29th March 1960.

I **And did you spend all your childhood and early life there?**

S No, as a family we shifted down to the bottom of the South Island to a little town, or outside a little town, called Balclutha, where my father took on the job of starting a farm training school to teach boys, teenagers, how to be farmers. And that's where I grew up really.

I **So your family then: did you have any real family background in science, medicine or anything like that?**

S Certainly not medicine. I think I probably in retrospect describe my father as an agricultural scientist in that he had a great love of animals; he had a diploma in agriculture from Lincoln University, and he had a BA, which you had to get in those days to teach. And he had an analytical way of looking at farm systems and a real drive to teach; he was a born teacher. So I come from a family of teachers on both sides; very strong genes those teaching genes!

I **Did you have an inclination towards science from an early age, would you say?**

S I almost remember when I discovered there was a thing called science, when I was given a book called Science. And immediately I knew that was for me; this marvellous thing called science. And I read avidly and drawn, absolutely drawn to it, especially the creativity side of it; immediately knew that's what I wanted to do. Had no idea how to do it; no role models really, and I still love it.

I **Did you get backing from your family with it?**

S Well, my dad died when he was quite young and I was quite young. So he died when I was 14 and he was actually my age, 51. He was killed in an accident; we were going down the river in a little yacht and the mast touched a power line. So that, we were a family of 5 children, and that really disturbed the family. And I think still has ripples going through our, well it still does definitely, through our family because it was traumatic. So pretty much had to find my own way, I think, yeah; mostly I had to find my own way. And it probably took a little bit longer because of that, I think.

I **You managed to get to university?**

S Yes, I got to university and I failed my first year completely. Too young, not enough direction; my own direction, really. Probably still recovering a bit from the loss of my father. Yeah, really. So then the following year, because they kick you out if you don't pass, I worked in a shearing gang, I worked as a drain layer, and I worked as a postie. And I also applied to be a motorcycle mechanic, and by then I was I think 19, and I was too old to get an apprenticeship. So they kicked me out of that too. [laughs] So going through that kind of hard work I realised

that I really, really wanted to be in a position to use my brain and also do things for people; so an underlying drive to do things for people. And it was as ill-defined as that, really. So then I went back to university and passed everything; mostly physics, actually, and I ended up doing two degrees in physics. Accidentally I ended up in a biochemistry department in Otago and accidentally ending up doing a project in physics but learning molecular biology. This was in the early 80s.

I **So what was your first work in biochemistry?**

S Making some equipment to do pulse field electrophoresis. So resolving DNA molecules and it took me about half a day to make the equipment, and it took me about two years to learn molecular biology, having no biology background whatsoever, but that didn't seem to be a big issue.

I **Have you always been a person who has what you might call a facility with regards to equipment and technology generally?**

S I think some people would argue no [laughs], probably my wife, but overall yes. I think I have a bit of an affinity. I used to fiddle with motorcycles, my cousin and I, and try to set various land speed records illegally here and there. I think so. I think I've got a physics brain that is interested in cause and effect and wondering what the gap in between cause and effect is, which I think is a geneticist brain. Actually I think a physics brain is a geneticist brain.

I **How about the pulse field equipment because that must have just come across the horizon at that point. What year are we now?**

S That was 1984 and we got a prepublication copy of Charles Cantor's paper talking about it originally, and so I made a copy of his equipment which I didn't particularly like actually, and we made modifications of that and then through doing that we discovered a new chromosome in Saccharomyces and we discovered that Candida albicans had 5 chromosomes. At that stage I think it only had 3 linkage groups and it wasn't accepted by the yeast community for a number of years, even though you could see them resolved on a gel. But through that process I had to learn basic molecular biology, genetics to some extent. So for a wee while there we led the field actually; strangely.

I **Who were you working with at that time?**

S I was working with another ex-physicist actually, a chap called Dick Wilkins, who took me on as a student. And I think it was his background, because his background was nuclear physics; he had a PhD in radiobiology. And he was kind of a collector of odd people and I was an odd person that washed up. I had a friend, Mike Eccles, who was doing his PhD at the same time in that lab, doing cancer research, and it was just this funny coalescence of unusual circumstances but I loved it; it was paradise. It didn't seem like there were any restrictions to what you could do and I think that was that stage in molecular biology that you didn't need to know a lot because there wasn't a lot known, so you could do naïve experiments that turned out to be, I don't know if they were remarkable, but they were things that had never been considered. Because at that stage, biology was still biology and there were a lot of biologists grappling with the use of molecular tools: cloning and that sort of thing. And so it's a little bit like now actually with whole genome sequencing coming along. We're going to leave a big generation behind who just can't embrace it; won't embrace it. And that was that time really. It was very interesting. It was fun. Really fun, actually. [laughs]

I **My memory is that you came across to UK some time not far off that in relation to the pulse field work. How did that happen?**

S Even though Kiwis can't fly, they Kiwis do fly and the head of the biochemistry department in Dunedin is, or was at that stage, a wonderful chap called George Peterson. And this was in the days when benevolence still existed and George sidled up to me one day, he was a gentleman

actually, and said, "Oh what were you think of doing, Russell?" And I said, "Well, look I'm quite keen to leave the country" as you do, "and I'm quite keen to do my PhD somewhere but I don't know where." And George said, "Well, you'll be needing a bit of money to do that." And I said, "Oh yes, I guess so." He said, "Well, I'll come up with some sort of job" and really the job was, well it was resolving the Duchenne region at that stage, but really it was more about financing leaving the country. And so my wife at the time and I blasted off and tripped around Europe in a Combi van and then we washed up broke back in the UK and I went looking for a job and I was offered a job at Amersham, that was then a radiobiology company. I was offered a job in the Medical Physics Department at Cardiff, measuring fallout from Chernobyl because of my physics background, and I came to see you and, you being the collector of people that you are [laughs], you said, "Oh, we've got this Wolf Hirschhorn work going on. Would you be interested in that?" And oh boy, I was interested; it was great. So that was, so I left the country in 1987, New Zealand, and arrived back during that big storm, remember the big storm that knocked all the trees down?

I Yes, I do.

S And was driving over the Severn Bridge in the Combi van and very nearly got blown off the Severn Bridge.

I That was the old bridge without any sides to it?

S Oh, we were blown right across three lanes; it was spectacular. And then they closed the bridge just after that. The roof of the Combi van blew up like a balloon. Boy, it was incredible. And I started in medical genetics early in January. But funnily enough when I was in Australia on the way, on my OE, I saw the opening of the Institute for Medical Genetics on TV because Prince Charles was pulling the curtain across the plaque, you know, and it had fallen off or something anyway, and I remember it.

I Did it? I never realised that had got on the television.

S Yeah it was, I saw that in Australia. Isn't that funny? I thought, ah I know this place. And it was, yeah…

I So remind me, did you become part of the specific Huntington's project right away?

S No, no. I worked on Wolf-Hirschhorn for a few months with Oliver, Oliver Quarrell. And Sandra Youngman was coming, toing and froing, from London where she was at ICRF with Hans Lehrach and Gill Bates. And then Sandra decided that she wanted to shift to London to carry on with that work, and at that stage you and Duncan Shaw asked me whether I wanted to stay. And I rather cheekily said, "Yeah, I'd quite like to do my PhD. Would that be possible?" And you said, "Ah well I'm sure we can work that out." [laughter] And that's what happened.

I What did you actually give as the title or subject for your PhD?

S I remember at the beginning wanting to have as the title 'The Isolation of the Huntington's Disease Gene' because that's the sort of person I am. But I remember it being modified to, actually I can't even remember the title. Certainly had Huntington's Disease in the title.

I It was probably something very broad -

S The molecular biology of Huntington's Disease, you know. Yes, I think it was.

I - which is always wise when you pick a title. Okay, now this was before Cardiff had joined the Collaborative Group, wasn't it?

S Yes, although Sandra had contact with the, or you had contact with the Collaborative Group mostly through, well through the use of the families, actually, that you had collected. Yes, it was, it was before that. And the trigger point I think was the discovery of linkage disequilibrium. That was the trigger point from what I remember anyway.

I So after the Wolf-Hirschhorn work, to my knowledge we never had any kind of grant or funding specifically for that?

S No, I came to know that there were magic ways of finding money. [laughter] And that, well it seemed magical to me, and I'm sure it wasn't; I'm sure it was darn hard work. But I originally came and said that I'd like to work for a while and then travel again, and you said, "Oh well, that's fine. We'll just see what we can do." Though I had some skills, I guess, but what I didn't count on was genetics and how much I would like it, and the people in the Department; very, very much the people.

I In terms of genetics, had you managed along the way, so to speak, to pick up any, not so much formal, but theoretical background of genetics?

S I knew that chromosomes existed; I knew that DNA was contained in chromosomes. Can I tell you about an experience that I had about 2 weeks into working on Huntington's Disease? So I genotyped all the families that we had with some new markers, and I ran gels and did RFLP analysis; and I was sitting there on this bench in the office, I can still picture it, and Linda Meredith was sitting beside me; and I remember looking at these things and I remember thinking, "You know, I can understand typing them, and I can understand that they've got different chromosomes. I can't understand how on earth this is supposed to help us find the gene." So I said to Linda, "How is this supposed to help us find the gene?" And Linda said, "There's this thing called meiotic recombination" and it was a wonderful. Revelation. And that was my education and actually I owe the wider group in Cardiff and the openness of the people there completely my education in genetics. I learnt genetics by doing it; by needing to know in order to get to the next step, and it's a wonderful way to learn because you need to know that day so you find out that day. So no, I guess. [laughs]

I Once the linkage disequilibrium had been found, remind me how quickly was it that that could be translated into more physical approaches to the gene.

S The linkage disequilibrium we discovered was complicated in that there were two loci really and they were a long way apart. We knew, did we know that they were a long way apart at the time? I think we had some evidence that they were a long way apart. And that was confusing; these two markers some distance from each other detecting the signal and seemingly detecting the signal in different ways. And it really didn't fit with the paradigm that, so now we know those markers are about a million base pairs apart, and that doesn't make sense; or it didn't make sense at the time. Why is this? The physical mapping of the region was largely undertaken by Hans' group, through the alignment of the yeast artificial chromosomes and the pulse field gel work, established the location of the markers and assisted in the identification of others. This map placed the markers that we had linkage disequilibrium on the map towards the telomere of chromosome 4.

My first Huntington's meeting was at Islamorada in Denis Shea's compound, participating in the wider Collaborative Group. And I was only invited along, I think, or we were only invited along, Duncan was there too, because of LD result. It was clear that some at the meeting didn't believe it. And I remember it was first thing in the morning in beautiful Islamorada, and I stood up and talked about linkage disequilibrium and David Housman stood up and argued with me. I didn't know who he was and we had an amazing argument about what this might mean. So much so that somebody, and I can't remember who it was, stood up at some point and sort of more or less told us to stop arguing and told David to sit down. This was an incredible, the best possible introduction to that group, that finding out right away that those robust discussions were possible. And as I didn't know who David was, it didn't worry me. And I think that's part of being a bit of an Antipodean as well, really. And the truth is the truth, you know, in genetics. I can't remember which one of us was right; I don't have a clue. It's all academic, really. But I guess the next major step beyond that was the physical mapping of the

region and then each group contributing with the skills, so Jim Gusella and Marcy MacDonald with patients and us with patients, trying to map recombination events, and trying to improve the linkage disequilibrium signal. There were two or three recombination events from the American work that suggested that the gene was closer and closer towards the telomere, which ultimately turned out that they were misdiagnoses. And we had two or three events that suggested the gene was more proximal. And I remember being asked at a meeting, very strongly actually, about how could we be sure that the diagnosis of our patients were correct? And I said that the patients have been seen by a single observer, Audrey Tyler; were the other patients seen by a single observer? And they weren't. And the combination of those recombination events, that put the gene more proximal away from the telomere; and the linkage disequilibrium provided the evidence for Jim and Marcy and us that it was a complete no brainer that the gene was more proximal. But there was about 2 years work from other groups imagining that the gene was closer and closer to the telomere. And that was quite a frustrating time, actually because there was, it just seemed so utterly obvious to Jim and Marcy and ourselves that the gene was where it was, and you'd know if it was being put in; so we had to put the effort into mapping and cloning that region and isolating CDNAs from that region.

I Were you in very close or regular contact with Jim and Marcy at this point?

S Yes, absolutely.

I Apart from the meetings?

S Well, the meetings were every 4 months or so, and absolutely, yes. And also with Michel Altherr, in John Wasmuth's group. John was a gentleman. I remember, so again, part of the social history: John coming to me, maybe on my second HD meeting and saying, "Look Russell, I know you're just doing your PhD but we would like you as the" what's the right way of putting it, "as the PI representing your group in these discussions. So we would like you as part of, with Hans and Francis and David and Jim and Marcy as kind of the representative" which was an incredible compliment. I recognised that at the time. It meant that I felt incredible responsibility to turn up at each one of these meetings with something new. And it was a great challenge, actually. And Nancy would always start the beginning of the meeting asking for what's new? She didn't want to know about what's old. [laughs] And that was great; really great. I enjoyed that. I enjoyed the pressure, actually.

I Am I right that there were several genes which kind of fell out along the way which turned out to be quite interesting genes in their own right? Not Huntington genes but… remind me which ones they were.

S Really the only one that I have in my mind is one of the fibroblast growth factors which turned out to be a gene for achondroplasia. There was a gene called Alpha adducin. We developed a lot of methodologies; we as the wider group, for isolating genes. So David Housman's group, Alan Buckler developed exon trapping, which was a method of being able to clone large chunks of DNA and then isolate exons. And so we scrabbled around, I labelled with incredible amounts of radioactivity, large chunks of DNA and screened cDNA libraries. So there was, I think I pulled out 12 genes or so in the region. Unfortunately none of them were the HD gene. I got genes either side of the gene, which is really quite annoying, even in retrospect. But the race was on to isolate genes so I pulled out these genes and actually developed sequencing in Cardiff; nobody had sequenced until I came along. It was quite funny, really; it needed to sequence so we developed sequencing. And then, this was before the internet really, so I used to read the sequence, these kilobases of sequence over the phone both to Jim, Marcy and also to John Wasmuth's group. And I remember getting the giggles halfway through this 10KB gene because it's an utterly ridiculous thing to do. [laughter] So that was very exciting; that was very exciting times.

I Now when it actually came to the gene itself, what do you… well what were you actually doing when we realised that Jim and Marcy had nailed it down?

S Well, I had a holiday of 3 weeks or so coming up in New Zealand and Jim and Marcy knew I was going on holiday so they called up before I went away and said, "Look, we've got this marker we want you to type through your families. Can you do that?" So I worked for a few days and typed this marker, so this again was an RFLP marker, I think, from memory. Yes it was. And this showed incredible skewing so it was very, very strong on linkage disequilibrium; it was wonderful. And then I went away and from speaking with Jim and Marcy afterwards that was that, in addition obviously in addition to their family data, that suggested they were very, very close to the gene. And then when I came back they rang, I can't remember when in the day it was, it kind of, it's one of those moments when time stands still and I think they were both on the phone, I think, and they said, "We've got the gene." And I just remember this, despite wanting to be the one that got it, I have to say, just this incredible sense of relief because it was utterly all consuming; totally consuming. And there were people who were burnt out through that chase and gave up science essentially because it was quite intense. And they said, "Oh, we're going to send you a fax through, and can you read the manuscript?" because they'd had a good go at writing it. And we've decided to call the protein Huntingtin, and I remember saying, "Oh, what a ridiculous name." And Jim saying, "Well, if you can think of a better one we'll call it that!" And apparently we couldn't think of a better one, well I couldn't, and it's caused confusion ever since, I think, actually. And then immediately it was a question of, beyond that it was a question of how generalizable was this result? But it was totally believable; totally convincing. This beautiful work; beautifully done. A real tribute to them, not that they've ever done anything that isn't beautiful, but it was magnificent and it opened the door to, for us to look through our families.

I That's a phase that I remember very well because you were more or less camped in the lab 24 hours a day for the next month or so.

S Yup. I slept on the, I shouldn't really say this probably, but I slept on the examination beds downstairs and my very good friend, Jerry Cheadle, dropped tools from what he was doing with his PhD in CF, and said, "Look, I'll help you do this" which he did in his meticulous way. Jerry is now a professor in genetics in Cardiff. And we developed an assay and we genotyped thousands of individuals. And we ran controls and did all this very, very carefully. It was incredibly intense; there were millicuries of P32 scattered about and we did most of this at night, so that it gave us an opportunity to clean up the hot lab and drop the radiation level down. Actually something I should tell you, but probably shouldn't tell you, when you're doing this work, we had to use P32 in order to get the signal right, so we used a heap of it. But of course it contaminated tips, pipette tips and things, and we couldn't think of a way of getting rid of them. We were generating an incredible amount of radioactive waste and in those days the solution was dilution effectively, and so at the end of this we had this big bag of these tips. So I had the idea that the best way of getting rid of this was we would get the Waring Blender from the other lab and we would just grind it all up into a fine slurry, and we'd wash it down the sink. It worked very well, actually. If the lid had come off, it wouldn't have been so good, but it worked very well. Jerry wasn't keen on doing that, so I did that bit. But we had a problem and we solved it. And it was magnificent, particularly seeing the age of onset correlation coming up; seeing the explanation for anticipation. Just seeing almost like this flower open in front of us of, "Ah, now we know. We know why things are the way they are." Or at least the beginning of an understanding. I think having, in the department, having seen the myotonic story unravel, well not unravel, but exposed in a similar way by the team and being a little, wee part of that, was wonderful preparation for the Huntington's work. It was a wonderful time. Sleep deprivation definitely.

I The only specific contribution I remember myself making at that point was to say to you, "For Heaven's sake, don't type the unaffecteds in case you find somebody's got a mutation."

S Yup! And that was wonderful and we didn't. There was the odd sample because in those stage, the sample names were written on the tube, and so the way we managed that was, as we had during the research, we were very careful. And I've taken that with me actually in medical genetics, that research is research and diagnostics are diagnostics, and there is no place for overlap, really. You'd go badly wrong if there was overlap. So before you saw the data, I went through the patient records and checked that everybody was deemed to be affected. And anybody that had, and there weren't very many, but anybody who had slipped through the system that were unaffected, or at risk, that data was never recorded. And when you're doing a few thousand individuals there's always some that sneak through the gap, and so maintaining that integrity, was extremely important. That was very important because the implications, obviously, are tremendous.

I I remember in the run up to the publication of that data, there was a fair amount of competition with other centres and I remember also that the other centres were amazed at just how much data we, or you, managed to produce within a few weeks.

S We turned it around very quickly but when you have an opportunity to, again that flower, to participate in knowing things that were a month before unknowable… I guess it kind of reflects my personality as well but I really like to know what I can know today and am very reluctant to wait till tomorrow. That's how I am really.

I I mean, this was a kind of one off time in everybody's life, really, but what made you want to stick, in a way, with Huntington's once you were going back to New Zealand and more into an animal based set up?

S A number of reasons. One is that I think the understanding of the diseases is tractable, and really ultimately I don't think it will be as complicated as all the plethora of data that's been generated at the moment indicates. So I have this, maybe simplistic view, but I have this feeling that the right idea at the right time will reveal something that will be very important and, so that's unfinished business, really. And also that I got to know Nancy well and clearly that's a personal thing; that I made extremely good friends through that time with the research group, particularly Jim and Marcy, but not just Jim and Marcy, Lesley Thompson; and partly friendship, partly community. I've fluctuated a little bit over the years in wondering whether the skills that I have could actually contribute, but I think there's still required some creativity. And also that knowledge, being able to synthesize some biology in the genetics. And quite frankly I think there's a lot of people working on Huntington's who don't understand the genetics of it really, and phenotype/genotype correlations and the power, like Jim talked about yesterday, the power of looking for modifiers and using the genetics which I regard as kind of the solid ground of the disease, and the rest is phenomenology associated with it. So being able to relate the inheritance of the variation in the disease to genes or loci and modifiers, I think, will reveal the true function of Huntington.

I And you reckon your sheep work is really going to make a different sort of stream of evidence that can complement what else is going on?

S I hope so. I hope so. I think it's an alternative. It will contribute or may contribute a bit. When we started the sheep project it was right in the middle of the flurry of the R62 mice, the acute onset models, and it was regarded as pretty mad, really. But my thinking at the time was, firstly Huntington's Disease is caused by the Huntington gene in addition to the repeat, so was interested in the full length, response for full length protein. And also that if these acute onset models, which looked like, kind of lysosomal disorders really, aggregative disorders, that there needed to be an alternative for looking at the slower onset of the disease. And

that's what I hope we've made. I think, just by chance really, there's some wonderful technologies now that will help us pull the disease apart in these animals. In effect we're using genetics but RNAseq for deep sequencing on its own, will reveal more. Unfortunately sheep is a bit of an orphan genome, the ovine genome is not well sequenced yet and so we need to use other tools in order to track down what the genes are that may be influencing the age of onset; and then metabolomics as well. So I think sheep as an alternate model with that data, specific data combined with the mice and the humans add another component to the interpretation of the disease, and particularly as I am sure we've generated a presymptomatic model now where at 6 months we're seeing very little changes; whereas at 18 months we're seeing inclusions, we're not seeing them at 6 months. So that's what I wanted. So we've got what I wanted. Time will tell whether it's useful. So there's a bit of luck involved.

I Russell, thank you very much, and is there anything you especially want to add that I haven't asked?

S Yeah, I want to say that the environment in Cardiff that you created: you and Duncan had this bunch of young people that you enabled to do their work through the provision of mentorship; provision of patients; the integration of clinical with molecular research; the wonderful relationships between people. Yes, there were tensions from time to time but in general the ambition was to find those darn genes and we had a lot of fun. And that environment didn't happen by chance. That was an environment that you created and nurtured, and I learnt, I guess since then, I've tried to recreate that environment wherever I've been: the full collaboration involvement with a lot of different people with different skills, and the not hiding things away. And so, I think a great degree of the success is owed to you, actually. And also the environment in medical genetics and the ethics of genetics there that you've done, that you put in place, has travelled around the world. So not just that, but the creative environment: how to create or how to encourage a creative environment. And so I'd like to say thank you very much for that opportunity and through that experience knowing how good it can be; and so I can strive for that, which is what I've been trying to do.

I Well, thank you Russell. That's very kind of you, and I'll switch the machine off.

S Very good!