

# Unique Conference 2005

## Conference 2005 Overview

From Friday October 21st to Sunday 23rd, over 250 *Unique* family members gathered in Daventry, UK for our group's 21st birthday conference. Families, friends, clinical geneticists, doctors, eminent scientists and behavioural and educational experts came from round the world to be with us: from California, Germany and Holland as well as the UK's four constituent countries, Northern Ireland, Scotland, Wales and England.

On Friday and Saturday evenings, families who had requested a session with a clinical geneticist were able to talk privately in individual genetics clinics with one of the remarkable team of professionals who so generously gave their time and expertise: Dr Helen Firth and Dr Simon Holden from Cambridge, Dr Alex Magee from Belfast, Dr John Tolmie from Glasgow and Dr Nicole Tartaglia from California.

On Saturday morning, having for the most part left their children happy and safe in the crèche, delegates gathered to listen to some serious science. *Unique's* Chief Medical Medical Advisor had prepared a captivating programme under the banner The Human Genome Project: What's in it for us? (see below).

In the afternoon, families gathered in smaller groups for workshops – on behaviour, sleep, sex and the 3Rs (rights, responsibilities and relationships), pre-implantation genetic diagnosis (PGD), non-invasive prenatal diagnosis and chromosomes in general. In most cases the workshop leaders brought a professional lifetime's expertise to these sessions: on behaviour, Dr Viv Hinchcliffe as headteacher of a special school for children with severe learning difficulties and as a psychologist; on sleep, Dr Luci Wiggs as a psychologist who has a special interest in the sleep patterns of children and adolescents with developmental disorders; on sex and the 3Rs, David Stewart, head teacher of the Shepherd Special School in Nottingham; on PGD, Dr Caroline Ogilvie, principal scientist at the Cytogenetics Department at Guy's Hospital who was part of the team that set up the PGD centre there and Dr Cindy Zaitsoff, a genetic counsellor and member of the PGD team; on non-invasive prenatal diagnosis, Professor Hultén; on sex chromosome aneuploidy, Drs Tartaglia and Holden; and on chromosomes in general, Drs Magee and Tolmie. The two complaints about the workshops were that families couldn't attend them all and they would have liked them to last twice as long!

Reports of the sleep, behaviour and sex and the 3Rs workshops are on pages 17 and 18; reports from the sex chromosome and PGD workshops will appear in the next newsletter.

At tea time, families and children came together for *Unique's* 21st birthday bash in the presence of Daventry MP Tim Boswell. Do read *Unique* dad Andrew Tickle's account and feel the lump rise to your throat, see page 19.

If you thought this action-packed programme would have exhausted families already, you would be wrong. The party had hardly started – as the tireless dancers showed, still partying into the small hours of Sunday with magic man Peter McKenna's DiscoMagic.

Sunday morning was wind-down time: two planned sessions of tai chi and yoga simplified to a single session for those families who needed an infusion of calmness in their lives and were not still nursing their heads from the night before.

By mid-morning, it was all over: the birthday balloons had gone home with the families, hugs and emotional goodbyes had signalled departure and *Unique* was 21 years old.

This very special conference just wouldn't have been possible without so many helpers: Linda, who supervised the crèche and the crèche helpers; Wendy and Julie who welcomed families with practised efficiency; Claire, Anthony and Steve, who acted as marshals; Patrick the IT man. Thank you, all of you, and everyone else who helped.

## The Human Genome Project: what is in it for us?

Professor Maj Hultén, *Unique's* Chief Medical Advisor, Professor of Medical Genetics at Warwick University, and 'a wonderful inspiration for many years', threw open the main scientific session of the conference in her inimitable style. Simply 'Maj' (pronounced 'my', not 'madge') to everyone, she welcomed the 200 or so delegates: 'It's hilarious to see so many people here.' Having established that around half the families were *Unique* conference newcomers, she launched into her subject: The Human Genome Project: what is in it for us?

Starting at first base, she explained that chromosomes – in Greek the two parts of the

word mean 'colour' and 'body' – are packages of DNA and proteins that were first seen under a microscope around 100 years ago. Fast forward fifty years to 1956 and human chromosomes were correctly counted for the first time (46, rather than 48). Developments gradually gathered pace: in 1970 chromosomes were stained with chemicals that produce alternate dark and light bands and the way of visualising them under a microscope known as chromosome banding emerged. Chromosome banding makes it possible to distinguish one chromosome from another. Different chemicals have been used over the years for staining, but the one in common use today is Giemsa dye – which is what the G in the term 'G-banding' refers to.

By the late 1980s – 1988 - 9 – molecular techniques had developed that made it possible to look at chromosomes in an entirely different way and in finer detail than is possible to by traditional banding techniques under a conventional microscope. The emergence of fluorescence in situ hybridisation (FISH) techniques made it possible to use specific probes to 'paint' parts of chromosome arms, whole arms and whole chromosomes in different colours and visualise them using a fluorescence microscope. Then, finally, in 2000, the sequence of the human genome was published, allowing the development of even more sophisticated methods, such as microarrays to get to grips with the fine detail of chromosomes.

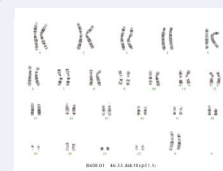
Maj knows the thrill of scientific discovery: she was in the laboratory when Joe-Hin Tjio and Professor Albert Levan first counted human chromosomes correctly and for those of you who would like to read about it, has written about this in a scientific journal (Hultén, Cytogenetic and Genome Research 2002, 96: 14 - 19). That thrill, it seems, has never left her.

As Director of the Regional Genetic Services in Birmingham for over 20 years, she also has a profound understanding of the human implications. Using a *Unique* child with a deletion from the short arm of chromosome 18 as an example (chief executive Beverly Searle's daughter Jenny), she explained how amazing it is that a chromosome disorder can be pinpointed quite precisely by examining G-banded chromosomes and then confirmed with FISH.

### Different ways of looking at the same chromosomes: an 18p11.1 deletion



Seen with G-banding.



Lined up for a karyotype.



With a FISH probe for short arm of 18 (18p).



With FISH probes for the centromere and 18p subtelomere.

All *Unique* families have had a chromosome analysis performed using G-banding, but fewer have had their chromosomes looked at in further detail by the new techniques. It seems likely, though, that as with Jenny, most will have been correctly diagnosed by G-banding alone. Further new technologies including in particular microarrays emerging from the Human Genome Project can reveal knowledge about the chromosomes in previously unimagined detail and in some occasional situations it has in fact emerged that the underlying chromosome rearrangement is more complex than initially thought.

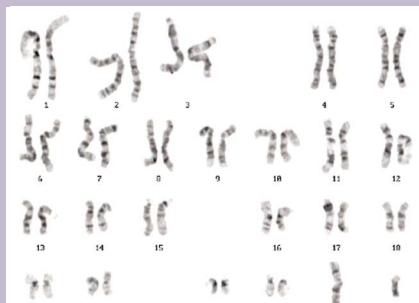


## Chromosomes in Colour

Dr Michael Speicher, from the Institute of Human Genetics at Munich Technical University, dazzled families with his images of fluorescently-labelled chromosomes. He showed that unimagined complexity may be revealed in rainbow fluoro-colour, by the advanced molecular cytogenetic techniques of FISH.

### What is G-banding?

G-banding is the technique for examining chromosomes that the very great majority of Unique families have experience of. It works like this: during cell division, the 23 pairs of human chromosomes condense and are visible under a light microscope. If the chromosomes are stained with a dye known as Giemsa, a pattern of light and dark bands is revealed.

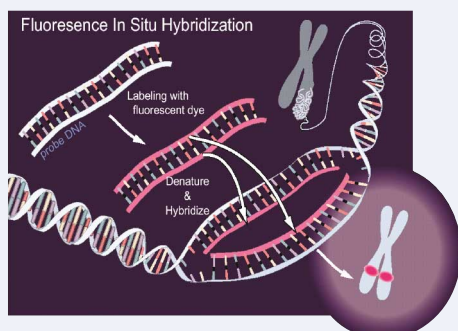


**Chromosomes seen with conventional G-banding.**

Each chromosome has its own specific order and pattern of dark and light bands that enables an experienced cytogeneticist to recognise it on sight when magnified (up to about 1000 times life size) under a light microscope.

Each darker or brighter band is clearly distinct from its neighbours. Each band contains many genes and even the thinnest bands potentially contain hundreds of genes.

However, there are some problems with G-banding. One problem is that the sequence of the dark: light bands can look very similar on different chromosomes or in different regions on the same chromosome. This can sometimes make rearrangements hard to identify precisely. Another problem is that G-banding frequently misses very small chromosome rearrangements. This is where molecular cytogenetic techniques come in.



[http://www.accessexcellence.org/AB/GG/nhgri\\_PDFs/ish.pdf](http://www.accessexcellence.org/AB/GG/nhgri_PDFs/ish.pdf)

### What is FISH?

FISH, short for fluorescence in situ hybridisation, is a technique that allows chromosomes to be examined in greater detail than is possible with conventional G-banding. FISH allows specific genetic material to be visualised in different colours and thus mapped to certain chromosome regions.



DNA is composed of two strands of complementary molecules that bind to each other like chemical magnets. The first step in FISH is to separate the two strands of DNA and prepare a sequence of single stranded DNA, known as a **DNA probe**.

### FISH

One of a number of colours of fluorescent dye is then tagged to the DNA probe (known as labelling). When the fluorescently labelled DNA probe is added to the sample containing the chromosomes being investigated, it will bind to the complementary strand of DNA, wherever it is. This binding process is called **hybridisation**. The dye allows it to be seen under a fluorescent microscope.

One problem with FISH is that each DNA probe is specific to a sequence on a chromosome. If you don't know which chromosome to look on, where do you start in making up and applying your DNA probe? Sometimes a clinical clue will suggest the right chromosome. For example, a child with a heart condition that is fairly common in people with a small deletion from chromosome 22q11 (DiGeorge syndrome) allowed the molecular cytogeneticist to home in on this specific segment and visualise this particular deletion by FISH.

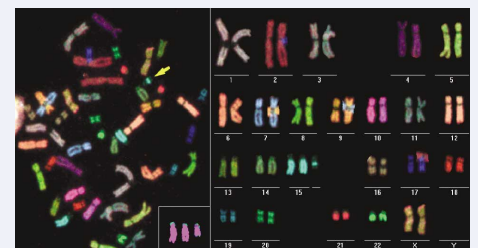
Often, though, there is no clinical information to go on. Many different probes and collections of probes now exist: painting probes specific to a chromosome, probes specific to a particular chromosome arm, probes for centromeres (the chromosome movement centre, localised to the junction between the short and the long arm) and probes for telomeres (the tips of the arms). Using these, a probe set can be individually tailored to a specific translocation, for example.

But Dr Speicher's team wanted to develop an approach that would allow all the chromosomes to be screened simultaneously. The technique they developed is known as **multiplex FISH (M-FISH)**, in which all the chromosomes are stained to a specific colour combination. The more colours used, the more specific M-FISH is. Using an automated process, a karyotype can be generated on a computer within a minute.

### Detection of subtle chromosome rearrangements

So how can M-FISH help, for example, those families where no chromosome disorder has been detected by conventional techniques, in spite of features suggesting an abnormality? Dr Speicher first showed an example where G-banding gave a normal karyotype but FISH showed an unbalanced rearrangement.

The starting point was a child with unusual facial

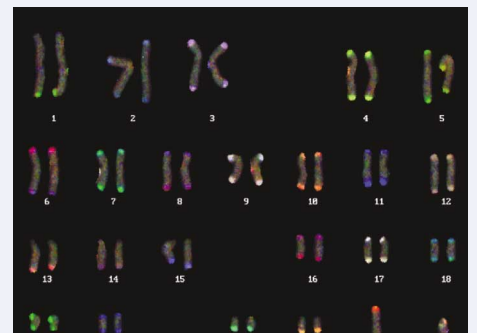


**A karyotype generated using FISH. There is a small additional chromosome composed of material from chromosome 15.**

features, but G-banding of the child's chromosomes revealed nothing abnormal. However, multiplex FISH showed a colour change on chromosome 18 with the extra colour matching chromosome 20. The interpretation was that a segment of chromosome 20 had been added to the end of chromosome 18, with the loss of part of 18. On re-examination of the parents' chromosomes using FISH, a balanced 18;20 translocation in the father became clear.

### Surprises in the subtelomeres

FISH can also help to identify rearrangements of the material in the bands close to the tips of the chromosomes – known as subtelomeric rearrangements. It is most revealing to use a set of probes specific to each chromosome end, built into a subtelomeric integrity assay.



**A karyotype generated using subtelomere-specific probes.**

Outcomes can be surprising. For example, a girl with only very mild learning difficulties, who was entirely healthy and had no unusual facial features, was referred for genetic counselling by her gynaecologist during pregnancy. She was unexpectedly found on FISH to have a deletion from the long arm of chromosome 6 with a





breakpoint at 6q27. Her mother and one of her sisters had the same loss. This was, as Dr Speicher has said, 'extraordinary', as loss or gain from the subtelomeric regions is supposed to lead to quite severe outcomes. 'Not every chromosomal rearrangement results in clinical symptoms. Subtelomeres are supposed to be significant, but in this family they were not. We still have to learn what it means when a piece is missing,' Dr Speicher said.

## Unimagined complexity

Using FISH, molecular geneticists may reveal an unexpected level of complexity that G-banding gives no hint of. This confounds the logical principle often observed by cytogeneticists and known as Occam's razor, where the simplest explanation for any phenomenon is the best one.

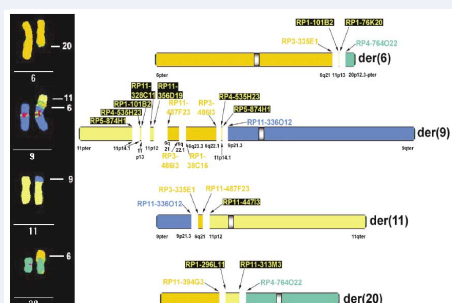
On this occasion, a patient at first appeared to have a balanced chromosomal rearrangement involving a simple insertion of material from chromosome 7q into chromosome 5. However, using M-FISH, she turned out to have a far more complex arrangement with six different breakpoints and a very large deletion from bands 7q34 and 7q35.

'A rearrangement that looks simple may turn out to be much more complex than we originally thought.'

Similarly, a child with an apparent rearrangement involving no more than chromosomes 8 and 14 on G-banding turned out to have an arrangement of unimagined complexity, involving five different chromosomes: 2, 5, 6, 8 and 14.

## More surprises

Where a complex chromosomal rearrangement has already been revealed in G-banding, there may still be surprises in store. Dr Speicher's team saw a 16-year-old girl who was short, somewhat overweight and had slight learning difficulties. Using G-banding, they observed an exchange between chromosomes 6, 9, 11 and 20. Then, using multicolour FISH, they confirmed the rearrangement but saw a far more complex picture with a total of 12 breakpoints.



## Unimagined complexity.

Examining the parents' chromosomes, they then found the same arrangement in the teenager's mother. Looking at the father's chromosomes, they found a previously unsuspected deletion. 'We can now characterise chromosomes at a very high level of resolution and many structural rearrangements turn out to have an incredible level of complexity that we hadn't appreciated with G-banding.' 'Many individuals have deletions and duplications in the genome with no apparent impact.'

## Chromosomes in Spots

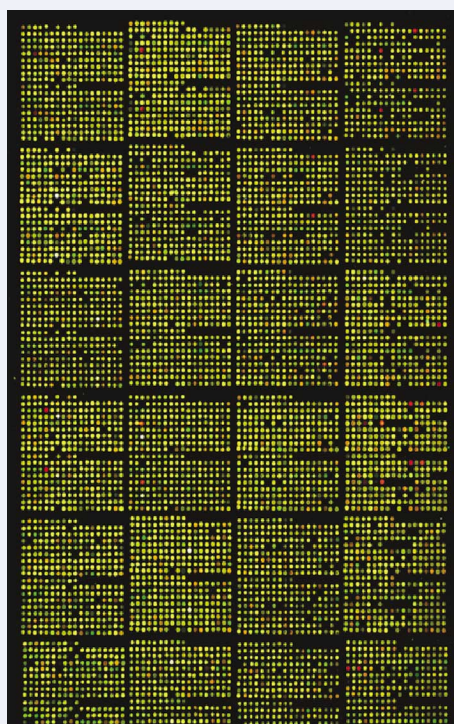
Dr Nigel Carter, leader of the molecular cytogenetics team at the Sanger Institute in Cambridge (where one third of the human genome was sequenced), and Dr Helen Firth, a consultant clinical geneticist at Addenbrooke's Hospital, told families about the use of new microarray techniques in chromosome analysis.

Dr Carter explained how a fairly new technology known as microarrays is being used to decipher chromosome rearrangements at a level of detail at least five times greater than can be achieved with conventional (G-banding) chromosome analysis. Although microarrays are still primarily available at research centres, they are increasingly being used worldwide to reach a diagnosis in clinical situations. Dr Firth then explained how data from people being diagnosed with microarrays is being collected and how it will be used to benefit patients in the future.

Too many or too few chromosomes cause genetic disorders, Dr Carter explained, as indeed does having too few or too many chromosome segments. Molecular technologies such as FISH may highlight pieces of DNA that are too small to be identified under a microscope, however greatly the chromosome is magnified.

A molecular technique such as FISH is fine, said Dr Carter, if you know where in the human genome to search for the rearrangement. But what if you don't? To search systematically the three billion base pairs (the rung-like pairs of complementary chemicals on the double helix of the human genome known by the first letters of their names – C, G, A and T) would be an impossible task. You would need to use 30,000 DNA probes in 30,000 different experiments.

However, using microarray technology, instead of

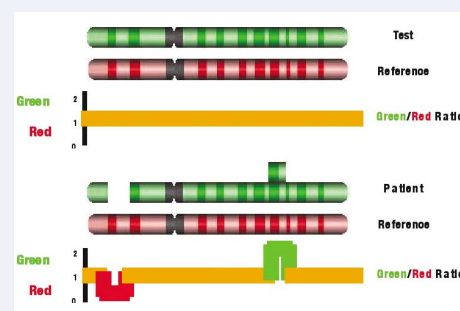


3523 clones in a microarray: from Fiegler et al. (2003) *Genes Chromosomes and Cancer* 36:361-374.

applying a DNA probe to a chromosome, as you would in a FISH test, around initially 3500 droplets (spots) of DNA (known as DNA clones) are applied to a single glass slide. The DNA from the patient's entire genome is then applied to the slide and all the chromosomes can be scanned in one go.

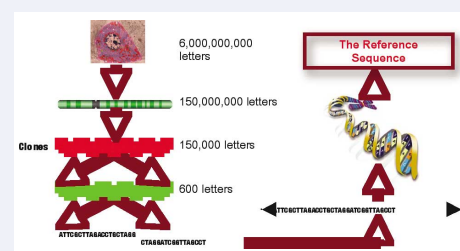
## Comparative Genomic Hybridisation

Look at the microarray above and you will see that most spots are yellow, some are red and some are green. The principle behind microarrays is a technique known as comparative genomic hybridisation, in which the functional DNA (genetic sequence) of the patient being tested is compared with control DNA of someone who has (as is normal) two copies. The control DNA is labelled red while DNA from the patient is labelled green and once the mixture of DNAs is applied to the slide, a ratio of greenness to redness is generated. If yellow appears, that means that the balance between red and green is even – suggesting that the correct amount of genetic material is present in the patient. If green appears, showing an increase in the green:red ratio, that means there is too much genetic material (duplication); red means a reduction in the red:green ratio and therefore too little DNA (deletion).



## HGP sequencing strategy

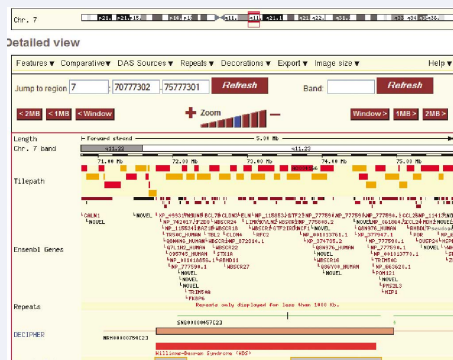
The technology that was used to create the draft full sequence of the human genome that was published in 2000 was harnessed for the Sanger Institute microarrays. The Human Genome Project sequencing strategy was to divide the continuum of the human genome into ever smaller chunks until manageable sequences of the chemical letters that form the base pairs could be read and mapped.



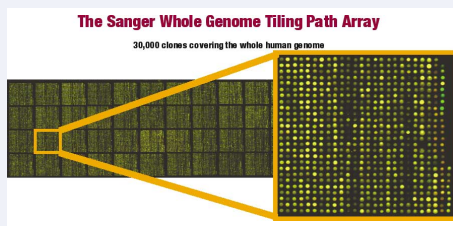
Sequencing machines can only read 100s of letters at a time so with billions to read, the genome was first split into chunks of around 150,000 letters (DNA clones) and then each of these into chunks of about 600 letters which were then sequenced. Using the overlaps between chunks, a so-called tilepath was constructed to give an ordered sequence of the genes in the



entire genome. The picture below shows how this works over a segment of chromosome 7.



Tiny droplets containing DNA (the 150,000 letter DNA clones) were then applied precisely in a unique sequence to a glass slide – initially by laboriously needle-dipping and dropping, though today this is done automatically. In the latest development, using what is known as the Sanger Whole Genome Tiling Path Array, 30,000 sequential clones are spotted onto a glass slide covering the entire human genome. The droplets represent DNA sequences that are spaced evenly and overlap across the human genome providing complete coverage.



## How are microarrays used?

Microarrays are already being used to help find a diagnosis for people with unexplained learning difficulties and other features that suggest a chromosome disorder where conventional G-banding analysis has shown apparently normal chromosomes. Out of 50 patients whose studies have been published so far, 12 microduplications or microdeletions have been identified, each one unique. This means that microarrays are a very sensitive test.

Interestingly, however, in five of the 12 families, the same microduplication or microdeletion as in the child was found in one parent – but the parent was healthy, had normal development and no unusual features. One way of looking at this perhaps surprising result is to suggest that microarrays do not always identify subtle chromosome rearrangements that cause disorders because they also pick up apparently harmless microdeletions and microduplications.

## Worldwide collaboration

A team from Paris also using microarrays has found a patient with exactly the same deletion from the long arm of chromosome 9 as one of Dr Carter's group of 12, with apparently the same breakpoint at 9q22.3. The clinical characteristics of the patients have been compared and some common features found which, when more patients have been identified, may turn out to be due to gene loss from the missing part of the long

arm of chromosome 9. Enthusiastically, Dr Carter and his colleagues have proposed a 9q22.3 deletion syndrome on the basis of these patients.

## Decipher

To capitalise on this technology, the Sanger Institute has launched DECIPHER, a database of microdeletions and microduplications identified using microarrays. The aim of the database is to collect information on chromosome disorders, most of which are too subtle to be seen under a microscope even at the highest resolution. This information may lead to the identification of the function of genes that are deleted or duplicated and in the long term to better medical care and genetic advice for individuals and families.

'We can now see all the genes, even if we don't yet know what they do,' said consultant clinical geneticist Dr Helen Firth. 'In many years this could lead to finding ways to compensate and treat but that is very much for the future. We are still in the early days of being able to bring things down to this level of detail. It'll be a few years before benefits for patients are clear, but we are hugely excited.'

## Chromosomes in Evolution

Humans are part of evolution and chromosome rearrangements may be one of the driving forces behind evolutionary advance, Dr Stefan Mueller, from the Institute for Anthropology and Human Genetics at Munich's Ludwig Maximilian's University, Germany, told the conference. The chromosome breaks and healing that underlie some of the structural chromosome disorders that affect **Unique** families are part of the same process that has accompanied the emergence of new species and the evolution of existing species over the past 300 million years.

*'It may be suggested that human carriers of structural chromosome rearrangements are part and parcel of the continuing evolution of our species.'*

Much of the content of chromosomes is the same, whether you are looking at dwarf deer, chickens or humans. However, while dwarf deer have just six chromosomes, humans have 46 and – lest you thought that more chromosomes make a more advanced species, chickens have 78. And just as we find deletions, duplications, inversions and translocations in humans, so they are found in animals as well. Chimpanzees, like humans, can have chromosome disorders and have their own version of Down syndrome.

Using techniques such as FISH and whole chromosome painting, Dr Mueller's research group has found that the chromosomes of humans in 2005 are composed of pieces of chromosomes of an early mammal that probably lived over 80 million years ago.

What is different is the arrangement of the material within the chromosomes.

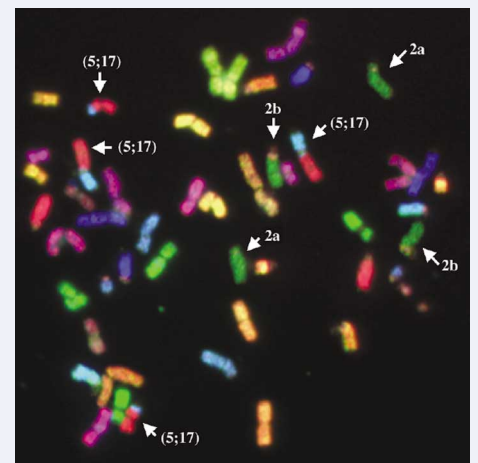
## From chimps to us: slow, quick, quick, slow

Chromosomes evolve over time, sometimes rapidly, sometimes slowly. There are times when they appear to evolve rapidly; at other times they remain constant.

Using a tool known as Zoo-FISH, Dr Mueller's team and others have shown that two separate chromosomes as found in chimpanzees joined in humans to form a single chromosome 2. Today, chickens have 78 chromosomes, which may have stayed rather unchanged since 300 million years. A mixture of very large (macro) chromosomes and microchromosomes are seen in both birds and turtles and possibly also in dinosaurs. Look at the chromosomes of the South American harpy (a type of eagle) and you will find that the large chromosomes of the chicken have broken into small pieces so this bird has 58 chromosomes with 20 rearrangements.

A glance at most non-primate mammals shows that they share with humans a tendency to keep their karyotype constant. Today's alley cat is but 11 chromosome breaks away from its ancestor 80 million years ago. There are, of course, exceptions: the mouse, dog and Indian muntjak chromosomes have evolved rapidly. The differences between a mouse in 2005 and its ancestor 80 million years ago are encapsulated in 170 chromosome breaks. The 60 chromosomes in cattle a million years ago have undergone 18 fusions to produce the six chromosomes of dwarf deer today.

Fast forward 20 million years and we reach 60 million years ago. Compare from this vantage point the chromosomes of the great apes with those of humans. This image is of gorilla chromosomes, showing the differences with a human karyotype.



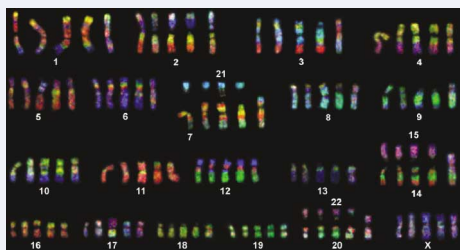
## Chromosome reshuffling

Compared with us, the gorilla has a reciprocal (balanced) translocation between chromosomes 5 and 17. The two parts of human chromosome 2 are still separate. The chromosomes of the great apes show large numbers of inversions within chromosomes – at least 24 that we know of. Lesser apes show even more derived karyotypes with large numbers of reciprocal translocations, fissions (separations), fusions and inversions.

## Spot the differences

Line up human 1-22 and X chromosomes with the counterparts of the primates (from left to right: human, chimpanzee, gorilla, orangutan and macaque chromosomes) and you can see evidence of these intrachromosomal rearrangements. For example chromosome 3 looks completely different in the orangutan. The





sharp-eyed will also notice that the human chromosomes with a short arm that has no effect on development (acrocentric chromosomes) are lined up with other chromosomes in this image. In the macaque chromosome 21 is matched with 7; 14 with 15 and 22 with 20. These chromosomes were only separated very recently in evolution.

## Why do chromosomes break and rejoin: the story of duplicated segments

But how, and why? What causes chromosomes to break and rejoin?

By analysing the evolutionary breakpoints of these intrachromosomal rearrangements, Dr Mueller showed the conference that they occur at points in the genome where the DNA sequences are almost identical, so-called duplicated segments. Each of these segments is small and harmless but there are hundreds of them and together they make up around five per cent of the human genome. The amalgamation of two chimp chromosomes into the single human chromosome 2 occurred within one of these duplicated sequences. So did the 5;17 translocation that occurred in the gorilla. Within humans today they are known to be important because they can produce inversions and lead to duplications, deletions and translocations. There is something about these sequences that sets the scene for chromosome rearrangements.

'It seems likely that they influence the behaviour of chromosomes when sperm and egg cells are formed, leading to structural rearrangements,' Dr Mueller said.

However, the outcome of these structural rearrangements is not known in advance. Like Richard Dawkins' blind clockmaker, 'Nature is acting upon us using the changes in our genome but it does not know in advance if the change is beneficial or not.'

## Behaviour workshop: understanding challenging behaviour

### Dr Viv Hinchcliffe

Many parents attended this workshop because they wanted to know why their children behaved in such a challenging way and what could be done to stop or change the behaviour. Dr Hinchcliffe used his extensive experience with children who have severe learning difficulties and who often display challenging behaviour, to get parents to think about the reasons for that behaviour.

Challenging/difficult behaviour can be used in a number of ways:-

- To communicate what people want or do not want.

- To exercise some control over their life.
- To avoid or escape from a particular situation where they feel anxious or afraid.
- To get a desirable result such as food, toy, activity.
- To get a sensory reward – self injury is a common method.
- To gain attention and make someone take notice.

It can be triggered by:-

- Biological or health problems; physical discomfort; poor sleep patterns; loud noises; others crowding them; depression.
- Certain sights, sounds, smells, people, etc.
- Boredom and lack of stimulation.

There is usually more than one reason for challenging behaviour and a number of factors can influence it. Dr Hinchcliffe stressed that "It is the behaviour which challenges, not the individual." Parents need to ask themselves what function the challenging behaviour serves for that child. Then it is possible to consider if there are alternatives that will serve that same function, at least as well as the challenging behaviour. A child could learn to signal that they were becoming stressed or agitated and use a PEC symbol to ask for a change in activity or a quiet place to go to, rather than throw a tantrum or furniture about to show they needed a change. If a child finds that tearing their hair out gives them short term relief from pent up emotions then offer them an alternative activity such as playing with a Rubik's cube or a set of worry beads. Changes in behaviour do not take place immediately but very slowly over a period of time; if the child shows any movement towards the preferred behaviour they are rewarded until eventually that behaviour replaces the undesirable behaviour.

Dr Hinchcliffe explained that children who have communication problems and severe learning difficulties need a way to communicate their needs. Some children use challenging behaviour to get something that they want – food, a preferred activity or as a way to refuse to do something, like getting ready for school in the morning. A visual picture or symbol timetable of what is going to happen over the next few minutes or hours will help prepare a child for a change in activity – it takes away the sudden surprise and makes a child less anxious. They need extra time to process information so language has to be simple and straightforward.

Children and young people need opportunities to make choices and have some independence. Dr Hinchcliffe suggested a shelf with a box or boxes containing toys that a child liked so that they could freely go and select a toy. This could also apply to food, where a cupboard or shelf would be set aside for them to go and choose from a number of food items (hopefully just the healthy variety).

Parents can often recognise the early signs of undesirable behaviour and it helps to have strategies to divert or distract their child. For example, glove puppets, magic tricks, funny songs and dances, toys that flash lights or make noises.

Parents should not be too hard on themselves – it

is not unusual to have a number of failures before finding a solution that works. Dr Hinchcliffe stressed that, in his experience, many of the extremely challenging children he has known did eventually grow into adults who had fewer and less challenging behaviour problems.

Several parents had individual questions they wanted to ask but there was not enough time to answer them all. Dr Hinchcliffe has said that if parents have questions about strategies to manage specific behaviours then they could contact him via Lydia Dickie at **Unique**. There is also a Behaviour Difficulties leaflet that will shortly be available to download from the **Unique** website and which Lydia can email to you now.

## Sex and the 3Rs

Anyone who thought that sex is an off-limits topic for a child with a learning disability or a rare chromosome disorder would change their mind after taking part in a workshop led by David Stewart, head teacher of the Shepherd School in Nottingham. Four mature students, Leigh Meakin, Michael Hibbert, Charlotte Gent and Liana Wilkins, told families from their own experience why sex education matters when you have a learning difficulty: it helps you to make choices; it helps you to value your own body and gives you self respect; it helps for deepening friendships.

Giving youngsters with special needs the same sex education as those without does not work. "Giving the same as everyone else isn't good enough," David Stewart said.

For too long, he said, the inherent vulnerability of youngsters with a learning difficulty has been intensified by leaving them in ignorance. They don't have access to the traditional sources of sex information: 'Tampax-lady' style school visits don't meet their needs; they may be withdrawn from the science or biology lessons into which sex education is incorporated; covering sex education once or twice in year 9 or 10 isn't enough for youngsters who need information frequently repeated. Information sources like the school playground are at best unreliable. Images of sex in magazines and on TV are misleading if you can't read the accompanying text or hear or understand the voice-over or dialogue.

Small wonder that, as a group exercise in the workshop revealed, the potentiality for sexual exploitation and abuse of people with a learning disability is, sadly, very real.

Make no mistake about it: sexual activity occurs. Families were pretty unanimous in agreeing that masturbation in both sexes is very common. For many youngsters, David Stewart pointed out, this could prove to be their only sexual outlet, so it should be pleasurable but appropriate. Unfortunate for the child excluded from secondary school for masturbating in the toilets, when his primary school had told him that this was the appropriate place.

Unfortunately, for many youngsters with a learning difficulty, sex leading to marriage or parenting is an option that may well not be available, David Stewart said. Small wonder that youngsters with a



learning difficulty are more likely to have mental health problems when they realise that the opportunities open to the rest of the world may just not be available to them.

This workshop was an awareness raising exercise conducted with extreme sensitivity. Shortage of time meant that it was not possible to fully explore the many issues raised, some of them difficult, others intensely private. To meet the need for special sex education resources, the Shepherd School has developed leaflets for young people and for parents on topics such as protecting your child, menstruation, loss, wet dreams, using public toilets, etc.

For more information visit their website at [www.shepherdschool.org.uk](http://www.shepherdschool.org.uk), telephone +44 (0) 115 915 3265 or write to them at Shepherd School, Harvey Road, Bilborough, Nottingham NG8 3BB, UK.

## Sleep

**Sleep deprivation is the lot of every parent. That it is a particular burden for parents of children with special needs was borne out by the huge popularity of the sleep workshop, led by Dr Luci Wiggs, honorary research fellow with the University of Oxford Section of Child and Adolescent Psychiatry. The surprise for some parents was that the tools and approach recommended are similar whether your child has a chromosome disorder or not.**

The consequences of sleep problems come as no surprise. Children who don't get enough sleep, Dr Wiggs said, are more likely to be hyperactive, may have a lowered resistance to infection and have more accidents. And that's just the children!

With grace and charm, Dr Wiggs led families through the stages of the normal sleep cycle, noting the highpoints when people naturally drift awake. She stressed that children need to learn to settle themselves at these points when they drift awake and that children are less likely to wake in the first third of the night, when they are deeply asleep, than when they are in rapid-eye-movement (REM) sleep later on. Then she showed how the sleep cycle links with other daily bodily rhythms such as light and dark and temperature. As we fall asleep, our body temperature drops and as we wake it rises. Light, too, strongly affects the biological clock.

Dr Wiggs' message to the families of children who can't settle, children who wake in the early hours, children who can't get off to sleep and children who insinuate themselves into their parents' bed was unflinchingly positive. It is always possible to make a difference. Change may take two days or a few months, but it will come.

In desperation, some families reach for the medicine bottle. Dr Wiggs didn't recommend it. The improvements are often slight, they lessen with time, children can become dependent on the medicine, some medications leave the child groggy the next day, some have withdrawal effects and all deprive the child of the chance to learn how to settle themselves to sleep naturally. For the occasional night, she conceded, medicines can be helpful.

Nor did she recommend melatonin, the sleep-promoting hormone released during darkness. Melatonin may be sedative and it may regularise the body clock, but there is no hard information on how safe it is, it is known to affect seizures (either inducing or reducing them) and it may delay puberty. The doses used in treatment are hugely in excess of natural levels in the bloodstream or brain. What is more, until trials have been set up – and that has yet to happen in the UK – there is no firm evidence that melatonin works. "Potentially, it's a new treatment," she said. "But we don't know yet."

Some children have a perfectly normal sleep pattern but they sleep at the wrong time. Most commonly children with this problem, known as sleep phase shift, sleep too late. They struggle when you try to put them to bed but have difficulty waking in the morning. Less common is an early sleep phase, when your child regularly falls asleep too early, only to wake up in the early hours. The way to deal with an early sleep phase, Dr Wiggs said, is to imperceptibly delay your child's daily routine, including bedtime, by ten minutes a day. To deal with a late sleep phase, you first advance the waking times a little each day, then advance bedtime to match. Gradually and imperceptibly does it.

For other persistent sleep problems, Dr Wiggs suggested the tried and tested tools of behaviour management that many parents are familiar with. Clear, consistent wind-down times and bedtime routines allow a child to anticipate what is coming. Removing anything that 'rewards' night waking or bedtime struggles; consistent management – particularly for children with a learning difficulty; keeping a sleep diary to record waking times, mood on waking, naps, bedtime, night wakings, response to night wakings, parents' bed time – all these are tools that help tackle the problem.

### Time for change

Dr Wiggs suggested families pick a time to tackle sleep difficulties when your child's life is otherwise fairly humdrum and when your child and you are in good health. Mark the change with a visible message – for example, by changing the bedroom furniture round; tell your other children what you

are going to do and support them, because this can be a hard time for them; enlist a friend or health visitor to discuss your progress with; warn the neighbours, as difficulties may get worse before they get better. If you can, talk through with your child what you are doing before and throughout the treatment; ensure that both parents, where this is relevant, toe the same line; persist – and your child's sleep difficulties really can get better, even in three to four nights.

### Settling to sleep

If your child has a problem settling to sleep, first note the time your child falls asleep naturally, then build up a bedtime routine to lead into it. The routine should be relaxing, predictable, not too stimulating and not too long; about 20 minutes is enough. As you leave your child, avoid eye contact and leave them while still awake so they learn to fall asleep alone. If it is still light and you want to reinforce darkness, you can even try putting dark glasses on your child. If your child goes into hospital, you may need to re-establish the routine from scratch afterwards.

*"The biggest predictor of a child with no sleep problems is a child who can fall asleep on their own."*

### Gradual withdrawal

If your child protests, you must choose whether to leave them to cry it out (effective but distressing) or choose the gentler option of gradual withdrawal. If your child insists you stay with them at night, set up a programme of gradual retreat, where every three nights you move further from your child until you are finally outside their room with the door closed. If your child tries to join you, you return them to bed without a fuss and without making eye contact.

### Checking (controlled crying)

If you cannot ignore your child because they are crying, first check that nothing is the matter; then decide how much crying and distress you can cope with (such as 10 minutes). When your child cries, wait for 10 minutes before going in; tell them to go back to bed and leave without a drink, cuddles or eye contact; reassure them and leave. Wait for a further 10 minutes and repeat your visit, but by now they may be asleep. On

### Things to encourage good sleep

- Make bedroom safe and unstimulating
- Set regular bedtime and waking time and stick to them
- Avoid late afternoon naps
- Keep activities low key in the hour before bedtime (quiet play, gentle music, soothing videos)
- Follow pre-bedtime settling routine, with symbols and other aids. Keep this brief, manageable (for you), relaxing and consistent
- Once in bedroom, settle rapidly (under four minutes); use the same 'good night' phrase each night when you leave; leave bedroom; lights off; close the door
- Put your child to bed awake and teach them to fall asleep alone
- Be as dull as possible when dealing with your child at night time.

There was no time at the end of the workshop for parents to ask many questions, but Dr Wiggs did recommend some reading, including:

*Solve your Child's Sleep Problems* by Dr Richard Ferber published by Dorling Kindersley £7.99

*Sleep Better! A Guide to Improving Sleep for Children with Special Needs* by V Mark Durand published by Brookes Publishing Co. This book is available from the National Autistic Society at £15.95 (£19.90 including postage) telephone +44 (0) 20 7833 2299 [www.nas.org.uk](http://www.nas.org.uk) or direct from [www.brookespublishing.com](http://www.brookespublishing.com) at \$24.95 plus shipping.



subsequent nights, extend the set number of minutes.

But Dr Wiggs stressed that the approach you choose must be based on what's right for your child.

## Parental bed

If your problem is that your child comes into your bed, then take them back to their bed and resettle them as at bedtime. Be persistent, even if it means taking them back 30 - 50 times a night at first (it often gets worse at first), and usually it will be over in a week. If your problem is that you are so deeply asleep that you don't hear your child coming into your room, hang bells on the door handle or place a musical dance mat on the floor to wake you as your child comes in.

## SCA workshop

In the sex chromosome aneuploidy (SCA) workshop, Dr Nicole Tartaglia spoke about medical and developmental issues in children with all types of sex chromosome aneuploidy, including XXY, XXX, XYY, XXXY, Tetrasomy X, Pentasomy X, XXXY and XXXXY Syndromes. Dr Tartaglia surveyed the audience and spoke specifically about the syndromes represented among them.

She began with a brief introduction about all SCA variations, and then spoke specifically about the medical problems that can occur in people with SCA and reviewed recommendations for the medical evaluations and follow-up needed for the various medical problems. For example, she spoke about testosterone treatment in adolescence for males with XXY, XYY and XXXY Syndromes, and also about the medical evaluation needed at puberty for girls with Tetrasomy and Pentasomy X.

After discussing the medical evaluations and treatments, she spoke about common developmental and behavioural problems in children with SCA, including developmental and speech delays, anxiety, tantrums, impulsivity, and inattention. She discussed the appropriate use of interventions and medications that could be used for treatment of these difficulties if they arise.

Dr Tartaglia is currently a fellow in Developmental Pediatrics at the University of California-Davis MIND Institute in Sacramento, California in the US. The MIND Institute (Medical Investigation of Neurodevelopmental Disorders) is a collaboration of paediatricians, psychiatrists, neurologists, psychologists, and basic scientists working together to understand neurodevelopmental disorders, and Dr Tartaglia runs the studies for patients with sex chromosome aneuploidy at the MIND Institute. She has worked with over 100 families with SCA over the past year and drew from past research and her experiences with these patients to develop recommendations for treatments for SCA patients. Dr Tartaglia says, 'It has been a pleasure to work with the SCA community and I look forward to continued work and research with this group. The families have taught me so much, and I thank them all for their participation in our research which has led to my ability to compile our recommendations and share their experiences with other families. The conference

was wonderful and I thank *Unique* for the opportunity to meet such a fantastic group of families.'

**Nicole Tartaglia, MD**  
Fellow, Developmental-Behavioral Pediatrics  
UC-Davis Medical Center MIND Institute  
2825 50th Street, Suite 2322  
Sacramento, CA 95817  
Tel: (916)703-0286

## Our time in Daventry – *Unique* Conference 2005

By Andrew Tickle

Well, I thought I'd better put 'pen to paper' or rather fingers to keyboard and summarise my thoughts, feelings and experiences of the last 2 days.

Arrived 10.30pm on Friday 21st October at The Daventry Hotel and despite some of the early arrivals having already gone to bed, there were others still up and about meeting old friends and making new ones. I was duly handed our conference pack which was as detailed, informative and organised as ever. I'm a project manager by profession and so really appreciated the time and effort which had gone in to preparing such an event like this – we knew what was going on when, who would be doing what and where we needed to go to find such... making it easier for all concerned. Peter, our son, capitalised on the long sleep he'd had in the car and so was raring to go, whereas Dad wanted to have a 'quiet pint' and head for bed. However, who could deny Peter the opportunity to play guitar and sing to any audience! My significant memory of that night is Professor Maj Hultén coming down to reception in her dressing gown asking if anyone had any earplugs and promptly sitting herself down with a drink and being entertained by our regular magic man – Peter (not related).

Saturday morning breakfast time and we hadn't been in the restaurant five minutes when who had wandered round various tables and decided it was time for an impromptu sing-a-long? Yes! You've guess right – our Peter! I think most families were keen to take their children to the crèche – whereas those who have been before will know, your children are well looked after in a safe, secure and entertaining environment – this would then free themselves up for the main conference. Everything ran like clockwork – Maj (Professor Hultén) made sure of that. Who could forget her 'subtle' 10 minutes gesture to Dr Michael Speicher to wrap up his very interesting presentation on 'Chromosomes In Colour'? A comfort break followed that enabled everyone to start networking, renew friendships and discuss the whys and wherefores of their child's condition, etc. Further presentations were given on 'Chromosomes in Spots' and 'Chromosomes in Evolution', all of which were very well presented and provoked interesting questions. After lunch and a reassurance that each child was okay, they were returned to the crèche and the various workshops began.

My wife, Fiona, and I first attended the 'Sex and

the 3Rs' workshop which was facilitated by David Stewart from The Shepherd School in Nottingham, together with some of his mature students. The subject matter was handled extremely well by all concerned and especially the students who were very honest and open in their thoughts and feelings. The second workshop we attended was 'Behavioural Matters' which focused on what is meant by behavioural difficulties, why do they happen and what to do in circumstances when and where they do. Ideally, we would have liked to have attended all the workshops as each was as interesting as the next, from what people we spoke to afterwards told us. After another comfort break, it was time for the final session, which was to involve various 'Thank you's' and *Unique's* 21st birthday celebrations. Tim Boswell, the local MP for Daventry, gave an interesting speech on the value and importance of organisations such as *Unique* and reaffirmed the political parties were united in their stance on matters such as disabilities, etc. We were then introduced to and entertained by Kristina



**Tina Branden-Whitaker.**

Branden-Whitaker who sang the *Unique* song which she had written for her daughter Evelina – whilst playing guitar and harmonica. It is hoped that this will be released as a CD and I encourage you and your friends and families to buy it... an absolutely beautiful and exquisite song! Tim Boswell then introduced our son on stage – Peter Tickle!



**Peter Tickle with dad Andy.**

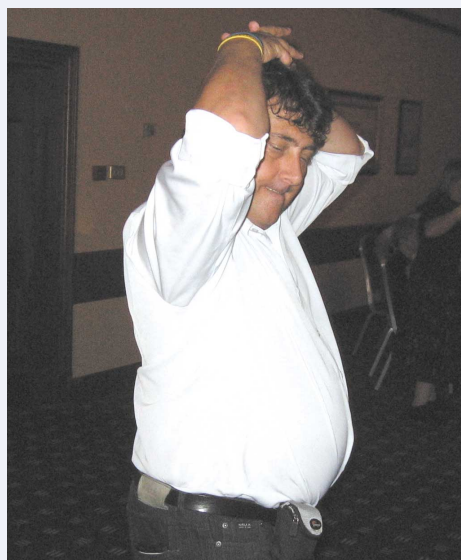
I used this opportunity to thank *Unique* for all the help, support and guidance they have given me and my family over the years. My way of recompense has been to seek donations from my employers – which many businesses are only too keen to make... just ask!... and despite my stocky frame to have run the London Marathon on behalf of *Unique*. By now, my emotions had got the better of me, and for those who were there you will know what I mean. I was immensely proud and privileged to be able to introduce my son who was so looking forward to entertaining everyone – particularly those he hadn't yet got round to. The obvious choice of the day was 'Happy Birthday', which everyone joined in, which is a requirement Peter insists on. This was followed by 'I Love You, You Love Me' and 'Getting To Know You' – both of these songs I believe echo the sentiments we have for all our children.





It was then on to the presentations to the various members of the **Unique** Committee. I should like to note at this point that these people are fantastic and truly deserve all the recognition they received and should continue to receive... how do you go about getting someone on the Honours List – anyone? The 21st birthday cake was then presented and cut by both Edna Knight and Tim Boswell and everyone was invited to partake in the champagne and orange juice.

After a break for an evening meal it was then... party time with professional magician Peter's Disco Magic! This was the time to really let your hair down and just do your thing! I, for one, had a great time and what was especially nice was to see everyone throughout the weekend looking out for each other's child – a really caring and sharing community. When I finally got to bed, our two daughters Sophie and Isobel were still playing with their newly acquired friends so we could rest easy.



**Andy T (that's Tickle not Travolta) strutting his stuff!**

On Sunday morning, I was distinctly under the impression that it was the end of British Summer Time and believed the clocks had been put back one hour and so was enjoying that 'extra hour in bed'. You can imagine my surprise when I checked with Reception at 10.00am – believing it to be 9.00am – and found that this was not the case and so not wanting one to miss breakfast, came rushing into the restaurant looking like someone who had been dragged through a hedge backwards! People were getting ready to leave and we didn't want to lose the opportunity to say 'Goodbye until the next time' to those that we had met over the weekend. For those we did meet and I didn't get chance to say it to: thanks

## Conference Items Found

Found in the crèche after the conference

- Purple chenille girl's cardigan age 11 - 12
- Avent Beaker
- Baby rattle with bells on it

If any of these items are yours, please contact Marion.

for being there, I had a great time, hope you did too and I look forward to seeing you again sometime soon.

Finally, I'd like to reinforce what Julie Griffin, **Unique's** finance and fundraising officer, said on Saturday regarding the finance and fundraising...

PLEASE approach whoever you work for and try and get them to make a donation – if you don't ask, you don't get! If possible, make a regular donation and therefore make use of the Gift Aid option which adds 28 per cent to whatever you donate.

*Thank you all on behalf of my family*

**Andrew Tickle**

## First UK meeting of XXYY families

"Summing it up in three words 'OH MY GOD'. For me it has been a life changing experience. Meeting everyone, strangers, who all have that special bond was totally awesome." This was a typical reaction to our wonderful get-together. The first-ever meeting in the UK of families with boys who are 48XXYY (two extra chromosomes) took place in Daventry on October 21st, the day before the **Unique** conference. They were very fortunate to have Dr Nicole Tartaglia of the University of California-Davis MIND Institute visiting. She has been conducting much-needed research into the symptoms and treatments for XXYY, as well as establishing comparisons and differences among other sex chromosome variants and asked to meet as many affected families as possible – what a challenge! Tina Bale and I decided to try, and with the help of **Unique** and the internet support group, XXYY Parentnetwork, we managed to bring together twenty-five families from as far afield as Cornwall



**Robert Orgel and sons Adam and Kane.**

## Conference Questionnaire

Well our conference is now over and went very well. A good time had by all (I hope). It was lovely to see you, both old faces and new. It is great to put faces to names. For those of you that came to the conference, I hope you enjoyed it. Can I ask that if you haven't already filled in and returned your conference evaluation questionnaire, could you please send it to me as soon as possible? (If you have already sent it to Edna, that is OK, as she sends them onto me). We welcome your comments, whether positive or negative.

This helps us to improve/include new ideas for future conferences.

Please return to:

**Marion Mitchell**

**6 Lavant Close, Gossops Green**

**Crawley RH11 8LN**

or email to: [marion@rarechromo.org](mailto:marion@rarechromo.org)

PS: If you have lost your questionnaire and would like a new one, please email/phone me and I will send you one.

*Thank you!*

and Tyne-and-Wear; with two families flying in from Denmark and one from Spain. Nineteen boys aged from 7 to 32 joined us, all XXYY apart from one with XYY and one XYYY. One of the parents, Robert Orgel, raised substantial funds by undertaking a fifteen mile sponsored bike ride with his affected twin sons, Adam and Kane – a really wonderful effort which helped enormously with the organisation, enabling us to hire meeting rooms and assist some people with costs to help them to attend. Dr Tartaglia's talks on "Common Medical and Behavioural Problems in XXYY" and "New Research Results and Projects" were so interesting, packed with information – something that all the parents had found so lacking in the past. The questions and answer sessions could have gone on for hours! She fitted in as many private meetings with parents as possible, but as time was short we were all asked in advance to fill in lengthy – 24 page! – questionnaires to help with the research.

As almost none of the families had ever met anyone in the same position as themselves before, plenty of time was left free for chatting. We were lucky to find some friends willing to keep an eye on the boys in the large playroom, (we stocked it well with toys, Play Stations and videos!) and they all seemed to have a wonderful time and were comfortable with each other right from the start. More than half the families had arrived on the evening before and we had all enjoyed a very social time at the local pub, with the boys looking instantly like long-lost friends! "It was such a magical experience!" "Never felt so comfortable with strangers before. I feel on a real high just knowing finally we aren't alone. Words really can't describe that feeling." Comments like these make it all so worthwhile, so many new friends with such a strong bond – now we are discussing what we do next year!

**Marion Masson**