8p23 deletions *and* inv dup del 8p

From 21–23 May 2010, *Unique* hosted the first ever meeting of families, geneticists and scientists with an interest in 8p23 deletions and the disorder known as inv dup del 8p – inverted duplication and deletion of 8p. This report includes the presentations specific to 8p23 deletions and inv dup del 8p as well as families' questions.

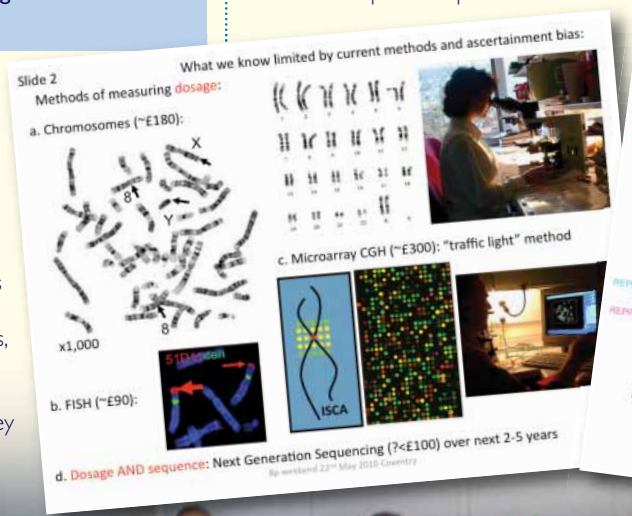
The Genetics of 8p- and inv dup del 8p

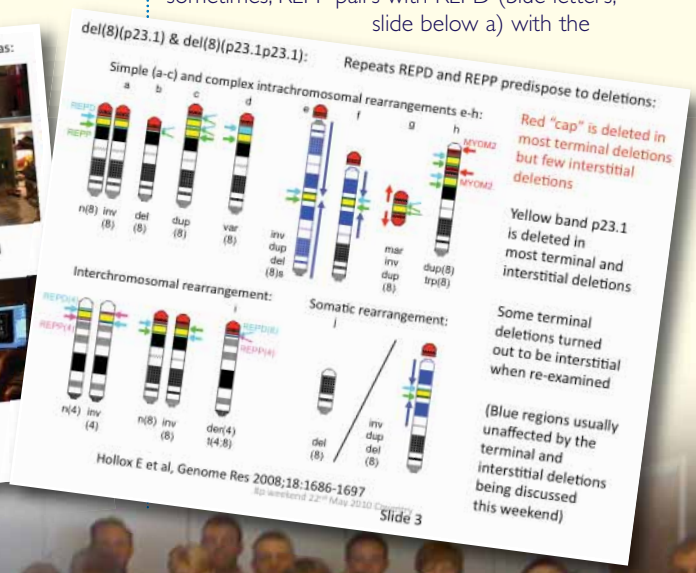
Dr John Barber, Honorary Senior Lecturer, Southampton University and formerly Head of Cytogenetics at the Wessex Regional Genetics Laboratory and Co-Director of the National Genetics Reference Laboratory (Wessex).

> *We don't know it all. Even in 2010, we are still finding things that are new.*

With an infectious enthusiasm, Dr Barber explained how chromosomes and DNA are investigated today – and how they probably will be tomorrow (slide right). For almost 50 years cytogeneticists have looked down microscopes, counting chromosomes and matching bands (slide right: a). More recently they have used a "FISH" technique, adding a fluorescent dye to a DNA probe that seeks out the piece of DNA on the chromosome that it matches (slide right: b). Today they are most excited about microarrays (array-CGH) (slide right: c). These divide all the chromosomes into 40,000 spots. The child's DNA is mixed with a standard (control) DNA and at each spot the question is asked: 'Is there more or less DNA in your child than in the control?' Coming down the track in the next two to five years is next generation sequencing which it's hoped will show missing bits (deletions), extra bits (duplications) and the DNA sequence so you can see gene mutations as well copy number changes, all in the one test.

> *We don't know anything you could have done to prevent these things. The number of cells we produce in our blood every day is said to be equal to the number of stars in the Milky Way. So the miracle is that so many of us are 'so called' normal rather than that a few of us are not.*





Chromosome 8's short arm: 8p

Most of the DNA sequence in 8p is unique to the short arm of chromosome 8, but in some places there are repeats (eg REPP, REPD, (slide below) which can act like a 'raised paving stone' and 'trip up' the replication machinery when a cell is reproduced or an egg or a sperm is formed. Firstly, these repeats can be a point of weakness at which a chromosome may be more likely to break. Secondly, a repeat, e.g. REPP in 8p23.1 (green letters, slide below a), will normally pair with its opposite number REPP on the other chromosome but, sometimes, REPP pairs with REPD (blue letters, slide below a) with the

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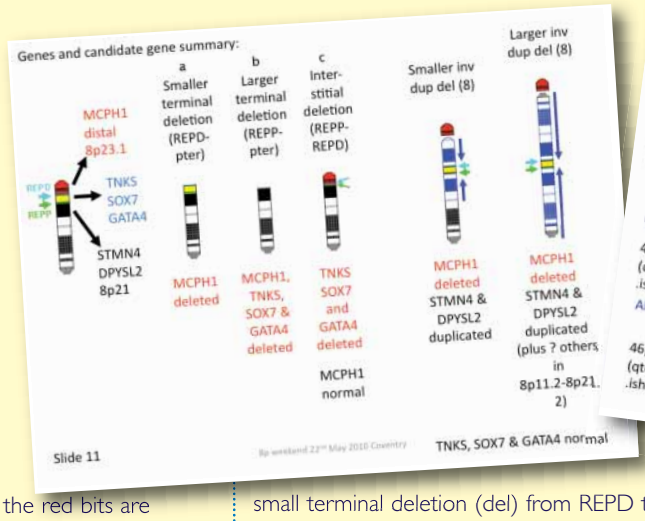
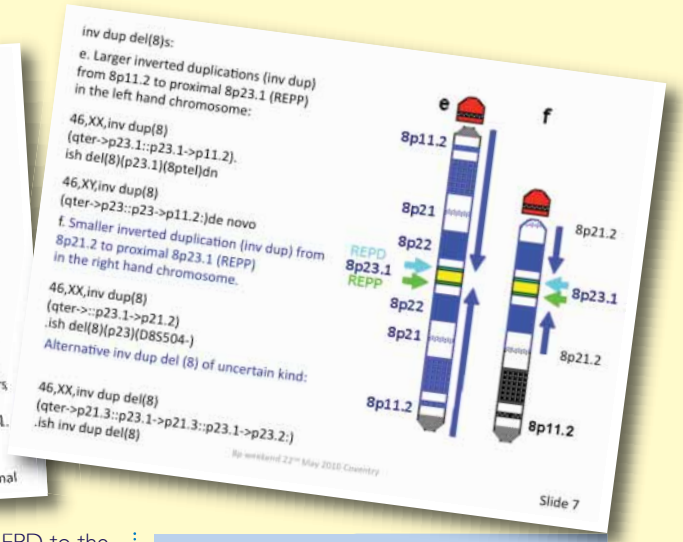
result that the DNA between them is deleted (slide previous page b).

In a terminal deletion 8p23.1, you can get a breakpoint at either of the repeats. Those with a breakpoint at REPD would have a smaller deletion and only be missing the red bit (slide above right a) but most people are thought to have a larger deletion with a break at REPP so that both the yellow and the red bits are deleted (slide above right b). In an interstitial deletion, the breaks occur at both REPP and REPD so that only the yellow bit between the repeats is missing (slide above right c).





The chromosome looks so solid that you think you can't argue with it. But what actually happens in life for your child may well be different to what's in the books. The books often describe people who've been in institutions or who haven't had a family who've really given them the best chances in life. So, the chromosome abnormality may be fixed, but the phenotypic consequences are not necessarily so.

8p is unusual for the variety of complex chromosome abnormalities that can be caused by the REPP and REPD repeats, the best known of which is the rearrangement known as **inv dup del 8p**. This consists of the relatively small terminal deletion (del) from REPD to the end of the chromosome (the red bit again) (slide far right e and f) and a relatively large duplication (dup) (the blue bit) that's 'upside down' or inverted (inv) in comparison with its usual orientation (blue arrows, slide far right e and f). This duplication usually extends from REPP down towards the middle of chromosome 8 and may be larger (slide far right e) or smaller (slide far right f) depending on the position of the third breakpoint in the short arm of chromosome 8 (8p11.2 in slide far right e and 8p21.2 in slide far right f). This means that the yellow segment between the deleted red bit and the duplicated blue bit remains normal in most inv dup del(8)s (slide far right e and f).

These repeats can also cause a variety of other structural abnormalities such as translocations (when different chromosomes exchange segments of DNA between each other). Just as there are repeats on the short arm of chromosome 8, there are also similar repeats on the short arm of chromosome 4; these repeats can sometimes interact to produce an unbalanced 4;8 translocation and children with Wolf-Hirschhorn syndrome.

In general the repeats cause the abnormalities, but anything can happen and you could have a break anywhere that is not related to the repeats.

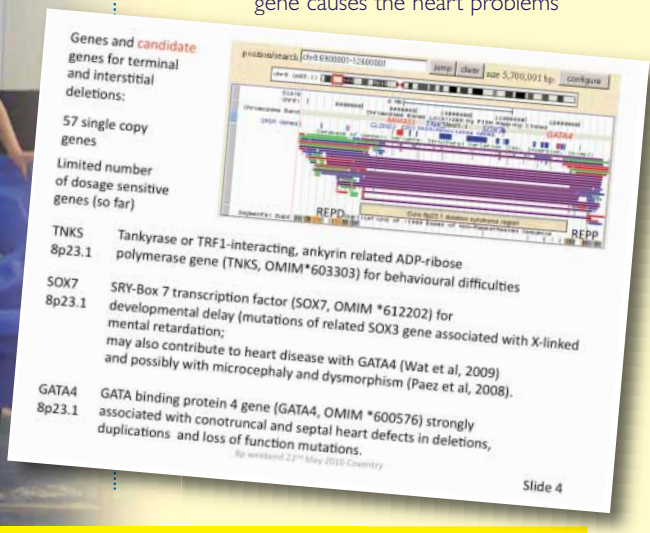
Key genes in del 8p23.1

Microarrays show which genes are missing or extra. In the core 8p23.1 deletion region (yellow in right slide b, page i) there are roughly 57 genes that are reduced from two copies to one copy. For many genes, one copy is enough and this does not matter, but for others it does. We are still at the early stages but there are now some 'candidate' genes for some of the phenotypic features that people may have (slides below and above left).

TNKS ('tinks') – *TNKS* may be one of the causes of behavioural difficulties and is deleted in most of the terminal and interstitial deletions of 8p23.1.

SOX7 – *SOX7* may be related to the developmental delay and possibly heart defects (see *GATA4* below) and is deleted in most of the terminal and interstitial deletions of 8p23.1.

GATA4 – We are confident that the *GATA4* gene causes the heart problems



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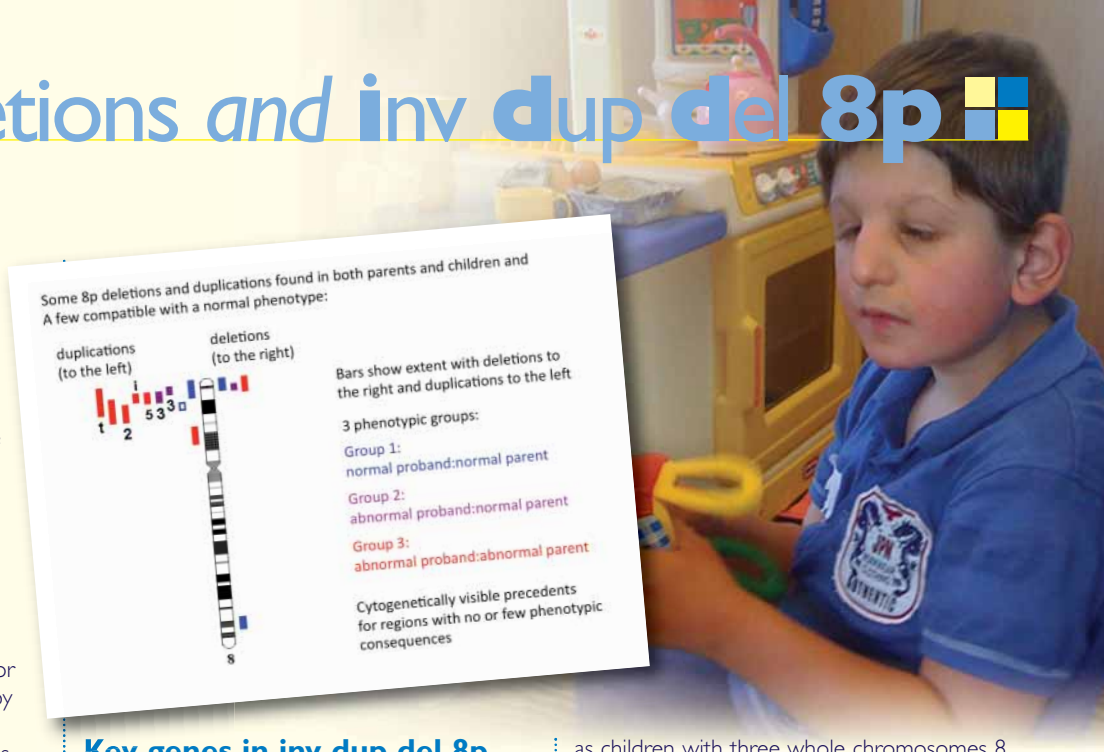
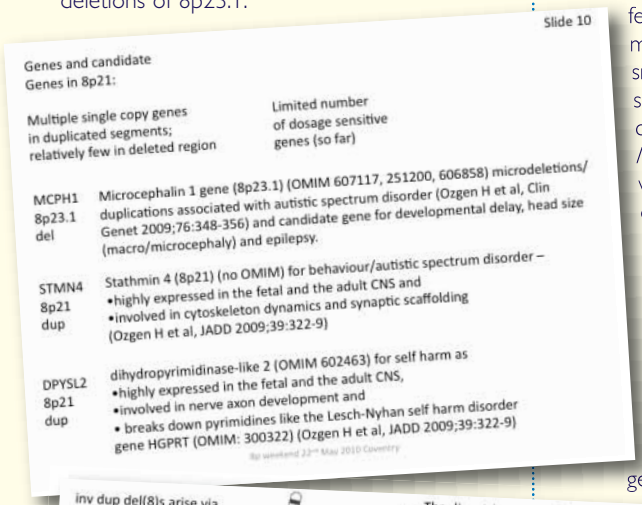
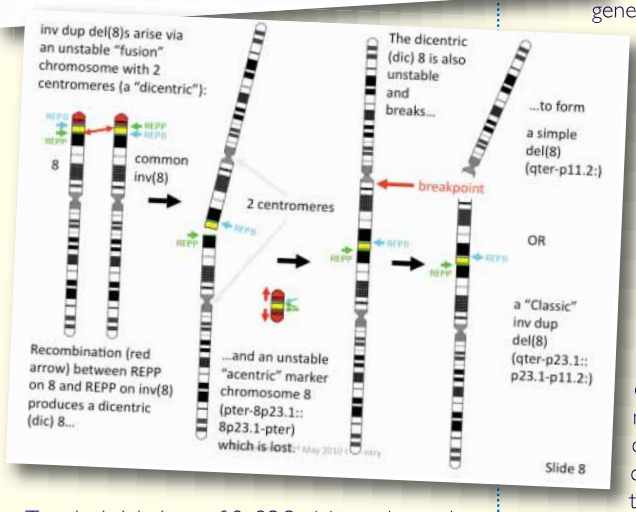


because heart defects are found in people with mutations of just this gene alone. Because *SOX7* is part of the same pathway of genes that control the development of the heart as *GATA4*, *SOX7* may provide an additional risk of developing heart disease as both genes are normally deleted in the terminal and interstitial deletions of 8p23.1. However, as a word of caution, not everyone has a heart defect even when both genes are deleted and therefore reduced to a single copy.

Although there are 57 genes in the core yellow interstitial deletion region, only five or six more genes are reduced to a single copy by deletions that include the red terminal region. Among these is: *MCPH1* – *MCPH1* is the microcephalin gene that is believed to have had a role in the evolution of head size in humans and has been tentatively linked with the autistic features present in some children. However, this gene is only deleted in terminal 8p23.1 deletions (and inv dup del(8s)) and, as far as we know, is not affected by interstitial deletions of 8p23.1.





Terminal deletions of 8p23.3, right at the end of the short arm, can be associated with a normal phenotype suggesting that one copy of the few genes involved is enough (blue bars, slide above).

Key genes in inv dup del 8p

With inv dup del 8 there are so many genes in the large duplications that we have much less of a feel for which the key ones might be but there are some candidates (slides left and page ii, above left):

MCPH1 – as above, *MCPH1* has been tentatively associated with autistic features but, while deleting a copy might be expected to give rise to a smaller head, microcephaly (small head size) is not a feature that all the children have. Duplications including *MCPH1* have also been associated with epilepsy but *MCPH1* is not duplicated in deletions of 8p23.1 or inv dup del 8.

STMN4 – *STMN4* is duplicated in most inv dup del 8 and may be associated with behaviour and autistic spectrum disorders.

DPYSL2 – *DPYSL2* is also duplicated in most inv dup del 8s and may be involved with self harm as a related gene on the X chromosome is known to be associated with self harm in children with Lesch-Nyhan syndrome.

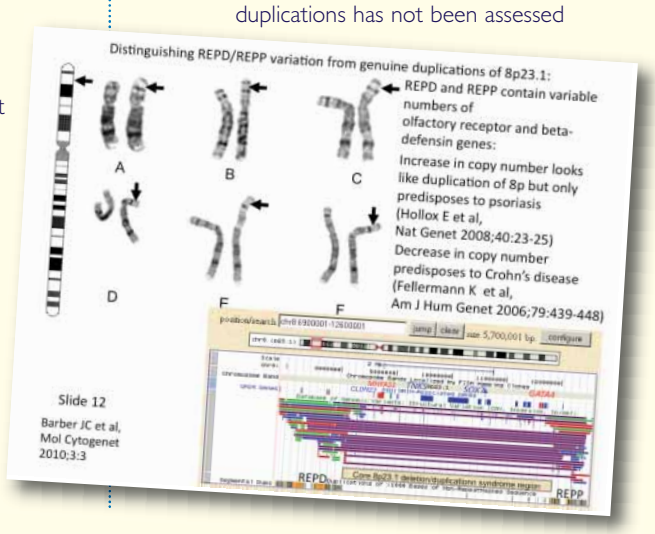
How do inv dup del 8ps arise?

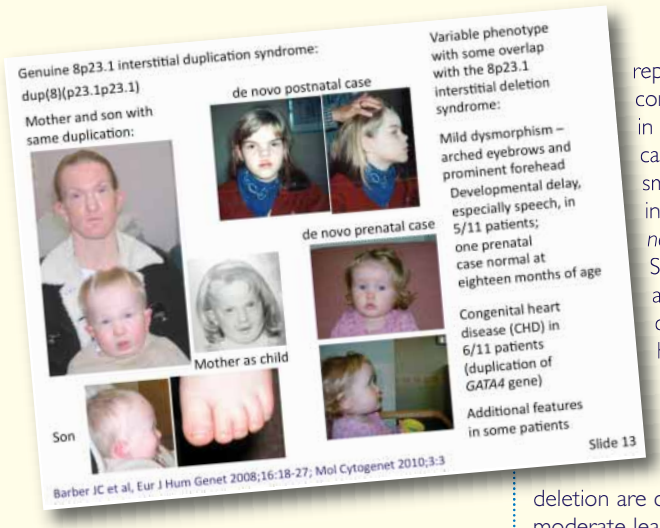
When eggs and sperm are formed, they do a last dance together and exchange segments so that, for each chromosome pair, you end up donating a mixture of grandparental chromosomes to your child. In this little dance, things may go wrong at the repeats. Our best model of what happens is that the two normal chromosomes 8 fuse into one huge unstable chromosome (slide left). This would be incompatible with life, as children with three whole chromosomes 8 do not usually survive until birth, but the giant unstable chromosome can break to give either an inv dup del 8 or a terminal 8p deletion.

Other duplications of 8p

The 8p23.1 interstitial duplication syndrome (slide page i, right c) involves the same DNA and genes between REPP and REPD as the 8p23.1 interstitial deletion syndrome. Duplication 8p23.1 has a variable phenotype with some overlap with the deletion syndrome. Common features include arched eyebrows, a slightly prominent forehead, developmental delay (especially of speech) and congenital heart disease (slide page iv).

The repeats themselves can also expand in number so that they look like a duplication of 8p23.1 under the microscope (slides page i, right d and below). However, extra copies of the repeats cause no syndrome whatsoever but only predispose to psoriasis, a relatively common skin complaint. It has also been claimed that if you decrease the number of copies of the repeats, you can be predisposed to Crohn's disease (a type of inflammatory bowel disease). This claim has not been supported by a recent larger study but the incidence of psoriasis and Crohn's disease among children with 8p23.1 deletions and duplications has not been assessed





and is something that you or your clinicians might want to look out for.

8p deletion and inv dup del 8p: A review of the conditions and their impact on the child and family

Dr Denise Williams, consultant clinical geneticist for the West Midlands, reviewed 8p deletions and inv dup del 8p and talked about their impact on the child and family.

She reviewed chromosomes and highlighted the huge amount of information they hold in such a tiny space. Each of the 100 trillion cells in the body contains 1.8 metres of DNA so tightly packed that it would fit on a pinhead. If you lined this DNA up, it would reach from the earth to the sun and back more than 600 times. It's amazing, she said, that things go right so much of the time.

When asked to see a child with a possible chromosome disorder, things she looks for include small size at birth; pregnancy problems; small size for the family; perhaps congenital defects of any organ, heart and kidney problems are particularly common. Developmental delay or learning difficulties also come into the pattern. There may also be minor signs like eyes set wide apart or joined toes. If a number of these features occur together she starts to think about a chromosome problem.

8p23 deletion

The deletion was first described in 1988 by Kerry Fagan, an Australian cytogeneticist. Just over 100 cases have been described in the medical literature, but there will be others not reported. The deletion is equally common in males and females and in all ethnic groups. The deletion size can vary, but is usually relatively small. It can occur for the first time in the child in a particular family *(de novo)*; or it can be inherited. Sometimes a parent has it with absolutely no problems and has children with it who themselves have or haven't had problems.

Everyone should be treated first and foremost as an individual. But the most common clinical features for people with an 8p23 deletion are congenital heart defects; mild to moderate learning difficulties – some people have no problems, others have quite severe difficulties. Some people have a small head (microcephaly) and perhaps have more problems because their brain is smaller. Behaviour difficulties are also reported to be common, especially hyperactivity, impulsiveness and poor concentration.

> *"We don't want to miss anything that is treatable."*

Two-thirds to three-quarters of children are born with a heart problem but the seriousness is incredibly variable. Some children have small holes in the heart that close on their own; others need surgery; and others with very complex heart problems have died.

> *"Pregnancy and birth weight are usually normal, but many families have concerns from birth, especially with feeding which can lead to failure to thrive. Babies can take all day to feed; there may be reflux which would need treating."*

In 20-30 per cent of babies the lining between the abdomen and chest hasn't closed properly (diaphragmatic hernia). This is a very significant problem but surgery may be possible.

Others have a cleft palate or an unusually high one. In boys the testes may be high or the hole at the end of the penis is in the wrong place (hypospadias) and this may need surgery. Epilepsy is relatively common but usually quite easy to treat. Babies can be floppy (hypotonia) or stiff (hypertonia) or have a combination. There may be vision problems such as a squint, long or short sightedness and children may benefit from glasses. Dental problems are more common than in typically-developing children. So vision and dental check-ups should be provided. Pregnancy is usually no problem but birth weight may be below average, although some babies are bigger. Feeding difficulties can be a problem early on but once that stage has passed, growth is usually normal. There may be common facial features, but these are subtle.

However, knowing how a particular child will be affected is difficult because you can't predict it just from the results of a chromosome test.

Inv dup del 8p

More than 50 cases have been reported, equally among males and females and in all ethnic groups. It's thought likely that the duplication causes the clinical problems. Again, every child should be treated as an individual.

The most common features include developmental delay, learning difficulties – perhaps especially speech and language delay – but very variable; floppiness; structural brain abnormalities; some children are stiff rather than floppy with contracted joints and club feet; dislocated hips are found in more than 50%; the spine can be curved in 40–75%; congenital heart disease is relatively frequent.

Most children will have a brain scan. Agenesis of the corpus callosum (ACC) – where the nerve fibres that join the two halves of the brain together are thin or missing – is seen in about 4/5 children. There are hundreds of causes of ACC and it is found in healthy people but in a child with a chromosome disorder it would be expected to contribute to the learning difficulties. The ventricles may be enlarged and this can cause hydrocephalus although this is unusual. The area of the brain called the cerebellum that is important in balance may contain fluid-filled cysts or be underdeveloped; and the head itself can be small. One in three children has seizures, but these are usually easily controlled. Some children present early with apnoea, where they stop breathing. Some children have kidney or bladder problems; some have a hernia, undescended testes or fluid around the testes; visual or dental problems; in one child the skull bones fused early. Some children have entered puberty a little early. As for behaviour, many children have very lovely behaviour and are loving children.

> *"Many families tell me their baby was so good and never cried. That's a little warning bell for me."*

Summary

There are individual differences but group similarities; many families have difficulty in getting a diagnosis and accessing services; they need support because of the uncertainties of the future; it can be isolating and lead to poverty; and the best people at giving information are support groups.

Behaviour in 8p- and inv dup del 8p

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

Before the weekend, families were sent an 8p23 survey. Chris Oliver presented an overview from the 15 forms completed so far. He explained some reasons for difficult behaviour in children and adults with a genetic disorder and suggested ways to approach it. He stressed the risks of making generalisations and that there is huge variability. There may be common characteristics but every child is unique whether they have a genetic disorder or not.

Gene to brain

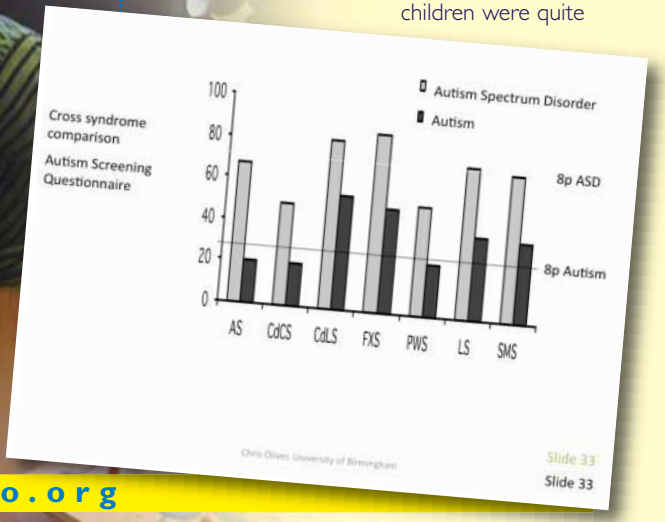
'The information contained within genes spells out a code for correct development. You can speculate that when a piece of information gets lost the code becomes undecipherable, disrupting development.

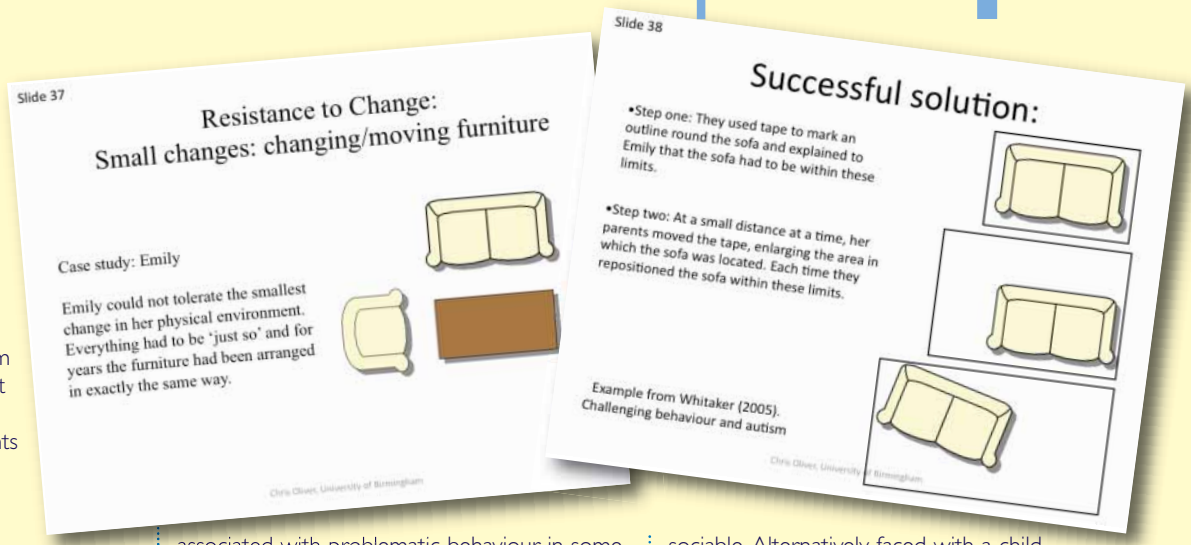
'If you look at brains on MRI scans, you don't see sections of the brains dedicated to particular behaviours. However, the prefrontal lobes are very important for controlling our behaviour. Looking at *Unique's* guide to 8p23- and our own data made me lean towards that part of the brain as perhaps not developing properly. It controls some of the flow of information; it's very important in controlling behaviour and is heavily implicated in autism spectrum disorder and ADHD, problems like impulsivity and an inability to stay focused.

'When children with other syndromes like Prader Willi syndrome (PWS) are asked to shift their attention, you often get a real temper outburst. Their ability to attention-switch is compromised so they tend to stick to routines; disrupting those routines makes a big demand. Children with PWS are often called obstinate or stubborn but they are not refusing wilfully: they find switching attention difficult.

8p23 survey

'The survey tries to capture differences between different syndrome groups. If we can see similarities, we may have seen the same pattern elsewhere before which gives us an idea what we can do. Of the responses so far, the age range was 4–26 and 2/3 were male. More than half have a mild visual impairment. The variability in intellectual disability and developmental delay was most striking. Some children were quite





able but showing behaviours normally seen in much more disabled children. We didn't see very high levels of self injury – about 1 in 3, possibly not very severe or problematic. But over 76 per cent showed physical aggression.

'We asked about autism spectrum disorder (ASD), a term used a bit too frequently. It's defined behaviourally by three impairments – in social interactions; in communication and with a lot of repetitive behaviours. Some of these can be seen in anyone with an intellectual disability, but that doesn't necessarily imply ASD or autism. These impairments can occur for many different reasons and we have to be very careful about using the diagnosis (slide page v). We found about 25% with autism and around 75% with ASD, but these are not the same as classical autism or ASD. We found people with 8p were sociable with familiar and unfamiliar people and this is not a classical autism presentation.

'However, within the group we had very high scores in repetitive questioning, repetitive phrases and conversation and there is some evidence that these behaviours are associated with problems in the frontal lobes. Repetitive behaviours are very difficult to stop completely but the main approach is to make gradual changes (slides above right).

'Even without the diagnosis, the National Autistic Society website (www.nas.org.uk) has great resources.'

Behaviour as communication

Professor Oliver then looked at self injury and aggression. Since pain is associated with self injury, pain is the first thing his team look for in someone self injuring. Around 1.5/10 typically developing children headbang, about half of whom have a middle ear infection.

About half of families reported gastrointestinal problems and reflux. Reflux is known to be associated with problematic behaviour in some syndromes but can be hard to identify. How does someone with a severe disability and poor communication tell you they are in pain? Using a 9-year-old girl with Cornelia de Lange syndrome as an example, he showed how difficult behaviours were linked with undertreatment of her reflux and how they resolved dramatically once the reflux was treated. Reflux, tooth decay and middle ear infections go together, he pointed out. One reason is that reflux contains acid which erodes tooth enamel causing decay.

Children with impaired communication may not be able to express pain directly. Professor Oliver's team look for a 'pain signature', 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

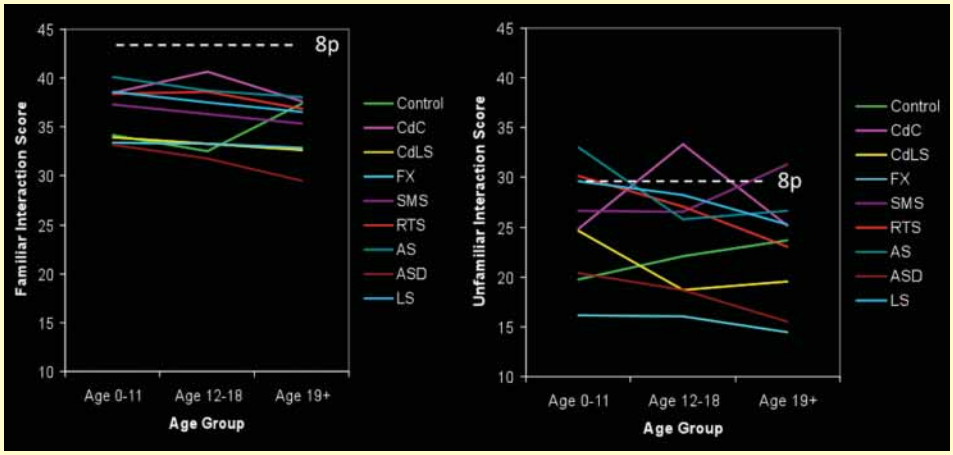
Learned behaviour

Self injury or aggression can occur as a learned behaviour if it is rewarded with attention and this positive reward makes the behaviour more likely to occur in the future. Speculatively, the attention may be particularly important for children with 8p23 because they are so sociable. Alternatively, faced with a child showing 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.

Parents need to realise how they respond. Faced with these behaviours, think: 'One two, what should I do?'. Does this need a row with direct eye contact or a cool response without much attention? Parents who ignore behaviours need to be aware that the early stages of ignoring increase the behaviour in a so-called 'extinction burst'. Responding then merely teaches the child to increase the behaviour to get the response they desire.

Summing up

Very early intervention matters, so seek help from clinical psychology through the GP. For children with limited communication it's very important to have effective communication systems. Finally, background mood interacts and sleep is a big issue. The survey showed a great deal of variability but it's known that a risk marker for aggression is impulsivity. In other groups impulsivity improves with age; descriptions in the *Unique* guide suggest it may in 8p23- too.



Question Time

Questions were answered by John Barber [JB]; Chris Oliver [CO]; Denise Williams [DW]; Hélène Miles from the Coventry Children's Community Learning Disability Team [HM]; Dr Eugen Strehle [ES], consultant paediatrician at North Tyneside General Hospital; Helen Woodrow [HW], Independent Speech and Language Therapist, Eg (Training) Ltd; and Beverly Searle [BS], *Unique* chief executive.

Q *You showed a picture of toes joined up. Is that a sign of a chromosome deletion?*

JB *This is called syndactyly or partial syndactyly and happens quite a lot in genetic conditions but also happens in people with no genetic condition at all. Isolated signs do not necessarily imply that you have something that could have given rise to the syndrome in your child.*

Q ***How many families are there with these deletions and syndromes?***

JB *Most laboratories in the UK deal with a population of about 3 million. For interstitial deletions of 8p, the Wessex Regional Genetics Laboratory had only two cases in records going back over 30 years – so we are dealing with relatively rare things. Sometimes we can estimate the population frequency: the duplication 8p23.1 syndrome occurs in about 1 in 60,000 newborns and the deletion syndrome is unlikely to be less common. Roughly 1: 20,000 newborns have inv dup del 8. There's a little inversion between the repeats REPP and REPD that seems to predispose to the inv dup del 8 but, as a quarter of all of us have that inversion but only 1:20,000 have inv dup del 8, the predisposition must be very weak.*

Q ***Most children are 10 and below. Are 8p deletions or inv dup del 8p getting more common? Is it environmental?***

JB *From a purely genetic point of view, we don't know of any direct causes other than the weak predispositions already mentioned. As far as we know, these rare conditions are not becoming more frequent but, as awareness of genetic conditions has grown and methods of testing have improved, it is possible that we are getting better at identifying new cases. If you look at the blood of Hiroshima victims, you can see the damaged chromosomes but the great majority of their children have been perfectly normal, and they've had an atomic bomb dropped on them! How many people are treated for cancer with aggressive chemicals and then go on to have normal children? It's as if the egg and sperm cells are tough little characters which are going to pass on their genes come what may! We don't have any reason to think that it's other than your replication machinery in the cell trying to produce eggs and sperm in the normal way but just getting tripped up from time to time.*

Q ***Will behaviour improve with age?***

CO *Improvement is described in the Unique guide. Impulsivity or overactivity becomes better with age in nearly every other syndrome and in typically developing children. The frontal lobes develop into the early 20s so if that underlies the difficulties you would expect improvement.*

Other parents agreed that behaviour improves with age, as children get more confident and sociable; one parent said it got worse – fewer episodes, but each one more violent and her son has been excluded from school. The parent of an adult said environment matters – his son is calmer living in more rural surroundings than in the hustle and bustle of town. A parent from Norway said that her son benefited from intensive 1:1 early behaviour intervention with trained staff.

Q ***My child has developed autistic tendencies over the last 10 years. Will these tendencies increase?***

CO *It depends what they are. In other disorders where the frontal lobes are involved, there may be some improvement but they have a natural drift towards these tendencies.*

Q ***My child is hyperactive and shouts a lot. We've tried Ritalin, Risperdal and Strattera. What would you recommend?***

HM *Strattera is a stimulant, risperidone is a calmer. We do use that type of medication but children can be quite sensitive to it and the adverse effects worse than the restlessness. Ritalin is a stimulant and has a big impact on sleep. For someone with high anxiety levels very small doses of risperidone have been shown to be successful but in some children we see an increase in the behaviour. We find if we put in a sensory diet with specific things like wedges to help the child sit still, the hyperactivity and some of the bad behaviours decrease. We'd try a holistic approach before medication.*

CO *Before using medication, it's good practice to do a functional analysis to see if the behaviour is occurring for a particular reason, whether you can spot the reasons, if you can build in more appropriate behaviours or manage them differently. These medications were tried on children with ADHD with broadly typical development so we don't necessarily know how they may affect someone with atypical development. I would ask what the side effects are and how you monitor them. Finally, ask how the child will be monitored and what happens if the medication doesn't work.*

HM *Since risperidone isn't licensed for children it has to be given under a special prescription.*

Q ***My child is still in nappies at night.***

CO *With a bell and pad device, urine forms an electrical contact and a bell wakes the child or adult so she or he learns to associate a full bladder with waking up. This is usually managed through continence services via a GP or community nurse. I'd never give up on toileting even in children with a profound disability. There is good evidence that children can become continent of both urine and faeces. It's important for children's quality of life and happiness.*

Q ***How do I handle other people's reactions when my daughter behaves badly in public? She looks like any other typically developing child.***

CO *It's difficult but when we went out with youngsters if someone had a tantrum and we were offered advice in public, we handed over a little card that said We work… This child is… We are working on his behaviour. Thanks for your advice. That tended to work.*

Parent *You have to learn to turn off.*

HW *We've had members of the public call the police. We often ignore the behaviour.*

Parent *Using direct payments, we buy in staff. One problem I now have is building up the carer's confidence in handling it when my adult son is out with him.*

HM *We advise that managing behavioural issues has to be consistent. We would support the carers and make sure they all feel confident with the strategies. We sometimes put symbols on cards on key rings to use discreetly in public. The difference in public is often if the parents stay calm.*

Q ***Are tantrums common in 8p?***

CO *From the descriptions in the Unique guide, it seems they are. In the survey we didn't use the term temper tantrum or outburst. I regret that because in other syndromes you do see disproportionate outbursts. In Smith Magenis syndrome you see them with incredibly high levels of impulsivity.*

Q ***Will children always be dependent on adult supervision?***

Parent *My son has done a lot better than we thought but will still need a support community. We hope he will leave school and home though at the moment the prospect terrifies him and he wants to be safe with us. We don't really know what*

will happen. Even at 16 I wouldn't want him on a bus by himself because he could easily get confused. I've watched him get on a train and he's done it quite well but we worry about who he'll meet. He is going to college in three months to learn more independence skills.

ES *It will depend on the level of learning disabilities. Someone with severe disabilities is more likely to need sheltered accommodation as an adult.*

Q ***Have other children with inv dup del 8p or 8p23- had any breathing issues? Is poor circulation, going blue in the cold, something to worry about?***

DW *Getting bluish fingers and toes is relatively common.*

ES *It could be an additional respiratory condition. It's important to have a chest X-ray to make sure there is no chest infection or aspiration. Blue hands and feet (= peripheral cyanosis) are quite common in babies and most often they grow out of it. Very rarely, children may have Raynaud's disease. The treatment is to keep the fingers and hands warm; for an adult consult your GP.*

Q ***Does Makaton work for a child with inv dup del 8p?***

Parent *My daughter processes slowly and despite understanding quite a lot, her response is delayed, whether speech or Makaton, and it's hard for her to get it out. She can speak, she can use Makaton and she has communication cards. Having the choice stops frustration.*

Parent *My daughter associates a Makaton sign (like 'drink') with a word but doesn't sign Makaton back to me. Makaton has helped me to understand that she understands.*

Parent *My son finds Makaton physically too difficult. He will put his hand in his mouth for a drink but if he's doing something and doesn't want to stop, he understands the sign that means it's finished.*

HW *Makaton works both for the child to use and for you to communicate basic things to the child. Families often reinforce messages with Makaton. It's useful for a child with good communication skills but no speech; it gives you another building block.*

Q ***Have any children attended mainstream school?***

Parent *Mine has been attending mainstream school with 35 hours 1:1 support and no problems. He will have an evaluation soon to see if he still needs that level of support.*

Parent *My son has always attended mainstream school, is doing very well, is confident, does the usual teenage things, and has no behaviour problems. His fine and gross motor skills aren't there so he has a mentor to scribe for him.*

Parent *My son has attended normal school since 5, progressed to secondary with no help, is very bright, chatty, the same as any other 14-year-old, is now sitting exams, and only lacks a bit of concentration. To make his day, he's just got the sportsman of the year trophy at football.*

Parent *My daughter is in mainstream, a bit slower than her classmates. The first two years were difficult because of her behaviour but she did better with a teacher who understood her more. When she was naughty, the teacher was harder on her but when she was good she really praised her. Her behaviour has improved a lot at junior school. Children who used to be frightened of her accept her now.*

Q ***Will my child's learning and development plateau and will he meet all his milestones? He's now 5 and mentally 2.5. Will that gap remain or will it increase?***

ES *It's very difficult to answer. Every child is different, the more you can stimulate the child at an early age, the more attention you can give to the child, the better the development is likely to be. Be optimistic and do as much as you can but with significant learning difficulties, the older you get the less likely any major change will be. By adolescence the picture will be clearer.*

HW *Special colleges and adult services have youngsters who are all still learning life skills such as bus training, cooking, shopping and travel training.*

BS *Edna Knight, who founded Unique, has daughters in their 30s and 40s who are still learning, albeit slower than others.*

Q ***What more would we learn if our son who was diagnosed 16 years ago had an array test now? Is it worth it? Can we get it?***

DW *When chromosomes were done in the past by looking down a microscope, you could see the break clearly but you didn't know exactly where it was. Array-CGH gives a lot more detail and you can see what genes are affected. It will give you more information but the information might not be useful to know or change anything. If you want an array test, it should be relatively straightforward through a genetics centre. But you may wait for months because it's a new technique and there is a backlog.*

All speakers' presentations are available on the *Unique* website. As well as the presentations in this report, they are: *Creating a 3D model of typical faces in 8p23.1 del & inv dup del 8p* by Professor Peter Hammond, professor of computational biology at the molecular medicine unit at the Institute of Child Health, University College London; *The Child with a Chromosomal Disorder from a Paediatric Perspective* by Dr Eugen Strehle, consultant paediatrician at North Tyneside General Hospital; *Cerebra Sleep Service* by Pattie Everitt, sleep counsellor; *Realistic expectations of development* by Hélène Miles from the Coventry Children's Community Learning Disability Team; *Communication and Beyond: Ideas and Approaches to Take Communication Further* by Helen Woodrow, Independent Speech and Language Therapist, Eg (Training) Ltd.

Professor Peter Hammond

Dr Eugen Strehle

Pattie Everitt