

## Contrary, tenacity and breakthroughs



“It’s becoming more difficult to publish research on rare disorders.”

*Building bridges in genetics: from patient to genome and back again* was the title of the inaugural speech given by clinical geneticist **CONNIE VAN RAVENSWAAIJ-ARTS**. It’s a pragmatic title, because while it may be all well and good to gather data about genetics and do research, in the end, such research needs to benefit patients. In the case of Van Ravenswaaij, that means patients and their parents: she specializes in children who have rare chromosomal abnormalities.

Chromosomes carry our 20,000 hereditary traits. In the Netherlands, about 175,000 children are born each year, and almost six hundred of them (one in three hundred) will have a chromosomal abnormality. Of these six hundred affected children, almost two hundred will have a very rare chromosomal abnormality. Two hundred children each year, all with a different, tiny error in their chromosomes.

“I was studying to become a clinical geneticist when I first noticed that there is not enough known about rare chromosome abnormalities to be able to inform parents sufficiently about what exactly is going on with their child. There was also not enough information to really be able to survey these young patients.”

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By Frans Meulenberg, for The Netherlands Organisation for Health Research and Development (*ZonMw*)

Much of Van Ravenswaaij's research focuses on aberrations in chromosome 6 ([www.rug.nl/research/genetics/research/chromosome\\_6/](http://www.rug.nl/research/genetics/research/chromosome_6/)). "These come in all shapes and sizes. Depending on the location and size of the abnormality, symptoms range from learning disabilities and behavioural problems to severe learning disability. To date, it's almost impossible to predict which child will have which symptoms, and how severe they will be."

"We shouldn't underestimate these problems," warns Van Ravenswaaij. "We're talking about thousands of different abnormalities, each with only five or ten patients worldwide. Many children are almost unique. No scientist can study this, and there's not much to be found in the scientific literature. Scientific journals rarely make space to publish extensive case studies of a single patient or of a very small group of patients. Unfortunately, it's becoming more and more difficult to publish research the size of a postage stamp. That's because articles about small numbers of patients with rare conditions are rarely cited in later publications. That leads to a low citation score for the article (and journal), which is an important measure of journal quality."

Some time ago, Van Ravenswaaij and her colleagues from Nijmegen, Zurich and London started an internet database to gather clinical data about children with rare chromosome abnormalities: [www.ecaruca.net](http://www.ecaruca.net). "Our idea was for physicians to be able to share data about the children known to them without needing to publish it in a journal. In practice, however, many physicians can't find the time to fill out a database like this." That's why Van Ravenswaaij recently changed tack by putting the parents in the lead, not the physicians.

### **Mothers help through Facebook**

How does a scientist go about gathering this sort of case information? A few years ago, a mother wanted to know more about her son's condition and mentioned there was a Facebook group for people with a chromosome 6 abnormality and their parents. Hundreds of people from around the world are members of this group. Wouldn't it be a good idea to collect data about the genetic aberration of these people? She said she'd be happy to help. For Van Ravenswaaij, this presented a unique research opportunity.

Van Ravenswaaij enlisted a student and developed a questionnaire. Within only a few months, dozens of patients from all over the world had contributed to the study, all with a chromosome 6 aberration. "In no time, we had more data about chromosome 6 than in all the scientific journals put together. We collected two types of information from all the participants: their genotype and their phenotype. The genotype is the genetic information that shows us exactly where their aberration is located on chromosome 6. The phenotype is the total of their physical characteristics, development and behaviour. Together, this can provide new information, for example, by matching a specific chromosome area with a specific symptom."

Facebook isn't known as a scientific force, but it is wonderful to see that the medium can work as a meeting place for scientists and patients. Parental input is essential to building the

details of each case. No database can provide the information that researchers find in the answers from parents. When did the child start talking or walking or becoming toilet trained? “This material can be seen as a historical archive, with a wealth of information. In this way, we hope to find out the causes of, for example, aberrant behaviour.”

The goal is to fully map chromosome 6. So physicians can say to parents: your child is missing this bit of chromosome 6, and that means he or she has an increased chance of a heart disease or an eye abnormality. Van Ravenswaaij: “That’s not just good for the parents to know; it can also lead to a concrete treatment plan. Scheduling a cardiogram each year, for instance. Or getting the eyes checked.”

At this time, work is ongoing to create an online version of the questionnaire for parents in many different languages. In time, our goal is to be able to provide information to parents on the potential effects of their child’s exact chromosome 6 abnormality.

### Parents as eye witnesses

Parents play an important role in the interaction between science and society. They see their child every day, and witness his or her development up close. After all, a parent’s love is unconditional. Parents are even dedicating themselves to raising research funding, for example by opening a PayPal account, Van Ravenswaaij says.

“A sum of, say, €5000 will trickle in slowly. However, Dutch research scientists are extremely expensive because the UMCs have high overhead costs. This is difficult to explain to parents but, as a researcher, I know every little bit helps and I feel obliged to do as much as I can in return for all their effort.”

Clinical geneticists are a different kind of medical specialist: they write letters to patients and their parents, with copies to the referring physician and general practitioner.

### Questions

It’s important not to underestimate what it means to have a baby with a chromosome abnormality. All kinds of questions come up: Why is this happening to us? What does this mean for the child? What will this baby’s future look like? Could this happen to us again?

Van Ravenswaaij is very much aware of this. “The certainty of a diagnosis gives parents, for the first time, some grip on the situation, however tenuous that may be. We have done a lot of research into CHARGE syndrome ([www.rug.nl/research/genetics/research/chargesyndrome/](http://www.rug.nl/research/genetics/research/chargesyndrome/)), where children show various degrees of congenital aberrations of the ears, eyes, and heart, among other symptoms. Since 2004, we know that this syndrome is caused by a change in the gene known as CHD7. Everyone has two CHD7 genes, one from mum and one from dad. If only one of these two CHD7 genes is abnormal, a child will develop the CHARGE syndrome. The syndrome’s phenotype can vary tremendously, though, which makes it impossible to predict from the type of genetic change what the

consequences will be for the child. Discovering the underlying genetic abnormality made it possible to test all the children being treated under this diagnosis. It turned out that several children didn't fall into this diagnosis category after all. For their parents, that one piece of information they had to hold on to dropped away, and that was very difficult for them."

In all of her studies, Van Ravenswaaij asks patients and their parents what they would like to see happen. An often-heard wish is to start a centre of expertise, because "that way, research questions will come up spontaneously, and one study will lead to the next." And so it happened: that centre of expertise now exists in Groningen ([www.rug.nl/research/genetics/research/chargesyndrome/charge-clinic](http://www.rug.nl/research/genetics/research/chargesyndrome/charge-clinic)). The added value of this centre of expertise is "the commitment to do clinical scientific research and to create clinical guidelines. We don't necessarily have to do everything ourselves, but we do have to remain open to new ideas. The various medical specialists in the expert team don't just advise, but also gather information."

## Testing

New techniques make it possible to do more exact chromosome testing. Previously, microscopes could only show us large abnormalities; now, even very small aberrations can be found. "Array technology allows us to look at chromosomes in a different way. First, the chromosomes – the patient's DNA – are cut into tiny pieces and labelled with a fluorescent colour. Next, you allow these pieces to stick to a great many unique pieces of DNA, the array, positioned in neat rows on a slide. By measuring the colour intensity of the pieces of DNA, you can determine which bits of chromosome are present in duplicate, as they should be, and which bits of chromosome the patient doesn't have the right number of. This technique makes it possible to show whether a gene is present, but not whether it carries a smaller error: called a mutation. With next generation sequencing, however, it's possible to analyse all 20,000 genes in a single test, in only a few hours."

Van Ravenswaaij says next generation sequencing has benefits and drawbacks: "The benefit of techniques like these is that we can reach a diagnosis more often. The drawback is that you find things we don't know, or don't yet know, how to interpret. Or, coincidentally, you find that someone is missing the gene that protects him or her from colon cancer, for example."

## Bycatch

In this, Van Ravenswaaij touches upon an important question: how do you deal with unrelated, secondary findings or 'bycatch'? "In this field, you shouldn't be afraid to miss things," Van Ravenswaaij says matter-of-factly. Her guideline is: "if you can do targeted research, keep your target in mind and don't widen your search."

She's happy to elaborate. "One problem in dealing with relevant findings and unrelated findings is: do the parents have the option not to receive certain information? For now, we

don't tell parents if an abnormality causes an increased chance of dementia. That's because dementia can't be treated. If a test shows an increased chance of colon cancer, for instance, we do tell the parents. You can screen for colon cancer, find it, treat it, and monitor it. Keep in mind, too, that a condition you find in the child may also be present in the parents."

These are only a few examples of the ethical dilemmas that are part of genetics research. No wonder that ethicists are included in the team working on a guideline for counselling those people seeking advice before and after new types of genetics-based diagnostics are used. Van Ravenswaaij is happy about that, but adds: "If it were up to me, I'd be much more concise about some of the ethical considerations..." These are the words of someone who is a practitioner through and through, and who'd much rather leave the fine print to the ethicists.

### Awareness

The field of genetics is developing rapidly. In the near future, we'll know exactly what everyone's genetic make-up is. With the title of her inaugural speech in mind, Van Ravenswaaij posits: "In short, the journey from patient to genome is moving along nicely, but the real challenge will be the way back."

Anyone who thinks geneticists are techies is very much mistaken. "As a clinical geneticist, you need to get out there, not remain in a university building or laboratory." Listening, really listening, is important, because "clinicians are inclined to want to decide what's best for their patients. But we barely know what the patients themselves want." People can only make an informed decision if they have enough information. There's a real need for extensive public education, because the large majority of people only know of one chromosomal abnormality: Down syndrome.

Van Ravenswaaij: "People need to know what genetic information really is. What you can do with it, and what it means for your relatives. In many cases, genetic testing is about hereditary forms of dementia or cancer. In that case, a physician isn't dealing with a single patient, but with an entire family who may not know about their genetic predisposition."

Physicians should also keep in mind that many parents may find it difficult to understand the implications of their child's genetic condition or may not have a good command of Dutch. "Short, clear internet videos can be a tremendous help during the counselling process before genetic testing is agreed to. It remains essential to get informed consent from patients or their parents before any genetic testing is done. Whether that's chromosome testing, analysing a single gene, or analysing a couple of thousand of them."

### A good pair of eyes

Van Ravenswaaij works in a small niche: patient numbers are low, active patient associations are often absent, developing medication for rare conditions (also called orphan diseases) is

outrageously expensive, research funding is difficult to obtain, and the subject matter – genetics – is complex, especially for lay people. All of this just serves to increase her motivation. The basic toolset of the clinical geneticist contains not only techniques, but also a classical instrument: a good pair of eyes. In essence, her work and her scientific vision amount to the same: “by taking a good look at patients and their genomes, we are able to learn much about human genetic material. Then, by again looking closely at our patients, we can learn how to interpret the variations these new techniques reveal in the genetic material. How the patient presents him- or herself is so important. The smallest differences can often be significant.”

Van Ravenswaaij is someone who thinks visually (“always have, even as a child”) and likes to make drawings to explain things. She also effortlessly finds metaphors, which genetics is full of: “We used to say we were looking for a needle in a haystack. Now we’ve got a stack of needles and we need to find the one that pricks.” Van Ravenswaaij experiences the need for a good pair of eyes each year in Surinam. “This is the fourth time I have spent two weeks in Surinam together with a clinical geneticist specialized in neurology, a paediatric neurologist, and a medical resident. Seeing well and listening well are essential instruments, because you don’t have any laboratory facilities there, nor are there any treatment options available. There’s no DNA to prove anything. But why would you even want to? This way, we learn to make tentative diagnoses on sight. At our last visit, we saw around 60 patients who were eagerly awaiting our arrival. And when we return to the Netherlands, it’s great to see a tentative diagnosis confirmed in our laboratory.”

Typical of Van Ravenswaaij is that she never ever loses sight of the human aspect. The love for her ‘orphan diseases’ is unmistakable in her message: “Keep watching the rare syndromes, because what you learn from them can tell you so much about other problems.”

This interview has been translated from a chapter of a book on Dutch healthcare researchers and their scientific work and vision. The book was compiled for ZonMw and published in June 2015. The full text in Dutch can be downloaded from [www.zonmw.nl/nl/actueel/nieuws/detail/item/dwarsdenken-en-doordouwen-denkonconventioneel-in-het-gezondheidsonderzoek/](http://www.zonmw.nl/nl/actueel/nieuws/detail/item/dwarsdenken-en-doordouwen-denkonconventioneel-in-het-gezondheidsonderzoek/)

**Conny van Ravenswaaij-Arts** (1961) studied medicine at Leiden University. In 1993, she received her doctoral degree from Radboud University Nijmegen (the Netherlands) for her thesis entitled *Heart rate variability: physiology and clinical applicability in very preterm infants*.

She pursued a specialization in clinical genetics and clinical cytogenetics. Since 2006, Van Ravenswaaij-Arts works for the University Medical Centre Groningen as a clinical geneticist at the Department of Genetics. In 2011, she was appointed Professor of Clinical Dysmorphology, with an emphasis on genome analysis. In her research in Nijmegen and Groningen, the patient has always taken centre stage, with rare chromosome abnormalities and CHARGE syndrome being areas of special interest.

### Links to further information

Further information on Conny van Ravenswaaij, see [www.rug.nl/research/genetics/staff/connyvanravenswaaij](http://www.rug.nl/research/genetics/staff/connyvanravenswaaij)

See also "*Bruggen bouwen in de genetica: van patiënt naar genoom en weer terug*" (Building bridges in genetics: from patient to genome and back again). (in Dutch) Inaugural lecture, University of Groningen, the Netherlands, 2012

[www.rug.nl/research/genetics/publications/connyvravenswaaijoratietekst.pdf](http://www.rug.nl/research/genetics/publications/connyvravenswaaijoratietekst.pdf)

Chromosome 6 syndrome [www.rug.nl/research/genetics/research/chromosome\\_6/](http://www.rug.nl/research/genetics/research/chromosome_6/)

Charge syndrome [www.rug.nl/research/genetics/research/chargesyndrome/](http://www.rug.nl/research/genetics/research/chargesyndrome/)

Charge Centre of Expertise [www.rug.nl/research/genetics/research/chargesyndrome/charge-clinic](http://www.rug.nl/research/genetics/research/chargesyndrome/charge-clinic)

Phelan-McDermid syndrome [www.rug.nl/research/genetics/research/phelan-mcdermid-syndrome/](http://www.rug.nl/research/genetics/research/phelan-mcdermid-syndrome/)

Ethical, legal social issues (ELSI) in clinical genetics, see [www.rug.nl/research/genetics/research/elsi](http://www.rug.nl/research/genetics/research/elsi)

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