



## WHAT CAN RARE GENETIC SYNDROMES TELL US ABOUT CANCER?

### Lessons from human overgrowth syndromes

Identifying genes that underlie rare overgrowth syndromes is shedding light on the genetic causes of childhood cancers.



**Nazneen Rahman**  
PhD MRCP

Dr Nazneen Rahman is a Team Leader in Cancer and Developmental Genetics in the Section of Cancer Genetics at The Institute of Cancer Research and an Honorary Consultant in Medical Genetics at The Royal Marsden NHS Foundation Trust

Growth and development in childhood is strongly influenced by our genes. Our genes are made of DNA and we have two copies of every gene, one that we inherit from our mother and one from our father. At conception the DNA from the egg and sperm come together to make the embryo and during this process alterations in the DNA inevitably occur. Usually these alterations do not have any obvious effect, but if a critical alteration occurs in an important gene, then the gene cannot work normally – this type of alteration is a mutation.

### Genetic mutations can cause overgrowth syndromes

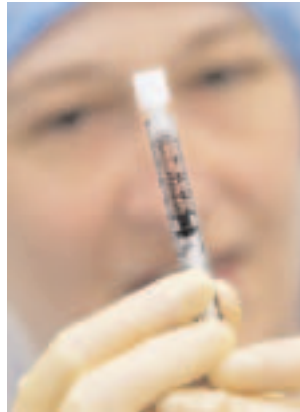
All the cells in our body arise from the first cell, so if a mutation occurs at conception all cells will carry the faulty gene. This may mean that development does not proceed normally and medical problems occur. The resulting diseases are known as genetic syndromes, some of which result in an increased risk of cancer. Notably, research into genetic cancer syndromes has led to the identification of many cancer predisposition genes such as the breast cancer gene, *BRCA2*, which was identified at The Institute.

In the Section of Cancer Genetics, our group is concentrating on trying to identify the causes of human overgrowth syndromes. An overgrowth syndrome is a condition in which there is excess growth either of the whole body or of one part of the body relative to another. These conditions can be associated with many other problems including learning difficulties, heart defects, kidney problems and cancer.

### Linking overgrowth syndromes and cancer?

Cancers occur because mutations in the DNA of a particular cell disrupt the function of genes that control how and when the cell grows and reproduces, allowing the cell to grow without restraint. Cancer therefore shares many similarities with overgrowth syndromes in which the normal control processes that govern the rate of growth are also disrupted. So it is not surprising that some overgrowth conditions are associated with cancer.

By identifying the genes that cause human overgrowth conditions we may also identify genes that are involved in cancer.



There have already been precedents establishing this connection. For example, *PTEN* is a gene that is disrupted in many different cancers including glioblastomas, endometrial, breast, thyroid and prostate cancers. If a child has a *PTEN* mutation that occurred at conception, or is inherited from one of their parents, they can suffer from a variety of genetic syndromes, such as Bannayan-Riley-Ruvalcaba syndrome or Cowden disease. People with these genetic syndromes have overgrowth, particularly affecting the size of the head, can also have learning difficulties and are at risk of polyps and breast and thyroid cancer.

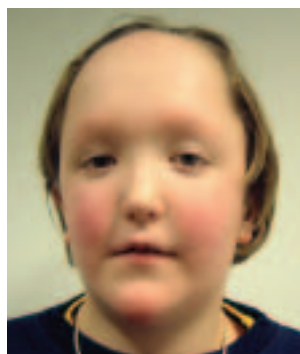
- to identify the genetic causes of overgrowth syndromes;
- to produce guidelines for the diagnosis and management of overgrowth conditions;
- to investigate how overgrowth syndrome genes are involved in cancer.

One condition that we have been focusing on is Sotos syndrome. Children with Sotos syndrome are much taller than other children of the same age, they have distinctive facial features and learning difficulties and can suffer from heart defects, curvature of the spine and sometimes cancer (Figure 1).

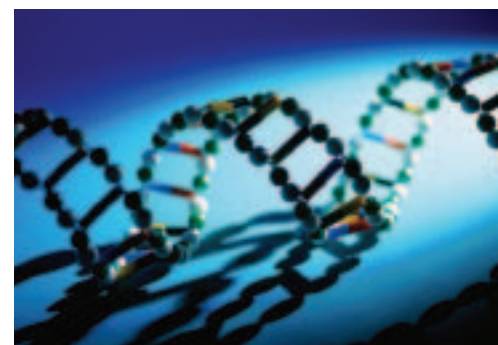
## How can we gather data on such rare conditions?

In 2002 we initiated the Childhood Overgrowth Study. Working with clinical genetics departments from across the UK, we collect information and samples for genetic analysis from children with overgrowth syndromes and their families. We have already recruited nearly 500 families. The aims of the study are:

- to find out how common childhood overgrowth syndromes are;
- to find out the nature and frequency of medical problems associated with overgrowth syndromes;

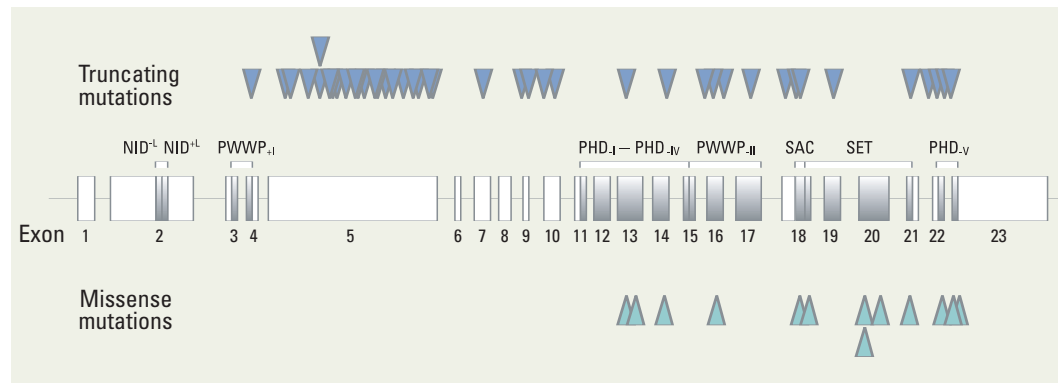


**Figure 1** Typical facial features of a child with Sotos syndrome.





**Figure 2** The *NSD1* gene showing the position of the various mutations that cause Sotos syndrome. The shaded areas of the gene are specific functional domains that can interact with other genes and proteins. The mutations above the gene truncate the gene so that it cannot work at all. The mutations below the gene simply alter one amino acid. These missense mutations only occur at critical amino acids in the functional domains.



## Mutations in *NSD1* gene cause Sotos syndrome

In 2002, the gene for Sotos syndrome, *NSD1*, was identified. *NSD1* controls how and when other genes are switched on by stimulating or repressing them in response to cues from the cellular environment. Children with Sotos syndrome have one copy of *NSD1* that is not working properly, usually because there is a mutation in the gene. These mutations are not random but instead are grouped in areas of the gene that we know are involved in binding other proteins (Figure 2).

Sometimes Sotos syndrome occurs because one whole copy of the *NSD1* gene is completely missing – known as a gene deletion. Children with *NSD1* deletions are usually much more severely affected and may have learning difficulties. Thankfully, only a minority of Sotos syndrome cases are due to gene deletions.

## Sotos syndrome is usually not inherited

We have now identified more than 150 cases of Sotos syndrome with *NSD1* mutations or deletions in children from across the world. In a collaborative study with researchers from Europe, Australia and the USA we are using the clinical and molecular data from these cases to draw up diagnostic and management guidelines for the care of children with Sotos syndrome.

We have also shown that the *NSD1* mutation almost always occurs for the first time in the child with Sotos syndrome and is not usually inherited from either parent. This is very reassuring for families as it means that other family members or any other children they may have in the future are not at risk of having Sotos syndrome.

## Is the *NSD1* gene involved in cancer?

Fortunately, only a small number of children with Sotos syndrome will develop cancer, but certain cancers, such as neuroblastoma and sacrococcygeal teratomas, certainly occur more often in children with Sotos syndrome than one would expect by chance.

The *NSD1* gene is also known to be involved in some forms of childhood leukaemia. Dr Lyndal Kearney in the Section of Haemato-Oncology has shown that some children with acute myeloid leukaemia carry a specific chromosomal abnormality called t(5;11)(q35;p15.5), which results in the *NSD1* gene being fused to another gene, called *NUP98* (Figure 3). It is unclear exactly how this fused gene promotes leukaemia, but it appears that the mechanism may be different from that by which *NSD1* causes Sotos syndrome.

In Sotos syndrome there is loss of function of one copy of *NSD1*. In leukaemias with t(5;11)(q35;p15.5) it seems likely that the fused *NSD1* gene is still working, but inappropriately. This may result in the wrong genes being stimulated or repressed by *NSD1* in the wrong cells or at the wrong time.

We are working with Dr Kearney and Dr Kathy Pritchard-Jones in the Section of Paediatric Oncology to look at the role of the *NSD1* gene in cancers, and in particular to see whether or not cancer cells carry *NSD1* mutations. We are screening *NSD1* for mutations and deletions in a large number of cancers, which should provide an answer to whether *NSD1* loss is involved in cancers and specifically which cancers are affected.

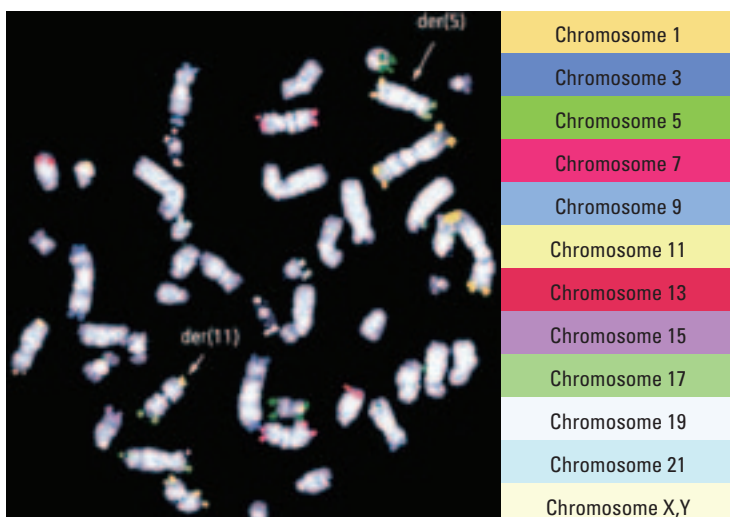
## What of the future?

Looking ahead we are beginning work to try to find the genetic causes of the hundreds of cases of childhood overgrowth that are not due to known overgrowth genes. We are particularly focusing on syndromes that are thought to have a risk of cancer. Childhood cancers, especially Wilms tumour, are often associated with overgrowth conditions. Wilms tumour is a cancer of the kidney that usually occurs in children under the age of five years. The tumour has all the hallmarks of the developing kidney and may be caused by growth signals that promote growth of the kidney in the embryo not being switched off correctly after birth.



Together with Dr Pritchard-Jones we are trying to identify the faulty genes that can lead to Wilms tumour. We will be looking at any genes we identify in overgrowth cases to see if they are involved in Wilms tumour more generally. We are also collecting data on families that have more than one case of Wilms tumour and cases with Wilms tumour and other medical problems, as both suggest that faulty genes may be present.

By investigating these rare genetic syndromes we hope to discover new information that will be helpful for families. We also hope our research will bring insights into the processes that control normal growth and development and how these processes can go wrong in cancer



**Figure 3** The  $t(5;11)(q35;p15.5)$  translocation in acute myeloid leukaemia shown by 12 colour multiplex FISH assay. One chromosome 5 (green) has chromosome 11 material (yellow) on the q arm. The corresponding chromosome 11 (yellow) has chromosome 5 material (green) on the p arm. This corresponds to the balanced translocation. The derivative chromosomes, der(5) and der(11), are indicated by arrows.