Kleefstra syndrome

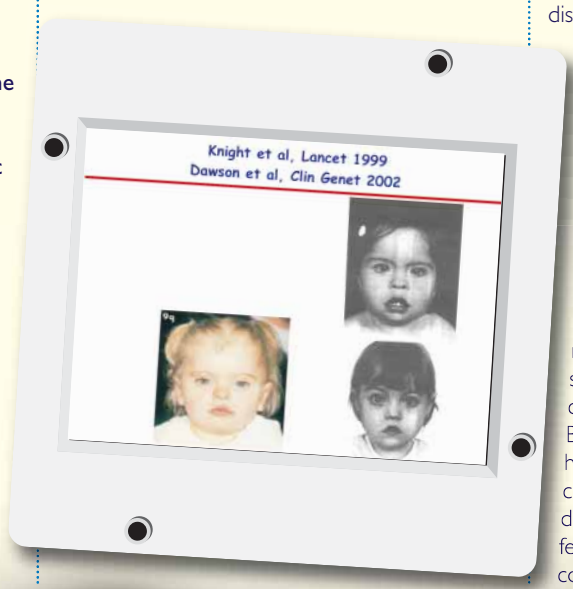
From 16–18 April 2010, *Unique* hosted the first ever meeting of families, geneticists and scientists spearheading research into Kleefstra syndrome – earlier known as 9q34.3 deletion syndrome. The meeting in Coventry, United Kingdom coincided with a flight ban due to ash from a volcano in Iceland, so Dr Tjitske Kleefstra and Dr Hans van Bokhoven gave their talks remotely. Dr Kleefstra also held 1:1 clinics remotely with families.

The story of Kleefstra syndrome: Dr Tjitske Kleefstra

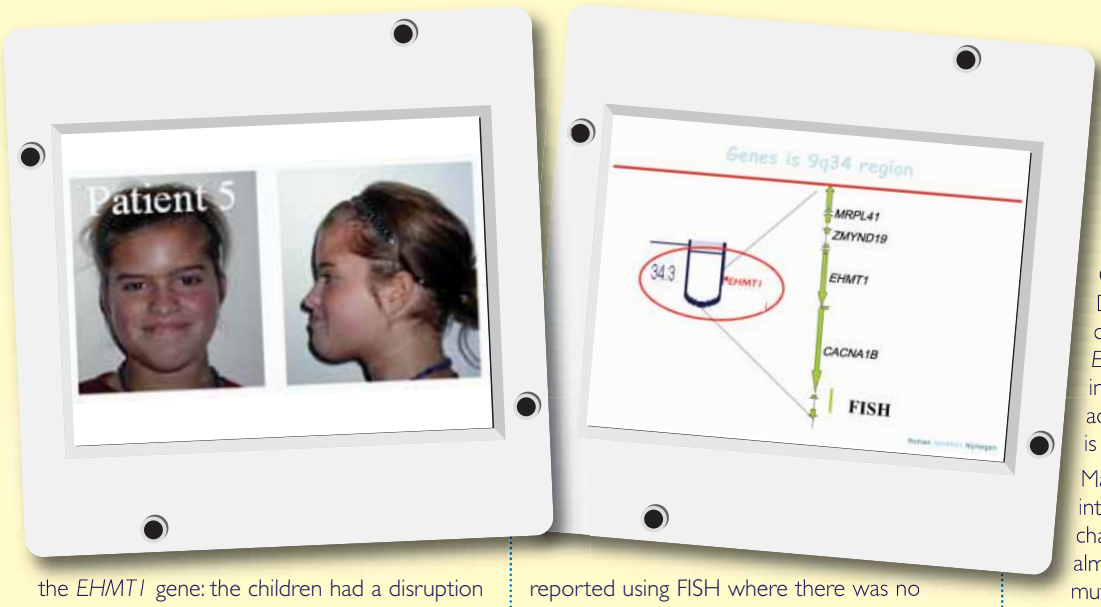
Dr Kleefstra is a clinical geneticist at the Department of Human Genetics, Radboud University Nijmegen Medical Centre, the Netherlands, after whom the syndrome earlier known as 9q34.3 deletion syndrome, 9q- syndrome or 9q subtelomeric deletion syndrome, is now named.

She said how proud she was to open the day. You pronounce her first and family names, which derive from Friesland, north Holland, 'Chitsker Clayfstrer'.

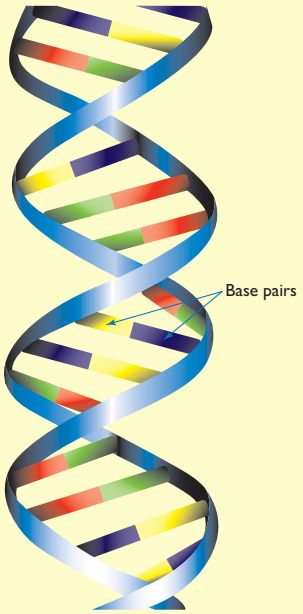
Dr Kleefstra's interest in the syndrome arose in 1999 when she met in clinic a girl with a then unexplained intellectual disability and found that she was carrying a so-called translocation between chromosomes X and 9. She was interested in the break points of this translocation because she and her colleagues hypothesised that genes at the break points might be disrupted. Dr Kleefstra and her colleagues did indeed find that the *EHMT1* gene in the middle of the 9q34.3 region was disrupted. Then in the late 1990s the first studies appeared showing that the telomeres (ends) not only of chromosome 9 but of many other chromosomes are important in the cause of intellectual disability and that rearrangements such as deletions in the subtelomere regions of chromosomes cause a significant number of cases of intellectual disability. One girl whose picture was published (far left) was one of the first children recorded as having a 9q subtelomere deletion. Later, more children were reported, like the two sisters (left) who both have a small 9q subtelomere deletion. Dr Kleefstra and her colleagues hypothesised that the *EHMT1* gene was causing the major abnormalities seen in these children. So they searched for others with the same clinical features seen in children with a 9q deletion but who were reported as having normal chromosome studies. In the first instance they found two children, a boy (above) and a girl (overleaf). Both had an intellectual disability as well as hypotonia (low muscle tone), a small head circumference, delay in speech and motor development and some recognisable facial features. In both children Dr Kleefstra and her colleagues found a disturbance (mutation) of



Kleefstra syndrome



the *EHMT1* gene: the children had a disruption of only one base pair of one of the building blocks of DNA instead of an entire 9q deletion. This study confirmed that the *EHMT1* gene was very important in causing the clinical features of the 9q deletion syndrome.



Two strands of DNA are held together in the shape of a double helix by the bonds between base pairs.

Later they identified more children, all with facial similarities which parents might recognise in their own children. *EHMT1* is just one gene in the 9q34.3 region (above right). There are many more and deletion sizes in individual children range from very small, encompassing only *EHMT1*, to a lot bigger, including more genes. At the moment, what the other genes contribute to the clinical features is still a matter of investigation.

Past studies

Chromosomal studies in the past were largely done by FISH analysis. Many cases were reported using FISH where there was no apparent 9q deletion but in fact while the region targeted by FISH was intact, the region including the *EHMT1* gene was deleted, making what is known as an interstitial deletion.

Studies today

Chromosomal studies are hardly performed under a microscope any more but instead using microarrays, which allow one to identify much more and to pinpoint more exactly the location of the deletion.

Nijmegen database

At present on the database at Nijmegen there are 17 patients with a disturbance (mutation) of *EHMT1* and 30 patients with a deletion that encompasses at least *EHMT1* or a part of *EHMT1* and one other gene. Comparing the features in both groups, Dr Kleefstra and her colleagues see few differences. Among individuals with *EHMT1* mutations, there are differences in the level of development and additional congenital anomalies and this is also true for those with deletions.

Major features in both groups include intellectual disability, hypotonia and characteristic facial features. Remarkably, almost half of the babies in the *EHMT1* mutation group were born with a high birth weight. Half of them also have childhood obesity. Other features – microcephaly (small head), heart defects, seizures, genital defects in males, gastro oesophageal reflux and urinary reflux – seem to be found equally in both groups. At the moment, the clinical consequences of *EHMT1* mutations and deletions including *EHMT1* seem indistinguishable.

The future? The next questionnaire…

When Dr Kleefstra and her colleagues started in 1999 they didn't even know that the *EHMT1* mutation existed. Now they know a lot more but many questions remain. Why do some children with the same genetic defect develop better than others? What about their behaviour? What about additional clinical features? Why do some have heart defects, others not? Why do some develop epilepsy and others not? With a lot of reports that children are prone to infection, what about immune system defects? What about progression into adolescence and adulthood?

Brian Foley, a parent of a child with a 9q deletion, has drawn up an extensive questionnaire. For your own copy, email **b.foley1@ntlworld.com**, call **+28 9087 8847** or write to **Brian and Eileen Foley, 50 Somerton Road, Belfast, Northern Ireland BT15 3LG**.

Finally Dr Kleefstra pointed out that a child is also a mix of their mother and father and some features are just not related to the 9q deletion. She offered to help any family with a child with a 9q deletion or *EHMT1* mutation and pointed out the ways to contact her: through the Kleefstra syndrome website; on Facebook; or best by email.

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Kleefstra Syndrome

Modeling the 9q34 deletion syndrome: Dr Hans van Bokhoven

Hans van Bokhoven is professor and leader of the Molecular Neurogenetics research unit at Radboud University Nijmegen Medical Centre, The Netherlands.

Dr van Bokhoven is studying Kleefstra syndrome using animals such as the Drosophila fruit fly and mice, hoping to gain more insight into the biological mechanisms around the *EHMT1* gene. He uses animals because they allow him to do research that would be impossible in humans and afford him insights into biological processes like organ development that aren't obtainable in humans. Animals also let him study the role of certain genes and proteins like *EHMT1* in the context of a complete organism. Using animals also allows disease models to be created, with a long-term aim of developing therapeutic interventions. But this of course is a long way off.

Humans have about 20,000 genes. Surprisingly, the mouse has a remarkably similar set of 20,000 genes, many essentially the same as human genes. Even the fruit fly is very similar, so many genes that humans have are also seen in fruit flies.

What does the *EHMT1* gene do?

What are genes? Genes contain instructions for development and function which are translated into the actual function in a two-step process. First, DNA is transcribed into a molecule called RNA. From the RNA, proteins are made which are the working units of our bodies. So the DNA and genes contain the instructions but the proteins do the real work. One of these genes and proteins is *EHMT1*, which is disrupted in Kleefstra syndrome. Our knowledge is still superficial but as far as we know the function of *EHMT1* protein is to condense the DNA, making it inaccessible to other proteins. Thus, this protein suppresses the activity of other genes by preventing the synthesis of RNA and proteins (below left).

Dr van Bokhoven and his colleagues are trying to identify the role of *EHMT1* in the nervous system and in early development and discover how mutations in the gene cause Kleefstra syndrome.

Researchers Dr Annette Schenck and Dr Jamie Kramer have studied what *EHMT1* does in the fruit fly. With an inactivated (mutated) *EHMT1* gene, the fruit fly developed the equivalent of Kleefstra syndrome. Its brain cells (neurons) contained no *EHMT1* protein. What was the effect?

Abnormal brain cell networks in flies

In many respects the neurons in the fly with the mutation look the same as in a normal fly, except for the expected network of branches (dendrites). These dendrites are used for communication between brain cells and are needed for learning and memory. When *EHMT1* is missing, the network of connexions appears to be disrupted (below).

Similar changes in the neuronal networks have been observed in many other similar human syndromes where intellectual disability is common, such as Fragile X or Down syndrome. The question is: Does the abnormal dendrite structure contribute to the intellectual disability? After a lot of assays in the Drosophila fruit fly, the answer seems to be 'Yes'.

What about the future?

In future the researchers want to expand the molecular mechanisms that result in the abnormal dendrite structure. They will then investigate whether they can influence these mechanisms. Can they repair the abnormalities? They could for example use drugs to return a mutant fruit fly to normal. But this has not yet been tried.

And in mice?

Dr van Bokhoven is also looking at the mouse, a mammal whose body closely resembles the shape and function of our own. A mouse has been created with an *Ehmt1* mutation that resembles the mutation in people with Kleefstra syndrome.

Many investigations into the behaviour of mice, including learning and memory, have concluded that mice have behavioural features that resemble humans. For example, autistic-like features are seen in the mutant animals. Learning and memory performance and the brain anatomy of the *Ehmt1* mutant mouse is currently being studied to see whether the mutant mice resemble also in this respect the brain phenotype of the human syndrome.

Dr van Bokhoven and his group have also looked at the skull and brain shape in *Ehmt1* mutant mice. Although a mouse

looks very different from a human, the development and architecture of its skull are much the same. They compared non-mutated mouse skulls with *Ehmt1* mutated mice, measuring the length of the skull, its width and the distance between the eye sockets – and found several differences.

The *Ehmt1* mutated mice have a shorter, wider skull, resembling the head shape seen in Kleefstra syndrome and known medically as brachycephaly. They also have a shorter nasal length, reflecting the short nose seen in many people with Kleefstra syndrome. In addition the eye sockets are further apart than normal (hypertelorism) just as in Kleefstra syndrome. In these respects the human phenotype seems to be mirrored in the mouse.

In summary

So why are Dr van Bokhoven and his group studying Kleefstra syndrome in animals? They have fly and mouse models of Kleefstra syndrome that share several aspects of the human condition. They now want to learn more about the biology of *EHMT1* protein in a whole organism. Very likely they will learn about other molecules that interact with *EHMT1* protein or are regulated by it and this may reveal that these molecules are involved in syndromes resembling Kleefstra syndrome. This could open up possibilities for diagnostic testing in these other syndromes.

The researchers' ultimate goal is to develop therapies. Although it will not be possible to cure Kleefstra syndrome completely, they can try to find drugs and compounds to alleviate some of the symptoms.

Question Time

HvB = *Dr Hans van Bokhoven*

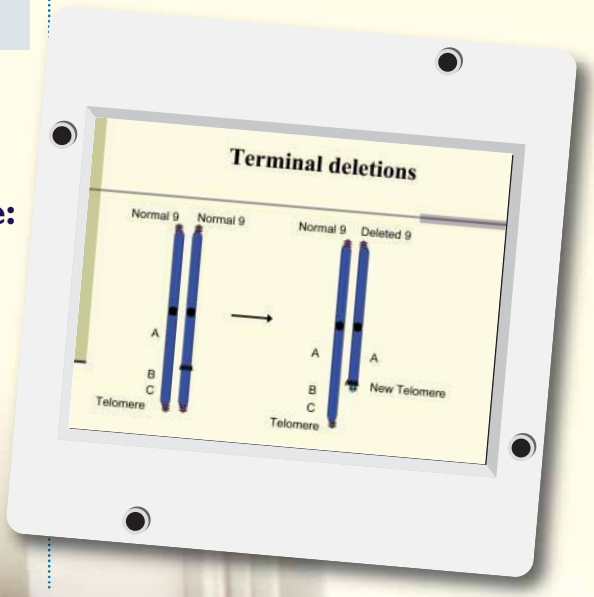
Q *Would any therapy have to be applied at a particular stage of development?*

HvB *It would be very difficult if not impossible to apply therapy to cure the condition completely because it is a developmental condition that has already affected the very early development of the human embryo and fetus. But we can hope to find drugs that improve the quality of life for young children at a later stage, symptoms like the epilepsy or other features that go with the condition and for now are impossible to treat.*

Cytogenetic and molecular analysis in people with 9q34.3 microdeletion syndrome: Dr Svetlana Yatsenko

Dr Yatsenko, a former research associate at Baylor College of Medicine, Houston, Texas, USA has a special interest in 9q34.3 deletions.interest in 9q34.3 deletions.

Dr Yatsenko introduced chromosomes, explaining that while the end of a chromosome (telomere) is just a protective cap, the region just before the end (subtelomere) contains unique information and genes. Most deletions visible under a microscope occur at the ends of chromosomes: about 70 per cent of children with a chromosomal condition have a deletion, duplication or translocation at the end of a chromosome. Around one newborn baby in 5000 has a terminal deletion of one chromosome or another, so it's not uncommon. Subtelomeres have a very large gene content so rearrangements are likely to have an impact. Many recognisable genetic syndromes result from subtelomeric deletions (below).



Using chromosome (cytogenetic) analysis, it's difficult even for a good technologist to precisely define some abnormalities, including in the 9q34.3 subtelomere region. For more precise definition, molecular analysis is needed. This is probably why the 9q microdeletion syndrome went unrecognised for many years. Even today many people remain undiagnosed because identifying the deletion is so difficult.

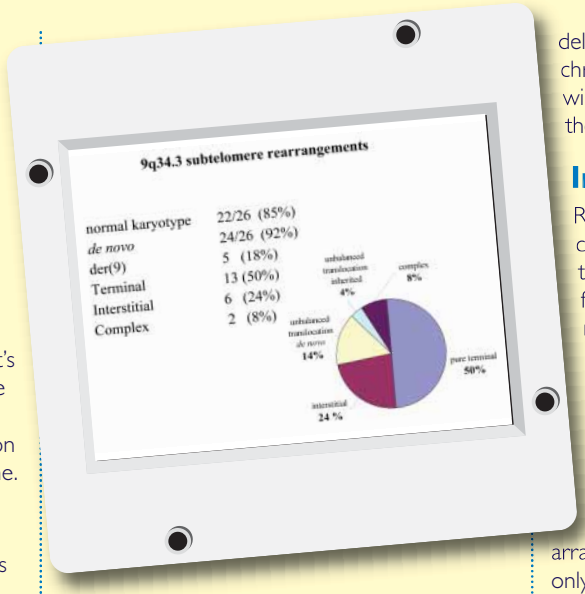
Much remains unknown: it's unknown how common the 9q microdeletion syndrome is. It's unknown if there is a correlation between the phenotype and the deletion size. But other things are known: such as whether the deletion is on the mother's or the father's chromosome. Some reasons why the chromosome became deleted are also known.

People have different types of deletion. One is a simple terminal deletion when one chromosome 9 breaks and the chromosome end heals with a new telomere. Another is when there are two breaks in the chromosome and the ends fuse, giving an interstitial deletion. Interstitial deletions can be missed by a subtelomere FISH study because the probe is located close to the telomere but not in the deleted region. Another possibility is when a translocation between chromosome 9 and another chromosome occurs in a parent. The parent would have no signs of abnormalities – but when a child is conceived, the child can have a deletion from chromosome 9 and an extra part of the other chromosome. A similar process can happen without a parental translocation: a deletion occurs, then the chromosome needs an end but instead of synthesising a new telomere, it attaches a part of another chromosome containing a telomere. That creates the same situation as in a parental translocation but this type of translocation is called de novo. Many other complex rearrangements can also occur.

Ultra high resolution array CGH

Array CGH gives a much more precisely defined deletion size: a high resolution array can define where breaks happen and which gene or genes are affected. Some arrays have gaps so array results sometimes give maximum and minimum deletion sizes, the minimum showing the probes that are definitely deleted and the maximum showing the probes that may be deleted.

Dr Yatsenko's team has designed a high resolution array covering the end of 9q and other subtelomeric regions. The array contains 44,000 probes just for the 9q region, with 2–3 probes per one kilobase (1000 base pairs). So this array can define a deletion with a precision of about 400 base pairs. This has revealed many unpredicted events and some complex rearrangements.



29 patients studied

Dr Yatsenko's team has studied 29 patients using these arrays. Broadly speaking, they have found four types of deletion:

1. Terminal deletions of different sizes. Only three patients studied have the same size deletion, suggesting in these cases that the DNA there may have some feature that predisposes it to break. The team is now studying if any DNA assembly there has difficulties repairing itself, perhaps contributing to the chromosome breaking there more commonly than elsewhere.
2. Interstitial deletions of different sizes, but encompassing part or all of the *EHMT1* gene.
3. Complex rearrangements, with double deletions or extra duplications or triplications.
4. Derivative chromosomes with both a deletion from 9q and a duplication from another chromosome arm, either inherited from a parent or as a new (de novo) occurrence.

Overall terminal deletions account for 50 per cent of the patients studied. Interstitial deletions and other rearrangements account for the other 50 per cent. Apart from some large translocations, none of those would be detected on a conventional chromosome test (above).

Differences if the deletion is on the chromosome 9 from the mother or father?

Dr Yatsenko's team have found that 62 per cent of the deletions occurred on the chromosome that came from the father. Rearrangements on the paternal chromosome were usually small. In contrast, the 38 per cent of rearrangements on the chromosome from the mother were usually big. They found no differences between the children when the deletion was on the maternal or the paternal chromosome and concluded that all children will probably be affected similarly regardless of the origin of chromosome.

In summary

Rearrangements of 9q are frequent chromosome disorders. Deletions from near the end of 9q are small: Dr Yatsenko's team found none larger than 4 Mb (1Mb or megabase is one million base pairs), although much larger deletions are found on other chromosomes. They cannot yet explain why this is the case. There is no obvious region where they see consistent breaks, unlike in other chromosome disorders where there are hotspots for breakage. In any case of 9q34.3 deletion, array CGH analysis should be considered not only to define the deletion size but also to pick up any complex rearrangements that may be making a difference.

Next directions

One of Dr Yatsenko and her colleagues' further aims is to match the phenotype with the size of the deletion. The 9q34.3 region is particularly rich in genes and using array CGH they can compare the clinical features between the children and see if there are genes other than *EHMT1* that are playing a role.

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Behaviour in 9q34 deletion syndrome: Professor Chris Oliver

Chris Oliver is Professor of Neurodevelopmental Disorders at the University of Birmingham and Director of the Cerebra Centre for Neurodevelopmental Disorders.

Professor Oliver's team is interested in the behavioural phenotypes of chromosomal and genetic disorders and researcher Tracey Grandfield is studying the behaviour of people with 9q34 deletions. Professor Oliver warned against treating everyone with a particular disorder the same: not only is each child unique, but children with 9q34 deletions have a lot in common with other children.

Genetics and behaviour

Genes affect behaviour in a less obviously direct way than they affect, for example, appearance. There probably isn't a gene for a particular behaviour, any more than there is a

particular part of the brain associated with a particular behaviour, but if genes contain coded instructions for development, then the code has to be complete and in the right order. If some of the code is missing, the development of the nervous system and the connections between the brain cells that underlie behaviour will be disrupted.

9q34 survey

Professor Oliver has sent out a 9q34 deletion behaviour survey. Early results from the first 15 responses give a snapshot of the syndrome that allows it to be compared with other genetic syndromes to understand features that are shared and features that are unique to 9q34. About 4/10 of the children have what can be thought of as autism – but autism in genetic syndromes is not always the same as autism in other contexts, perhaps particularly in people with 9q34 who have a surprisingly high level of sociability, above all other syndromes (below). This level of sociability isn't seen in autistic spectrum disorders. Indiscriminate sociability can be a problem in more able people because it makes them more vulnerable to exploitation. In 9q34, strategies that help in better characterised syndromes like Angelman syndrome (also with a high level of sociability) could also help people with 9q34.

About 4/10 show some form of self injury, compared with only about a quarter of people with an intellectual disability generally, and nearly two thirds show aggression – a high level. Pain is associated with self injury: among typically developing children, around 1.5/10 headbang, about half of whom have a middle ear infection. So Professor Oliver suggested that families are alert to signs of 'hidden' pain, especially gastrointestinal reflux, reported by about half the families. Once reflux in a child with Cornelia de Lange syndrome was treated, her self injury plummeted: she was a lot happier. Reflux, tooth decay and middle ear infection go together, Professor Oliver pointed out, because reflux contains acid which erodes tooth enamel causing decay.

Forty per cent of families said their child had gastrointestinal problems but Professor Oliver wondered if there might be more unrecognised problems. How does someone with a severe disability and poor communication let you know they are in pain? Many of the behaviours that families reported in the survey could be associated with reflux, such as tooth grinding (in 7/15), chewing on clothes, drinking excessively or constantly growling. In Cornelia de Lange, children with reflux drink a lot in the morning, perhaps to wash away the pain and irritation built up by reflux overnight. Other behaviours to watch for include sleeping sitting or propped up and frequent night waking. These behaviours should prompt families to consult a gastrointestinal specialist.

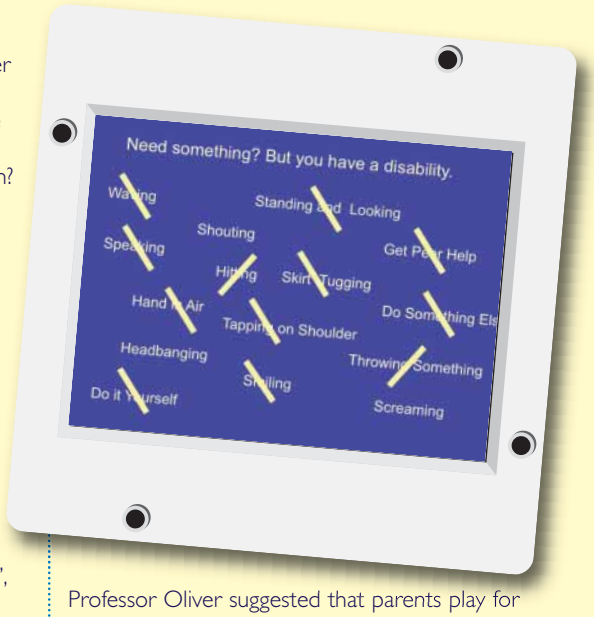
Every child also has their own 'pain signature', identifiable following the acronym FLACC.

F = Facial expression, usually two lines down the middle of the forehead, a sign of pain across all cultures
L = Legs tend to move
A = Active – children don't stay still
C = Crying
C = Consolability – you usually can't console them

Learned behaviour

The most important thing about any problem behaviour is how it makes other people respond. Self injury or aggression can become a learned behaviour because it's often rewarded, albeit unintentionally, with increased attention. This can act as a positive reward, making the behaviour more likely to be repeated. Speculatively, attention may be particularly important for sociable children with 9q34. Alternatively, faced with a child who shows challenging behaviour when asked to do something they don't want to, the adult may stop making that demand. This too is a reward. Both situations can create a learning trap, with an increase in the behaviour over a two year period.

So parents need to be aware of how they respond. Faced with problem behaviours,



Professor Oliver suggested that parents play for time by thinking 'One two, what should I do?' Does it need a big row and lots of eye contact or a very cool response without much attention? If parents choose to ignore the behaviour, they need to be aware that the early stages of ignoring behaviours increase the behaviour in what is known as an 'extinction burst'. Responding then merely teaches the child to 'ratchet it up a bit' to get the response they desire.

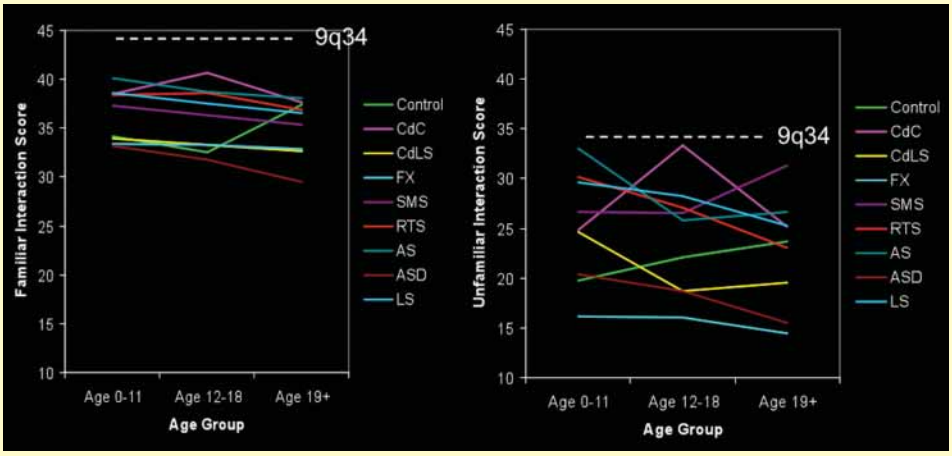
Behaviour as communication

A typically developing child has a wide range of communication strategies but a child with a learning or physical disability has a smaller repertoire and may resort to some really tricky behaviours to convey messages. Functional communication training (available via clinical psychology) and applied behavioural analysis show very good evidence that they can help. Using this approach and giving children the capacity to control their immediate environment, Professor Oliver's team has shown a decrease in aggression and a rise in functional communication in six children with Angelman syndrome, showing that children can unlearn one (problematic) behaviour and learn another (acceptable) one.

In summary

There's variability, of course, between individuals. Professor Oliver remained unconvinced that 9q34 is best thought of as an autism spectrum disorder. Some behaviours in people with 9q34 may look like autism but they have a different derivation and need to be better understood. He recommended that families resolve any health problems first. Clinical psychology and applied behaviour analysis may both be helpful. And effective communication systems are really important.

'Finally, in trying to lobby for your children chain yourself to the doctor's desk and refuse to leave until you've got a bit further. Speak softly but carry that big stick.'



Question Time

CO = *Professor Chris Oliver*
HM = *Hélène Miles*
SA = *Simon Ashby*
ES = *Dr Eugen Strehle*
SY = *Dr Svetlana Yatsenko*

Biting

Q ***How do you discourage a child from biting and once they have bitten, how do you release their jaws?***

CO *When people are fighting, typically you try to separate them, which is never a good idea. You actually push against and keep everything exactly where it is until eventually they let go. As for the underlying frustration, there are usually two reasons. One is impulsivity. You can't wait, so if you are asked to wait or to do something you don't want to, that appears to be a bit of a trigger. Back of the hand biting is not uncommon across people with a severe disability under those circumstances.*

We would first say: are there situations where we can reliably trigger that behaviour? Then we would decide what we would rather the child did in that situation. Then we'd set situations up and encourage the alternative response and reward it heavily, artificially initially but fading with time.

HM *We'd also look at the child's sensory needs. What is the child without communication getting out of biting? Children with a learning disability receive and process stimulation very differently. The pressure may be quite nice and we wouldn't want to stop a need to bite. We'd maybe incorporate some sensory experiences throughout the day, some calming strategies, maybe some deep pressure-type massage and activities – and make the need to get something out of the deep chewing and biting more appropriate. We also use things like chewy sticks or firm dog toys.*

SA *If ever he manages to communicate his frustration in an appropriate way, it's also validating that communication and rewarding it heavily.*

Self stimulation

Q ***The nicest way to put this is my daughter does self-stimulating. It can be so extreme, it looks as if she's fitting. When she's unwell it gets excessive and she can be quite aggressive if you don't let her. Sometimes it can get excessive when she's tired and can't sleep. While I don't mind if she does it around sleep time, it upsets me when it's intense.***

HM *It's not uncommon. We've found we need to work on it early because the longer it goes on, the more entrenched it becomes and the more difficult to break. If you can intervene and redirect the behaviour, that's fine. If your child gets really distressed when you do that, the behaviour is quite entrenched. It is sensory; it starts off as a sensory need but when the child realises the behaviour is quite nice, it then can become entrenched. If you try to redirect her once it gets into that intense stage, then you'll get aggression. Looking at the social environment, it's also giving the message that it's not OK to do it in front of other people. As soon as the child can differentiate, they can learn that they can only do it in the bedroom or in the bathroom.*

Parent *We've had a couple of strategies that worked at school where they say 'Hands on knees'. We haven't tried to stop it at home, but she knows it's a private thing, not to be done in front of others and she goes upstairs and closes the door.*

HM *At 3½ it's still easy to move her and as she grows up she will make the association that it's no on the settee but OK in my bedroom. Maybe some more sensory experiences incorporated in her day so she's getting the same feelings without having to self stimulate. It may be worth having a sensory assessment in case she has some hypersensitivity needs. She might be able to do some exercises that would give her the same feeling but not in the same way. And try keeping a diary of when she does it. We would first check out there wasn't any urinary infection or thrush and possibly ask the paediatrician if there are any other physical causes.*

Life expectancy

Q ***Are we looking at a normal life expectancy for these children?***

CO *We don't know because the diagnosis is quite recent. Generally if you look at the life expectancy of someone with a severe intellectual disability, it's around 55. One would assume that if you have more health conditions then you are more at risk.*

ES *Underlying health issues like heart disease can have an effect, depending on whether it is fully corrected or not. Also children are more prone to infections perhaps because their muscle tone is reduced and their breathing is not so strong and they cannot cough up secretions as easily. The chromosome disorder does not necessarily have an effect on life expectancy and while the overall life expectancy for someone with a severe learning disability may be reduced to 55, it will depend on the individual and their situation.*

SY *We know about four patients beyond their 40s, but that doesn't mean that others don't exist. It's because genetic tests are mostly done on children. We don't know how many older patients there are.*

Toilet training

Q *My son has a problem with toilet training. I'm not sure whether it's a behaviour problem or whether it's a learning problem. He's nearly 10 and we've been trying since he was about 5. He now holds his wee when you try and teach him how to go to the toilet. He also does that in times of stress or excitement. His paediatrician assures us that he has good sensation and that it's a good sign that he can hold on. But he holds it to the point where he is contorted and he must clearly be in discomfort and will only let go when he is in bed. We're at a loss as to how to help him. We've spoken to continence advisory and our paediatrician.*

CO *It sounds as if he has rules about where he goes to the toilet and where he doesn't. It sounds like one of those things you see in people with an autism spectrum disorder about developing rules and being anxious or in typically developing children about being anxious about going to the toilet in different places. You might think about it as a kind of anxiety-related behaviour.*

Q *I can see that as he is getting older that level of noticeable anxiety is increasing.*

CO *I would seek referral to clinical psychology via your GP because it sounds as if it's downstream of an anxiety disorder and clinical psychology may be able to help in trying to understand why he has developed those particular rules.*

SA *We helped one autistic lad with a social story. Essentially we gave him a new script to replace his previous set of rules and that helped.*

Parent *He has quite set rules for things that happen on a day-to-day and week-to-week basis. He holds a two week timetable in his head even for things he doesn't like.*

CO *The general advice about changing those rules is not to make huge changes. People respond better to a very gradual change. I might go to the National Autistic Society (NAS) website* ***(www.nas.org.uk)****.*

HM *On the NAS website there are stories that you can download. Also there are some brilliant books for a child who relates to pictures. It may help to reintroduce pictorial sequences.*

Possibilities of treatment

Q *Before this weekend I worked on the assumption that having a genetic disorder was so fundamental that it wasn't treatable but in the session this morning there was some talk about drugs that might be able to repair neurons in the brain. Do you know how long it might be before such a therapy is available and what the expectation might be of how successful it could be?*

SY *Deletions can be variable in size and we know that the critical gene EHMT1 is deleted in all patients but there are additional genes that may play a role, triggering seizure disorders or other features. We have no idea yet which genes are responsible for the other features. It is a developmental defect so you cannot reverse all the features but some of them like seizures can be treated by knowing which gene is responsible because potentially it can be blocked at some point and the seizures prevented. Treatment can change the quality of life for children but it will not treat the situation or the condition.*

Q *I had the impression this morning that you couldn't replace or correct the gene but my daughter has perivascular dysplasias throughout the brain and one large lesion. It sounded as if there might be some treatment in the future to repair some of the damage. Neurons and drug therapy was something I hadn't considered before.*

SY *I would not be so positive about the early possibility of treatment, especially with neurons in the brain. The damage is done. Research now is increasing rapidly: five years ago we had no idea about this condition and now we know the genes that cause it. I hope we will know much more not only about the critical genes that are responsible, but maybe other genes as well. A better understanding may bring ideas for treating certain things, but not all.*

Professor Peter Hammond

Dr Eugen Strehle

Marion Miller

This report includes the presentations that were specific to Kleefstra syndrome and families' questions. The other speakers, whose presentations were more general, were: Professor Peter Hammond, professor of computational biology at the molecular medicine unit at the Institute of Child Health, University College London, on *Creating a 3D model of typical faces in 9q34 deletion syndrome*; Dr Eugen Strehle, consultant paediatrician at North Tyneside General Hospital, on *The Child with a Chromosomal Disorder from a Paediatric Perspective*; Hélène Miles and Simon Ashby from the Coventry Children's Community Learning Disability Team on *Realistic expectations of development* and Marion Miller, sleep counsellor, on *Sleep issues and how to tackle them*.