Nature Reviews Genetics | AOP, published online 17 May 2011; doi:10.1038/nrg3014

AN INTERVIEW WITH...

Patricia Jacobs

The 2011 March of Dimes Prize in Developmental Biology has been jointly awarded to Patricia Jacobs, of Southampton University Medical School and the Wessex Regional Genetics Laboratory, and to David Page, of the Whitehead Institute, Massachusetts Institute of Technology and Howard Hughes Medical Institute, for their pioneering research on the X and Y chromosomes. The prize recognizes researchers whose work has contributed to our understanding of the science that underlies birth defects. We talked to the winners about their achievements and the impact these have had on human health. This month's interview is with Patricia Jacobs, who spoke to Louisa Flintoft. The interview with David Page will appear in our July issue.

Your 1959* Nature *paper on Klinefelter's syndrome (in which human males have an extra X chromosome) was the first to identify a chromosomal abnormality that underlies a human condition. What made this discovery possible?

I entered the field at just the right time. The correct human-chromosome number was only described in 1956 — it was 46 and not 48 as had been previously supposed. The sex chromatin body had also been described by Barr and Bertram, first of all in cats. They found that this was a rather uniform feature of mammalian species: females had a 'blob' in the nucleus that males didn't have. So it was assumed that females had two sex chromosomes, both of which constitute the sex chromatin body (or blob), and males had only one. The other thing that was assumed was that sex determination in humans was exactly the same as in *Drosophila*, and that meant that the Y chromosome had nothing to do with the sex, which was thought to be determined by the ratio of X chromosomes to autosomes.

Then, individuals were found who had discordant sex chromatin: males who had a blob — these were Klinefelter males — and females who didn't, who were mostly females with Turner's syndrome. It was assumed that both of these were complete sex reversals: that the Klinefelter males would have two X chromosomes and that the females would be 46,XY. I was given my first job at the newly established Medical Research Council unit in Edinburgh working on the chromosome constitution of radiation-induced leukaemia, but appropriate individuals with leukaemia were very hard to come by. So I had a little time on my hands and a clinician there offered me a bone-marrow sample of a man with Klinefelter's syndrome. He had 47 chromosomes. We didn't have banding then, but as far as I could see he had an XXY sex-chromosome constitution. And that meant that the Y chromosome was male-determining, which turned out to be the case in all mammals. I think one of the advantages I had was that I didn't know that everyone thought that sex determination in man was the same as in *Drosophila*, and so I just recorded what I saw. I had no preconceived ideas.

What impact did your findings have?

The finding was very quickly confirmed and Down's syndrome was also shown to be due to an extra chromosome, namely number 21. Then, Turner's syndrome females were found to have a single X chromosome. After that, it was an explosion — I think that the development of human cytogenetics kick-started the whole field of modern clinical genetics. Another important development was the blood-culture technique. Nowadays, you would never be able to take bone marrow from patients just to look at their chromosomes. But blood culture meant you could look at virtually anyone's chromosomes, and we did. What happened then was that people recognized that a number of other human syndromes might be caused by abnormal chromosomes. Then, researchers started finding other developmentally abnormal people and looked at their chromosomes and started to describe conditions that had not previously been recognized that were due to additional chromosomes; for example, trisomies 13 and 18, both of which are compatible with live birth.

How have technologies changed our understanding of chromosomal abnormalities?

It's been incremental. When we first started out, chromosomes were uniformly stained. But then, in the late 1960s and early 1970s, techniques became available for banding chromosomes. Prior to that, chromosomes had all looked very similar, but now you distinguish each chromosome pair by its pattern of banding and start to make sense of structural abnormalities. Techniques continued to improve over the years and very recently we have had an order-of-magnitude advance with array comparative genomic hybridization (array-CGH), which detects very small deletions and duplications below the level of resolution of the light microscope. There are thousands of these. This is where the field is going. You can look at patients who have abnormalities that appear to the clinician as if they would be caused by a chromosomal abnormality, but who appear normal on conventional cytogenetic analysis. Using array-CGH, about 20% of such patients turn out to have a duplication or deletion of clinical significance.

What difference has the ability to identify chromosomal abnormalities made to patients and their families?

It has made a considerable difference. First, there's the desire to know why your offspring are the way they are. Even if nothing can be done about it, you want to know why, and what the probability is of you having another child with the same abnormality. And, apart from differences in chromosome number, there are a huge number of structural chromosome abnormalities, most of which are associated with some kind of pathology. For example, in Down's syndrome there is a small proportion of cases with a translocation involving chromosome 21, which can be passed through families. In these cases, you offer cytogenetic testing to other family members.

In terms of treatments, it's more difficult. You can look at the genes that are involved, which could provide clues to possible therapies. But, for rarer abnormalities, it's more difficult. Rare conditions are not well catered for in terms of therapy.