

Understanding
chromosome
disorders

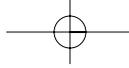
Unique

The
Little Yellow
Book

A Guide to Rare Chromosome Disorders

by

Dr Beverly Searle BSc(Hons) PHD CBIOL MSB and
Professor Maj Hultén PHD MD FRCPATH



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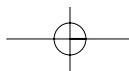
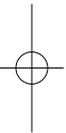
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welcome to unique

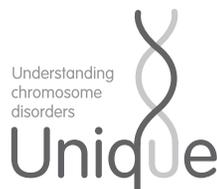
Dear Parent,

Welcome to **Unique**. We hope that through membership of the group you will feel supported in caring for your very special child who has a rare chromosomal disorder.

Perhaps your child is still a baby or has passed the baby stage but has only just been diagnosed. However old your child, discovering that he or she has a rare chromosomal disorder can come as a great shock. You might be feeling a mixture of emotions; sadness, confusion, numbness, anger, guilt, "why me?", isolation or bewilderment. Perhaps your reaction to your child has surprised you. You might be feeling overwhelmed at your lack of knowledge about your child's condition or despairing that your child's condition hasn't even got a proper name. Whatever your feelings, rest assured that other members of **Unique**, including the group's organisers, have experienced at least some, if not all, of them. We know how much it can help to talk to people who understand what you are going through and even what you are talking about. You are not alone.

We have prepared this booklet to give you a basic understanding of chromosomes and rare chromosome disorders and to tell you a little bit about ourselves and the group. Please feel free to use the group's services. If you have a question, we will do our very best to answer it or point you in the direction of someone who can.

Very best wishes,



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our history

Unique has been a source of mutual support and self-help to families of children with a rare chromosome disorder since it was founded by Edna Knight MBE in the UK in 1984 as the Trisomy 9 Support Group.

In 1989, with the support of the In Touch Trust and Contact a Family, the group expanded to include families whose children have any rare chromosome disorder. In 1993 the group was granted Charity Status and the new logo *Unique* was adopted.

In 1996, *Unique* launched its comprehensive computerised database to collect information about all aspects of how specific rare chromosome disorders affect individual members over a lifetime. In January 1999, *Unique* was awarded a 3 year grant by the National Lottery Charities Board to fund a full-time Development Officer and a part-time Family Support Officer. In April 1999, the group's first website was launched and membership stood at just 1192 families.

In 2003, other short-term grants allowed the group to employ a full-time Information Officer to research and produce family-friendly information guides on specific rare chromosome disorders. At the same time, a part-time Assistant Information Officer was employed to produce information on topics such as behaviour, communication, education and so on. A part-time Finance and Fundraising Officer joined us in 2004.

By early 2013, group membership had risen steeply to over 10,000 families, representing over 14,000 individuals with a rare chromosome disorder in over 90 countries worldwide. With at least 100 new families now joining us each month, the rate of



growth of our membership shows no signs of slowing down! As more sophisticated methods of analysing people's chromosomes and DNA, like microarrays and next generation sequencing, many more previously undiagnosed people will be receiving a diagnosis of a rare genetic or genomic disorder. Consequently we expect our membership to continue to rise rapidly for the foreseeable future. Of necessity, our team has had to grow to keep pace with the huge increase in our workload.

Over these many years, we have worked very hard to raise awareness of *Unique* among families and individuals affected by rare chromosome disorders. We have also been spreading awareness of rare chromosome disorders to professionals and to the general public so that they too have an appreciation of the extraordinary challenges our members face. However, securing grants to pay for this work is becoming much more difficult with fewer funding opportunities available and many more charities competing for the same grants. Please help us with donations and fundraising so that we can continue our essential work.

Unique has adopted and works to an equal opportunities policy and is registered under the Data Protection Act (registration number Z9206140).

the unique team



Unique has a voluntary Trustee Board comprising a majority of parents who, along with other Trustees, use their wide and varied professional expertise to ensure the group is run to the highest standards. The Board supports the group's officers who carry out the day to day frontline work.

Edna Knight MBE – The Group's Founder, Life President and Trustee

“ I helped to establish Unique from the beginning. I have four daughters, two with a duplication of part of the short arm of chromosome 9 - Wendy (17.7.65) and Julie (26.10.71). My youngest daughter Claire (6.8.82) has a balanced insertional translocation like myself, whilst my second daughter Linda has normal chromosomes. Wendy and Julie are doing well after very slow starts. They have reading skills and are able to travel alone on buses locally. Wendy attends a sheltered development centre and goes out to large local companies and colleges for work experience. Julie works with support from the Shaw Trust. I am pleased with their progress so far and they are still progressing and learning to do new things. Their development, skills and achievements have continued to expand well into their 20s, 30s and 40s.

As a Trustee, I keep a watchful eye on the progress of Unique and liaise with the staff team and fellow Trustees, without whom the group could not run. With the employment of Beverly Searle as Chief Executive Officer, a considerable element of the burden of running the group was lifted from me. I am here to help with the smooth running of the group and to encourage others. There are a great many diverse activities within Unique such as coordinating the compilation and dispatch of the thrice-yearly newsletter, collating information for the regular



Claire, Edna, Linda, Wendy and Julie.



Trevor, Beverly and Jenny.

conference and working with many other members on various tasks. Most importantly though I am here both to ensure that the organisation keeps to its own guidelines and to run a group that is both informative and sensitive to the needs of parents. ”

Beverly Searle – Chief Executive Officer

“ I was appointed to the post of Development Officer in April 1999 and in 2003 I was made Development Director. More recently I became Chief Executive Officer. I worked for Unique in a voluntary capacity for some years as Database coordinator and was a member of the management committee from the early 1990’s. I joined the group shortly after the birth of my daughter, Jenny, in February 1990. Jenny had a complete deletion of the short arm of chromosome 18; she was profoundly learning and physically disabled and had complex health needs. Jenny’s elder brother Jonathan has a mild heart defect, although his chromosomes are normal. In 2011, Jonathan qualified as a medical doctor.

Before I had my children, I worked for many years as a research scientist, being awarded the degree of PhD for my research into aspects of the biochemistry and genetics of yeast. What a coincidence then that one of my children should be born with a chromosomal defect! After the children were born, I worked part time as a freelance abstractor of current literature for a pharmacological/medical publishing company.

After Jenny’s birth, I devoted a great deal of my time and energy to promoting the needs of families with disabled children. As one time Vice-Chair of Action for Carers (Surrey) and a founder member of the East Surrey Carer’s Support Association, I have had a lot of experience working with Social Services and Health Authority representatives. I also served for four years as a Non-Executive Director of a NHS Trust for People with Learning Disabilities.

Most enjoyably, though, I have been involved in the running of Unique. My husband Trevor is a computer software specialist and together we developed Unique’s members’ database and the group’s website.

When I first had Jenny, I was very upset and really thought that was the end of any decent life for us. It was difficult at times but I can honestly say that in most ways, my life has changed immeasurably for the better and I have met some wonderful people because of Jenny. As for Jenny, despite her disabilities, she was a delightful young woman and her sweet nature shone through. Sadly we lost her when she was 21 years old but felt very lucky and privileged to have had her in our lives.

I am responsible to the Trustees for the day to day running of Unique and development of our services; I manage our staff team, respond to enquiries from new families and professionals and aim to raise the profile of rare chromosome disorders and the work of Unique.👉

Prisca Middlemiss – Senior Information Officer

“One of my earliest childhood memories is of my father coming home from work and announcing that the number of human chromosomes had at last been correctly counted. A Swede, Albert Levan, and an Indonesian, Joe-Hin Tjio, had overturned the prevailing wisdom that humans, like chimpanzees and gorillas, had 24 pairs of chromosomes. Using improved techniques, as Maj Hultén so charmingly recounts, these scientists had shown that we actually have 23 pairs. As an academic physiologist, my father thought the momentous genetic discoveries of the 1950s would interest his three young children.

He was right, but it wasn't for another thirty years that these facts were to take on a personal significance for my husband Nigel and myself, when our second son Toby was born with a variety of medical problems. Sadly, Toby never recovered from surgery the night after his birth to repair his diaphragmatic hernia. Before he died, blood samples were sent for analysis and within weeks we learned that the underlying cause of his multiple anomalies was a partial trisomy of chromosome 22.

Stepwise investigations then revealed that not only did I carry an 11;22 balanced translocation but my brother Fabian and my sister Ann had exactly the same chromosomal re-arrangement. As my mother had normal chromosomes, the conclusion that the translocation was



Top: Dad
(Professor John
Mills); middle:
Fabian, Prisca,
Ann; bottom:
Sophie.



passed on by my father was inescapable. He was no longer alive to discover this but would, I think, have been intrigued and, given my parents' apparently problem-free reproductive history, mildly surprised.

Amniocentesis in my next pregnancy showed the same balanced 11;22 translocation, so since the birth of our daughter Sophie in 1983 it now spans three generations.

Professionally, I have worked in medical journalism for most of my life, starting out as editor of the then British Diabetic Association's journal *Balance*, and later contributing to a range of medical and consumer publications, as well as writing three child health handbooks.

Working as Unique's Senior Information Officer offers a wonderful opportunity for the personal and professional strands of my life to intertwine. It is very exciting indeed to come on board for the launch of Unique's innovative project to compile and publish information on the rare and, in some cases, very rare chromosome disorders that affect each of us.☺☺

Marion Mitchell – Family Support Officer



Marion, Robert and Steve.

“I joined the group in May 1995, just after my son Robert was diagnosed with an inverted duplication of chromosome 15 at the age of one. In 1996 I became Information Officer for the group and in 1999 Administrative Officer. In June 2003 I became Family Support Officer. I send out all of the new members welcome packs and I manage our social networking groups on facebook. I coordinate our local contacts' around the world and since 1996/7 I have organised/co-organised Unique's past conference weekends. I also research and help write Unique's parents' guides on practical matters. As area representative for West Sussex, I help to raise the profile of Unique in the county.

In 2012 Robert was re-diagnosed with two extra marker chromosomes 15 including partial octasomy (8 copies) of the segment 15q13q14. In 2012 Robert also became an adult and we have been undergoing transition from child to adult services for the past year. In 2013 he is about to

leave his school of 17 years and move into adult daycare services.

Rob has profound learning difficulties, is non-verbal, has epilepsy and eczema.

I am married to Steve and Rob is our only child together. I also have two step children and two step grandchildren.

My working background involved years of retail experience including retail management and customer services.☺☺



Jenny Knight – Finance Officer

“I was appointed to the post of Finance Officer for Unique in July 2011 having been a member of Unique for many years. I have one son who will be 29 this year and twin boys, George and Henry, who will be 18 this year. George possibly has a rare chromosome disorder although we don't have a chromosome disorder diagnosis as yet. He has been diagnosed with Worster Drought Syndrome and has a very severe speech and language disorder. We have recently joined the “Deciphering Developmental Disorders” study which will hopefully provide a further diagnosis for George.☺☺



Jenny with sons Henry and George.

Craig Mitchell – Chief Operating Officer

“My first contact with Unique was in late 2003 when my daughter Ella was 9 months old and diagnosed with a 6p 25 deletion. She was our first born and this was the culmination of a difficult period during which she had suffered infantile spasms (a severe form of epilepsy) and we had spent some time with her in Guy's Hospital in London. Very few of the doctors had seen infantile spasms and after a number of fruitless consultations my wife Gemma and I resorted to videoing the spasms. This was a difficult thing to have to do but it helped in getting a diagnosis and appropriate treatment for her.

After it was diagnosed the doctors were great but knew very little about Ella's rare chromosome disorder and we were referred to a geneticist who in turn told us about Unique. Having trawled the internet and read lots of hard



Craig, Ella and Holly.



to understand and sometimes quite scary medical literature, we found the information from Unique to be both accessible and straightforward. We realised immediately that we had a source of support and information and that there were lots of other families out there struggling to come to terms with a diagnosis but definitely not alone.

Through our membership of Unique we have become very good friends with a family who have a daughter with a completely different chromosome disorder to Ella's. They know and understand only too well the challenges we face and vice versa. I think that's one of the keys with Unique: families who may be facing quite different challenges are able to come together and provide mutual help and support.

Ella now attends a special school near our home in Kent as she has learning difficulties with autism. She wears glasses and has grommets fitted in her ears, has hypermobile joints and some mobility issues as she has a pronated right ankle and very flat feet. She also suffers with a skin condition on her legs called morphoea. Ella has very little speech and is learning to communicate in her own way (using some Makaton signs) although she can become very frustrated and quite angry. Despite these challenges she is an absolute joy, full of life and (usually) very happy.

On Christmas day 2007, Gemma gave birth to Ella's sister Holly (Holly has normal chromosomes) and though this meant some upheaval for Ella, her initial indifference to her sister is now passing and she is learning to share her space. In fact, she often listens to Holly more than to her parents!

I joined Unique in May 2008 as the charity's first Operations Manager and am currently Chief Operating Officer. My role involves supporting the specialist services team, growing the organisation's capacity to meet the needs of an increasing membership and perhaps most importantly, overseeing our fundraising efforts. Since joining I've been amazed at how much is done by such a small team and on a relative shoestring! I am very fortunate to be able to work in an organisation which I

not only believe in strongly but one which was such a help to my own family.☺☺

Sarah Wynn – Information Officer

“For many years I have been working as a medical research scientist. In 1999 I was awarded a PhD in Genetics from Imperial College, the subject of my thesis being Down’s syndrome. I then spent a number of years working as a scientist at the University of Hong Kong. It was while living and working in Hong Kong that I suffered three consecutive miscarriages. Subsequent investigations to try to determine the cause revealed that my husband, Marc, carries a 5;7 balanced translocation.

In my quest for more information I discovered Unique and we became members in the summer of 2004. Meanwhile, we had returned to live in the UK and I took up a new research position at the National Institute of Medical Research. I became pregnant again. After the initial nervousness, the pregnancy progressed well and we decided to undergo chorionic villus sampling (CVS) to determine the baby’s chromosome make-up. The results revealed that Daisy also carries the same balanced chromosomal re-arrangement. We have since had a second daughter, Martha, who has normal chromosomes, and after three more miscarriages a son, Isaac who has also inherited his father’s translocation.

Since 2007 I have been one of Unique’s information officers which involves publishing information guides to rare chromosome disorders, and getting involved with research projects and raising the profile of Unique with researchers and healthcare professionals. I also help Beverly with the many enquiries from new families and professionals.

Maj Hultén – Chief Medical Advisor

“When I was little I lived in a small town in southern Sweden. Every Sunday I saw marches of unusual looking children walking hand in hand in the street outside our house. My mother told me that they lived all together, because their parents had found it difficult to look after them. She also said that sometimes it could happen that

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Sarah and Daisy.

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Maj Hultén.

there was more than one child in a family with similar problems.

I was hooked and years later decided to study Psychology and Education at the University of Stockholm to learn more about what could cause such problems – and how they could be overcome. I took my exams, but was disappointed not finding any real answers to my questions. Genetics I thought then might be a better bet. This also turned out to be frustrating, not least because formalities at the time dictated that courses in Genetics were only open to students who had spent several years studying Zoology and Botany – and who had also passed an entrance exam. Luckily I managed to strike a deal with the Professor to the effect that if against all odds, I would be ranking no 1 in the Genetics Entrance Exam, he would accept me regardless. This was hard work, but it did work.

I found the Genetics course fascinating, yet disappointing, primarily because the curriculum mostly concerned bacteria, fruitflies and plants – and statistics, hardly anything that could explain learning disabilities in children.

In my final year I had to do a special project, taking a couple of months. I was offered a number of projects (17 in total) pushing around and counting different types of fruitflies under a dissecting microscope. I declined them all, and said I should like to look at human chromosomes. This turned out to be a decisive turning point. It was arranged for me to be supervised by a Professor Levan, who had been looking at mouse chromosomes, particularly in tumours. (As it happened this was in the same small town in southern Sweden, where I had grown up).

I was given a project, studying the effects of radiation treatment on mouse tumours...

But, lo and behold, I later found out that work on human chromosomes was actually going on in the same Department! The night before Christmas Eve in 1955 I was offered to peer down the microscope to look at beautiful spreads of human chromosomes. This was the first time human chromosomes could be correctly counted and proper photographs taken.

It is a truism to say that I can remember it as if it was yesterday – the stinging smell of the chromosome stain (Acetic Orcein) blending together with that of Turkish coffee made by the visiting scientist, Joe Hin Tjio, who had produced the chromosome preparations, squashing the cells between two pieces of glass – making his thumbs bright red also. Sitting on a high laboratory stool I was drumming my legs against the bench in excitement, while pointing out to Dr Tjio that it could now be possible to find out if some people with learning disabilities may have chromosome abnormalities such as trisomies, monosomies, translocations, insertions, inversions, rings, duplications and deletions, previously only seen in fruitflies and plants, as if he would not have realised this by himself.

I decided on the spot to study medicine, hoping that Medical Genetics would one day become a discipline, where the study of chromosomes would be very important. This was now more than 40 years ago. I have worked with chromosomes and genetic counselling ever since. One of the challenges I faced was to convince Edna Knight to take me on board as Medical Advisor to the Rare Chromosome Disorder Support Group. I am glad she eventually did – around 15 years ago. My vision is that Unique is renowned not only for the help the group provides to families in the UK and many other countries worldwide but also for the powerful stimulus it has provided for the formation of similar groups in many, many other countries.

I should add that my brother has had a child with a Chromosome Disorder, a deletion of the long arm of chromosome 8. He and my sister-in-law have not had the benefit of a Support Group. My vision is that Unique one day will be renowned not only for the help the Group provides to families in the UK (and some other countries already) but also for the powerful stimulus it has meant for the creation of similar Groups in many, many other countries. As far as I am aware Rare Chromosome Disorders are equally common among all races and all different parts of the world. So, in this respect we are not Unique! I also nourish a dream that never again should a doctor turn around to parents saying – ‘Your child has got a very rare Chromosome Disorder. I am afraid I know





nothing about it!' As I am sure many parents have, I have found this very off putting. It should of course not have happened in the past, and let us hope the mission of Unique will imply this type of ignorance becomes increasingly rare in the future. ☺☺

consequences of rare chromosome disorders

The effects of rare chromosome disorders can be very varied. The vast majority of carriers of balanced rearrangements will have no symptoms but might have problems in reproduction. Where there has been a loss or gain of chromosome material, the symptoms arising might include a combination of physical problems, health problems, learning difficulties and/or challenging behaviour. The combination and severity of effects occurring very much depend upon which parts of which chromosomes are involved. The outcome for the affected children can be quite different. In general, loss of a segment of a chromosome is more serious than the presence of an extra copy of the same segment. Defects of chromosomes 1 to 22 are usually far more serious than those of the sex chromosomes X and Y. It is very important that a child's chromosome disorder is specified in as much detail as possible. The description of a person's chromosome make-up is called their GENOTYPE.

Sometimes children with the same genotype will show similar problems. However, even children with the same genotype can differ in some or even nearly all of their problems. Why should this be? The genotype as seen under a light microscope is called a KARYOTYPE and only gives us the "big" picture. New technologies like array CGH analysis and next generation sequencing (NGS) allow us to look at chromosome and DNA changes at a much greater magnification and often show us that the actual breakpoints in the chromosome might be many genes apart. But even that does not explain all the differences. Even brothers and sisters with the same genotype inherited as the result of a parent's



chromosome rearrangement can still develop differently. There are many other factors besides a person's chromosome disorder that affect how they develop, for example, the unique mixture of genes on their other normal chromosomes, the environment in which they are raised and so forth. Sometimes a particular chromosome disorder will give a similar pattern of problems. If enough children are born with this similar pattern, then this can be called a SYNDROME.

There are also some general characteristics of rare chromosomal disorders that occur in the majority of affected people to varying degrees. For instance, most people with any loss or gain of material from chromosomes 1 to 22 will have some degree of learning disability and developmental delay. This is because there are many genes located across all these chromosomes that code for normal development of the brain. Defects in any one of them could have a harmful effect on normal development.

You might have been dismayed if the doctors and geneticists that you have consulted about your child's chromosome disorder are not able to give you a definite idea of how your child will be affected in the long term, especially if the disorder is particularly rare. You might think that the doctors simply do not want to help or can't be bothered to find out. Nothing could be further from the truth. The point is that, like any other child, your child is UNIQUE and while there might have been other similar chromosome disorders reported in the medical literature, it does not mean to say that your child will develop in the same way. Like any of us, doctors do not have a crystal ball to look into the future. They might only be able to give you an idea of the possible problems that might arise.

You, or your family and friends, might have asked what can be done to "cure" a chromosome disorder in your baby or child. Nothing can be done about

the actual chromosome defect because every single one of the billions of affected cells would have to have the missing chromosome material and all the genes involved added or extra chromosome material taken away and this is not possible yet with today's technology. However, symptoms caused by the chromosome disorder can be treated as they arise and the best environment given in order for the child with the chromosome disorder to reach their full potential.



what can unique do to help?

Having a child with a rare chromosome disorder can be a huge shock and can stir up a whole range of emotions and a great desire to learn more about your child's disorder. All of us who help run the group have been through these experiences and know how you are feeling. Most parents' first reaction, quite understandably, is to "find" another, older child with the same disorder as their child. Whilst this might be possible for some, it still does not mean that the two children will develop in the same way. However, just talking to other parents with a child with a rare chromosomal disorder can be a great relief and can help to alleviate feelings of isolation and "why me?".

As part of its services, *Unique* runs a helpline (+44 (0) 1883 330766) for new and existing families and professionals to find out more information about the group and about specific rare chromosomal disorders. A comprehensive computerised database has been developed detailing the effects of specific rare chromosomal disorders amongst members. The database can be used to link families on the basis of a specific rare chromosomal disorder. Often of more practical benefit, however, is to link families on the basis of problems as they arise, whether these are medical, developmental, behavioural, social, educational and so on. *Unique* also maintains close links with other similar groups around the world, thus increasing the "pool" of possible family contacts. Information about a specific rare chromosomal disorder can be prepared from the *Unique* database whilst not revealing the identity of the families concerned. *Unique* has also developed a

website (www.rarechromo.org) and can be contacted by email (info@rarechromo.org).

Many local groups and contacts have been formed throughout the UK (and even in a few other countries). Families affected by any rare chromosomal disorder can come together locally for general support and friendship and to pass on information about services available in their neighbourhood. *Unique* publishes a regular magazine in which families can write about their experiences and exchange useful information. The group also holds study days and a regular conference in various venues across the UK where families and professionals can meet and discuss latest developments. *Unique* can also act as a go-between to enable families to participate in any research projects relevant to their child's condition.

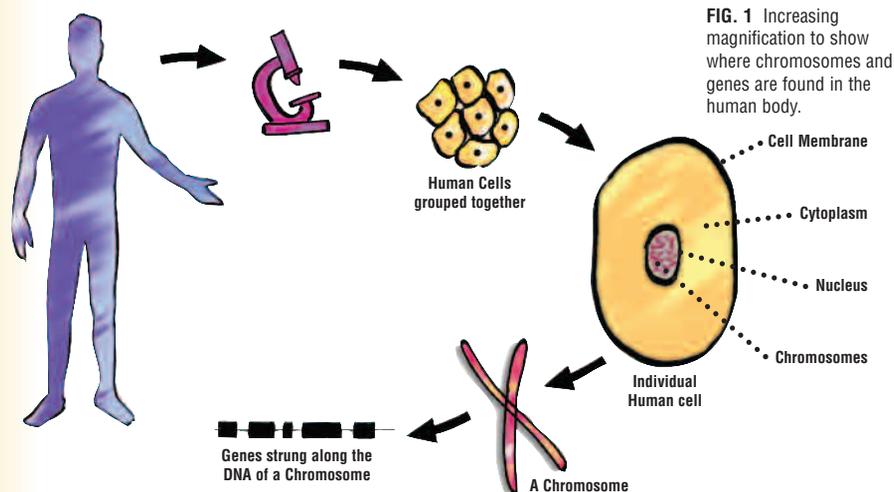
Whatever your specific needs, *Unique* will try to provide you with tailor-made information and help relevant to your child's disorder. Please make use of these services – ***Unique*** is ***YOUR*** group.



all about chromosomes and genes

When parents discover that their child has a rare chromosomal disorder, they often find themselves confronted with a very steep learning curve. Any information learnt about genetics in biology classes at school may be a distant memory. Here we will try to provide you with the basic facts about chromosomes and the different types of rare chromosome disorders. If you find the information a bit complicated, please don't be put off but do ask if you aren't sure what anything means.

Cells, Chromosomes, DNA and Genes



The human body is made up of billions of individual CELLS. With the exception of the red blood cells, each of these cells contains a structure called the NUCLEUS, which is held within a thick fluid called the CYTOPLASM. Inside the nucleus are found the CHROMOSOMES, which contain the GENES. Genes

are “strung” along the chromosomes, a bit like beads along a necklace. Genes are the instructions that tell the body how to develop and work properly.

Apart from the mother’s EGG cells or the father’s SPERM cells, every cell in the human body normally contains 23 PAIRS of chromosomes, making 46 chromosomes in total in each cell. This number of chromosomes is known as the DIPLOID number. The Human Genome Project has shown there to be about 30,000 genes in every cell. These genes are spread unevenly across the chromosomes, some chromosomes having many more genes than other chromosomes and some parts of each chromosome holding more genes than other parts. Of the 23 pairs of chromosomes in each of these cells, one member of each pair is normally inherited from the father and the other member is normally inherited from the mother. Members of each pair of chromosomes are called HOMOLOGOUS chromosomes. The first 22 pairs of chromosomes are called the AUTOSOMES and are numbered from 1 to 22 according to their length, starting with number 1 as the longest. The chromosomes in the 23rd pair are called the SEX CHROMOSOMES. Sex chromosomes are labelled X or Y. Males normally have one copy of the X chromosome and one copy of the Y chromosome in each cell; it is the Y chromosome that determines “maleness”. Females, on the other hand, normally have two copies of the X chromosome but no Y chromosome.

The number of chromosomes in the egg or sperm is different from that in other body cells. The mother’s eggs each contain only 23 chromosomes (the HAPLOID number), made up of one copy of each autosomal chromosome (1 to 22) along with one copy of the X chromosome. The sperm from the father also contain 23 chromosomes, again made up of one copy of each autosomal chromosome but also either one copy of the X chromosome or one copy of the Y chromosome. So it is the father’s sperm that



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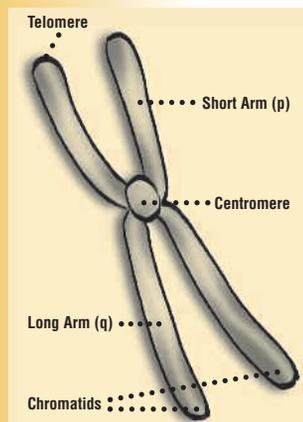


FIG. 2 The structure of a chromosome.



FIG. 3 The DNA double helix.

determines whether a child will be a boy (XY) or a girl (XX).

Under the microscope, chromosomes look like long, thread-like bodies. They have a SHORT ARM (labelled “p”, which stands for petit, the French word for small) and a LONG ARM (labelled “q”). Linking the two arms is a narrower region called the CENTROMERE. The ends of the chromosomes are called the TELOMERES. The telomeres stop the chromosome from unravelling, a bit like the plastic tips of a shoe-lace.

Chromosomes are so named because they are able to take up certain dyes or stains. “Chromos” is the Greek word for coloured and “soma” is the Greek word for “body”. Different stains give each chromosome a particular pattern of light and dark bands. It is the location of the centromere and the specific banding pattern of a chromosome that allows it to be identified.

Chromosomes are built up of a chemical called DNA (DeoxyriboNucleic Acid) and some proteins. Genes are composed of small stretches of some of the DNA in chromosomes.

The DNA is held in a twisted shape called a DOUBLE HELIX. This double helix is tightly coiled but these coils are then coiled again and then yet again, a bit like if you twist a shoe-lace until it is coiled tightly into a ball. If you uncoiled all the DNA in just one diploid cell until it was pulled out to its fullest extent, it would measure around two metres! If all the DNA from the billions of cells in a mature adult human were stretched out end to end, it could be wrapped around the Equator up to 5 million times!

DNA has two very important jobs. It works very much like an assembly line in a factory. It acts as the TEMPLATE or blueprint for assembly of all the proteins in our bodies. When most people think of protein, they tend to think of it as an important part of the food they eat or as a major component of the

structure of their muscles. While some proteins are indeed very important as part of the structure of our bodies, others have essential parts to play in controlling how our bodies work properly. Some proteins act as enzymes, which make the chemical reactions in our bodies happen more easily and quickly, while others act as hormones, which help control our body's proper functioning and development. Some proteins even help control the production of other proteins by different genes. The process of protein production is a very complex one and yet, most of the time, the correct proteins are made to keep our bodies working properly and healthily. With rare chromosomal disorders, though, many genes might be missing or extra and so essential proteins are either not made at all or are made in too many copies or are made incorrectly or at the wrong time. The second important function of DNA is to pass on the genetic blueprint from old cells to new cells and from parent to child. An accurate copy of the DNA in each chromosome has to be made every time a new cell is formed.

Chromosome and DNA Analysis

Specialist scientists called cytogeneticists examine a person's chromosomes or DNA for defects. Usually, they will analyse the chromosomes or DNA in the white cells (lymphocytes) in a person's blood. They can also analyse the chromosomes or DNA found in the cells of other body tissues like bone marrow or skin or they might analyse the cells from chorionic villus or amniotic fluid samples to see if a fetus is carrying an abnormality. The cell samples have first to be grown up under special laboratory conditions and this can be very time-consuming, especially if chorionic villus or amniocentesis samples are to be analysed. This is one reason why it can take several weeks for the results of a chromosome analysis to be reported.

Cytogeneticists will use special chemicals to stop the



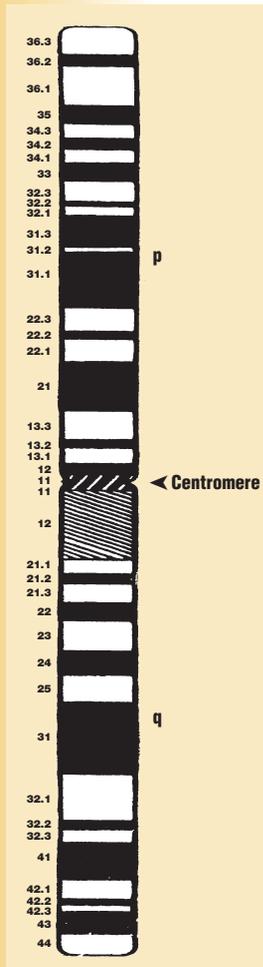


Fig. 4 Ideogram of G-Banded Chromosome 1.

Fig. 5 FISH analysis using two DNA probes for chromosome 22. In green is the control probe and in red is the TUPLE probe which it can be seen is present on one copy of chromosome 22 but missing (deleted) from the second chromosome 22.

cells they are examining at an appropriate stage when the chromosomes are at their most compact. At this stage, called METAPHASE, the chromosomes can be stained with different dyes. The stain used most often is called GIEMSA in a technique producing G-BANDED chromosomes.

Different stains give the chromosomes a characteristic pattern of light and dark bands which helps with their identification. Sometimes the chromosomes are analysed when they are a little less compact so that more bands can be seen and smaller extra or missing pieces of DNA can be identified. This is called High Resolution Analysis. Diagrams of chromosomes showing these banding patterns are called IDEOGRAMS (see Fig 4). Other newer analytical techniques have been developed which are used in addition or as an alternative to these staining methods. These newer techniques include, for example, Fluorescence In Situ Hybridisation (FISH) and microarray comparative genomic hybridisation (array-CGH).

FISH

With FISH, known segments of DNA tagged with fluorescent dyes (so called DNA 'probes') are mixed with specially pre-treated preparations from a tissue sample (most often chromosome preparations from blood samples). These specific DNA probes bind to ("paint") small parts of a chromosome in different



Courtesy of the West Midlands Regional Genetics Laboratory

fluorescent colours which can then be visualised under a special fluorescent microscope. In this way it is possible to determine the number of copies of small sections of chromosomes. This technique is useful if it is known or suspected which of the 23 chromosomes might be involved. If, however, it is not known (or suspected) which chromosome might be involved array-CGH might be used.

Microarray comparative genomic hybridisation (array-CGH)

With array-CGH analysis, DNA is usually extracted from a blood sample. This technique utilises a microarray which is, in simple terms, a glass slide on which there are thousands of 'spots' of a reference (control) DNA sample. The control sample is from a person who is known to have two complete copies of each chromosome (as is usual). The person of interest's DNA is compared with the reference DNA. An analysis of the ratio of the two sets of DNA can determine whether there is the correct amount of DNA, too much (a duplication) or too little (a deletion). This technique is extremely sensitive and therefore much smaller gains or losses of DNA (called microdeletions or microduplications) throughout the entire human genome (ie across all the chromosomes) can be detected than was possible with karyotyping. Unique has published more detailed information guides on analytical techniques and these are available from our website www.rarechromo.org.

As we have already mentioned, a person's chromosomal make-up is called their KARYOTYPE. Obviously, it would be impractical always to have to show a photograph of someone's chromosomes in order to describe any chromosomal disorder they might have. As a consequence, scientists have devised a standardized code to describe a person's karyotype. This system is called the International System for Human Cytogenetic Nomenclature



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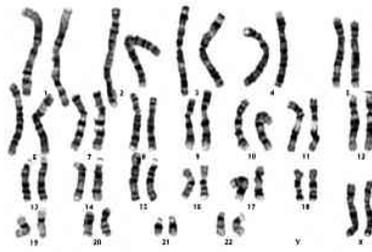


Fig. 6 Normal Female Karyotype.



Fig. 7 Normal Male Karyotype.

karyotype codes are written so that the number of chromosomes in a person's cells come first, followed by their sex chromosome make-up and then by a description of any chromosomal disorder. Using this method, a normal male karyotype would be described as 46,XY and a normal female karyotype as 46,XX.

Any breakpoints in chromosomes are described by a standardised numbering system based on the banding patterns produced in G-banded chromosomes. The bands allow the chromosomes to be mapped into REGIONS, which in turn are divided into BANDS and then into SUB-BANDS. This is a bit like being able to identify a house along a road if you know the house number. With the ISCN numbering system, the higher the number of the breakpoint, the further away from the centromere it is located. To help you understand this system more clearly, take a look at some examples of karyotype descriptions.

(ISCN). The most recent version was published in 2013 and it now includes nomenclature for molecular cytogenetic techniques such as FISH and microarrays. This means that anyone understanding the code will have a fairly precise description of a person's chromosomal disorder.

In general, under the ISCN convention,

46,XX,del(8)(p23.1pter)

This karyotype tells us that this person has 46 chromosomes in each of their cells. The person has two X chromosomes and so is a female. The "del" stands for deletion and so the female has a deletion of part of chromosome 8. The chromosome has broken in the short arm ("p") at region 2, band 3, sub-band 1 and the rest of the short arm up to the terminus or end (pter) is missing. So band 8p23.1 is the BREAKPOINT in this deletion.

47,XY,+9/46,XY

This describes a male (X and Y chromosomes present) with 47 chromosomes in one cell line, the extra chromosome being a complete copy of chromosome 9, with a second cell line with a normal chromosomal make-up. This is what we would call Trisomy 9 Mosaic.

46,XX,r(22)

This describes a female with 46 chromosomes, one copy of chromosome 22 being a ring chromosome. There is no indication given of the breakpoints.

46,XY,t(2;5)(p22;p15.1)

This describes a male with 46 chromosomes and a balanced reciprocal translocation between chromosomes 2 and 5 with breakpoints at bands 2p22 and 5p15.1. The segments 2p22 to 2pter and 5p15.1 to 5pter have swapped places with each other but no chromosomal material has been lost or gained.

46,XY,der(5)t(2;5)(p22;p15.1) mat

This describes a male with 46 chromosomes and an unbalanced translocation involving chromosomes 2 and 5. One chromosome 5 is a derivative (der) chromosome with loss of part of the short arm from band 5p15.1 to 5pter. An extra piece of chromosome 2 from 2p22 to 2pter has been attached to the derivative chromosome at 5p15.1. This means that the person with this unbalanced translocation has a deletion of part of chromosome 5 combined with a duplication of part of chromosome 2. The translocation has arisen as a result of a balanced translocation in the mother (mat).



Instead of, or in addition, to a karyotype, you may be given the results of molecular analysis such as FISH or a microarray.

Results of a FISH analysis might look something like this:

46,XY.ish del(9)(q34.3)(D9S2168-)dn

This means:

46	The total number of chromosomes in your child's cells
XY	The two sex chromosomes, XY for males; XX for females
.ish	The analysis was by FISH
del	A deletion, or material is missing
(9)	The deletion is from chromosome 9
(q34.3)	The chromosome has broken at band 9q34.3, indicating a small deletion of the end of the chromosome just short of the 'telomere'
(D9S2168-)	A marker or probe whose position on the human genome is known, in this case marker D9S2168, is missing
dn	dn stands for de novo The parents' chromosomes have been checked and no rearrangement found involving 9q34.3

With microarray analysis breakpoints at either end of a deletion or duplication are denoted either by the name of a DNA “clone” or by a base pair coordinate. A base pair is simply one of the “rungs” on the ladder of the double helix of DNA (Fig. 8). The results are likely to read something like this:

arr [hg19] 16p11.2(29673954-30198600)x1

This means:

arr	The analysis was by array-CGH
[hg19]	Human Genome build 19. This is the reference DNA sequence that the base pair numbers refer to. As more information about the human genome is found, new “builds” of the genome are made and the base pair numbers may be adjusted
16p11.2	A change was found in band 16p11.2
(29673954-30198600)x1	The first base pair shown to be missing is number 29673954 The last base pair shown to be missing is 30198600 The microdeletion is 524,646 base pairs in size
x1	means is only one copy of these base pairs, not two – one on each chromosome 16 – as you would normally expect

bp	1 base pair
1kb	1,000 base pairs
1Mb	1,000,000 base pairs

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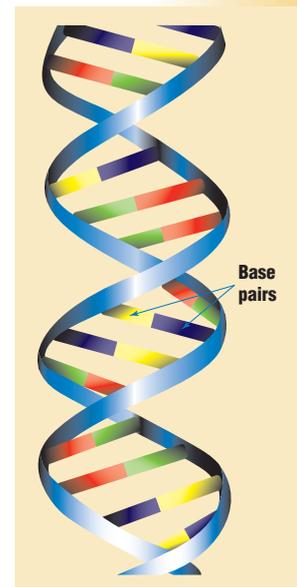


Fig. 8 Two strands of DNA are held together in the shape of a double helix by the bonds between base pairs.



You might already have been your child's karyotype or the results of molecular analysis such as FISH or microarray and would like to work out exactly what the code means. If you do not know your child's results, ask your doctor or geneticist for them, preferably with a copy of the original laboratory report(s), so that you have a correct description of your child's chromosomal disorder. Here is a list of the more common symbols used in karyotype descriptions and molecular analysis results.

Symbols used in karyotypes and molecular analysis results

Symbol	Description
add	Additional material of unknown origin
arr	Microarray
arrow (->)	From - to
Brackets, square ([])	Surround number of cells
cen	Centromere
cgh	Comparative genomic hybridisation
single colon (:)	Chromosomal break
double colon (::)	Chromosomal break and reunion
comma (,)	Separates chromosome numbers, sex chromosomes and chromosome abnormalities
decimal point (.)	Denotes sub-bands
del	Deletion
de novo	Designates a chromosomal abnormality which has not been inherited
der	Derivative chromosome
dic	Dicentric
dup	Duplication
h	Heterochromatin
hg	Human genome build

i	Isochromosome
idic	Isodicentric chromosome
ins	Insertion
inv	Inversion
ish	In situ hybridisation
mar	Marker chromosome (extra chromosome of unknown origin)
mat	Maternal origin
minus sign (-)	Loss
MLPA	Multiple ligation-dependent probe amplification
mos	Mosaic
multiplication sign (x)	Multiple copies of rearranged chromosomes or number of copies of a chromosomal region
p	Short arm of chromosome
parentheses ()	Surround structurally altered chromosomes and breakpoints
pat	Paternal origin
period (.)	Separates various analytical techniques
plus sign (+)	Gain
psu	Pseudo
q	Long arm of chromosome
question mark (?)	Questionable identification of a chromosome or chromosome structure
r	Ring chromosome
rcp	Reciprocal
rea	Rearrangement
rec	Recombinant chromosome
rob	Robertsonian translocation
s	Satellite



semicolon (;)	Separates altered chromosomes and breakpoints in structural rearrangements involving more than one chromosome
slant line (/)	Separates cell lines (used in mosaic karyotypes)
subtel	Subtelomeric region
t	Translocation
tel	Telomere
ter	Terminal (end of chromosome)
trp	Triplication
upd	Uniparental disomy
var	Variant or variable region
wcp	Whole chromosome paint

rare chromosome disorders

Some changes or mutations in chromosomes are so small they only affect the composition of the DNA within a single gene and these are known as point mutations. However, when changes in chromosomes affect whole copies of one or more genes, they are called chromosome aberrations or disorders. Such chromosome disorders can be classified into two main types, NUMERICAL DISORDERS and STRUCTURAL DISORDERS. If these disorders arise during the formation of the egg or the sperm cells, then the disorder would be passed on to every cell in the body of a child produced. If the disorder arises in one of the new cells produced soon after the egg has been fertilized by the sperm, then only a proportion of the child's cells will be affected and this is called MOSAICISM.

Unique publishes information guides on many different individual chromosome disorders and these are freely available from our website or on request. For rarer chromosome disorders not covered by the guides, *Unique* might hold information in the offline database. Please contact us with your information requests.

NUMERICAL DISORDERS

If cells carry complete extra sets of chromosomes, this is known as POLYPLOIDY. When there is one extra set, to give 69 chromosomes in total, this is called TRIPLOIDY.

If only some of the body's cells carry the extra set of chromosomes, then this is known as Triploid Mosaicism, or Diploid Triploid Mosaicism or even Mixoploidy.

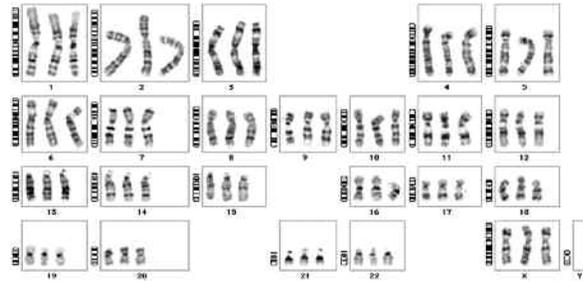


Fig. 9 Ideogram and Triploid Karyotype.

When individual whole chromosomes are missing or extra, this is called ANEUPLOIDY. This can happen with any of the autosomal chromosomes (1 to 22) or the sex chromosomes (X and Y).

If one extra complete chromosome is present, this is known as TRISOMY and the number of chromosomes in each affected cell would be 47. Probably the most well-known example of Trisomy is Down Syndrome (Trisomy 21).

Two extra complete chromosomes would be called TETRASOMY and the number of chromosomes would be 48. If a complete chromosome is missing, this is known as MONOSOMY and the number of chromosomes in each cell would be 45.

STRUCTURAL DISORDERS

Structural disorders occur because of breakages in a chromosome. They can occur spontaneously (this is called DE NOVO) or they can be inherited from a parent. Structural disorders include various types of translocation, deletions, ring chromosomes, duplications, inversions and isochromosomes.

Translocations

A translocation happens when DNA is transferred from one non-homologous chromosome to another. They include reciprocal translocations, Robertsonian translocations and insertional translocations. Translocations can be balanced or unbalanced.



Fig.10 Karyotype showing a single extra chromosome (T21).

Balanced Reciprocal Translocations and Unbalanced Translocations

Balanced reciprocal translocations as a whole are thought to occur at a rate of about 1 in 500 in the general population. Balanced reciprocal translocations happen when breaks occur in two or more different chromosomes and the resulting fragments of DNA swap places. No chromosomal material has been lost or gained and so the vast majority of carriers of a balanced reciprocal translocation do not have any symptoms. There can be rare exceptions to this. Symptoms can occur occasionally when children are born with *de novo* balanced reciprocal translocations, especially when more than two different chromosomes are involved. This is thought to be due, at least in part, to disruption of important genes at the chromosome breakpoints. However, if the child carries the same balanced reciprocal translocation as their symptomless parent, then they should also not experience symptoms caused by the translocation. The problems with balanced reciprocal translocations arise because carriers are at risk of producing offspring with part of one chromosome missing and part of another extra. Such translocations are unbalanced and may lead to miscarriage or the birth of children with symptoms including learning difficulties and physical disabilities. Balanced reciprocal translocations tend to be unique to individual families and so it is very important that families consult a genetic counsellor so that the specific risks of miscarriage and bearing children with disabilities can be discussed.

Robertsonian Translocations

Robertsonian translocations occur when the short arm of certain chromosomes (chromosomes 13, 14, 15, 21 or 22) are lost and the remaining long arms fuse together. Loss of the short arms of these

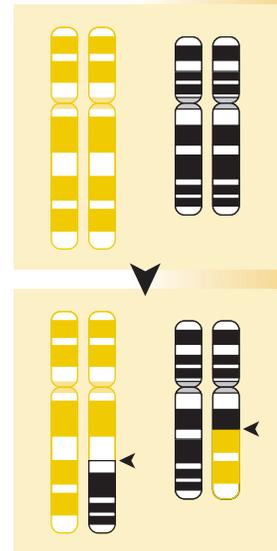
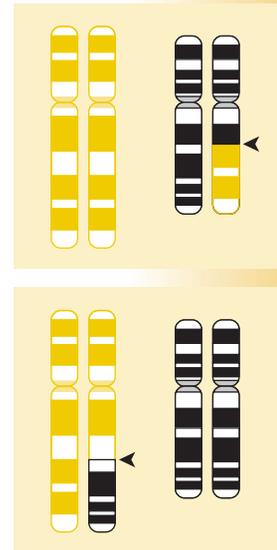


FIG. 11 Ideogram showing a balanced reciprocal translocation (above) and two possible unbalanced translocations that can arise in the offspring (below).



▶ denotes breakpoints

chromosomes should not cause any symptoms. A person with a Robertsonian translocation has a total chromosome number of 45. Robertsonian translocations are relatively common in the general population (about 1 in 1000), the most frequent being fusion of the long arms of chromosomes 13 and 14. The significance of a Robertsonian Translocation is the risk of miscarriage or of producing children with an unbalanced chromosome make-up.

Insertions

Insertions occur when a segment of one chromosome is inserted into a gap in another chromosome. If someone carries a balanced insertional rearrangement, they should not have any symptoms (unless a critical gene is disrupted at the breakpoints) but they are at risk of producing a child with either a deletion or a duplication of chromosomal material but not both disorders.



FIG 12 The Knight family with ideograms of their chromosomes 9 and 20. Edna (left) has a balanced insertion of part of chromosome 9 in chromosome 20, as has daughter Claire (not shown). Julie and Wendy (centre) have partial duplications of the short arm of chromosome 9, while Linda (right) has normal chromosomes.

Deletions

A **DELETION** involves loss of a part (a segment) of a chromosome and is sometimes known as a **PARTIAL MONOSOMY**. Deletions can occur in any part of any chromosome. If the segment is lost from near to the

centromere, this is called a PROXIMAL DELETION. If the segment is lost from nearer to the end of the chromosome (the telomere), then the deletion is called a DISTAL DELETION. If there is just one break in the chromosome, then the deletion is called a TERMINAL DELETION. (Terminal just refers to the end of the chromosome and does not infer that the deletion will be lethal to the child.) If there are two breaks in the arm of the chromosome with the intervening segment being lost and the remaining parts of the chromosome joining up, then this is called an INTERSTITIAL DELETION. Some deletions are so small they cannot be seen down a light microscope and are called MICRODELETIONS.

Rings

A RING chromosome usually forms when the ends of both arms of the same chromosome are deleted. The remaining broken ends of the chromosome are “sticky” and join together to make a ring shape. Usually, it is the missing DNA that is significant. In effect, the person with a ring chromosome has a terminal deletion of both the short and the long arms of the chromosome. However, if the ring chromosome is present as an extra (or SUPERNUMERARY) chromosome, then it is the chromosomal material that has NOT been deleted that is significant. The material in the extra ring chromosome has effectively been duplicated. Some geneticists believe that there can also be a general effect caused by any ring chromosome, poor growth and developmental delay being the outcome.

Duplications

A DUPLICATION occurs when an extra copy of a segment of a chromosome is present. A duplication is sometimes known as a PARTIAL TRISOMY. If a person has two extra copies of a chromosomal segment, then this is known as a TRIPLICATION or a PARTIAL TETRASOMY. Some duplications are so

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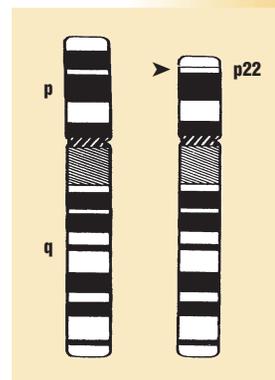


FIG 13 Ideogram showing a partial deletion of the short arm of chromosome 9 (right) along with its normal homologous chromosome (left).

▶ denotes breakpoint

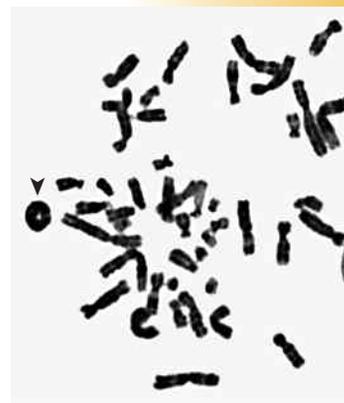


FIG 14 Ring Chromosome.

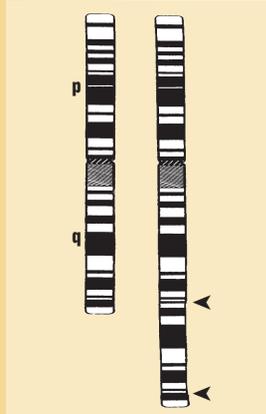


FIG 15 Ideogram showing partial duplication of the long arm of chromosome 1 (right) along with its normal homologous chromosome (left).
▶ denotes breakpoint

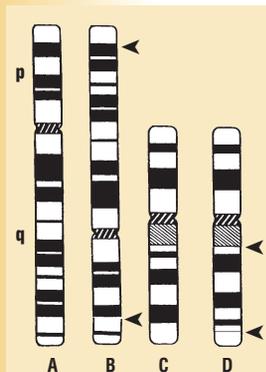


FIG 16 Ideogram of a pericentric inversion of chromosome 10 (B) with its normal homologous chromosome (A) and of a paracentric inversion of chromosome 16 (D) and its normal homologous chromosome (C). The inverted segments lie between the black arrows.

small they cannot be seen down a light microscope and are called **MICRODUPLICATIONS**.

Inversions

Inversions occur when there are two breaks in a single chromosome. The segment between the breakpoints turns through 180 degrees and reinserts itself into the “gap” left in the chromosome. If both breaks occur in the same arm of the chromosome, this is called a **PARACENTRIC INVERSION**. If one break occurs in the short arm and the other in the long arm of the chromosome, then this is called a **PERICENTRIC INVERSION**. Usually, inversions do not cause problems in the carrier (unless important genes are disrupted) but there is a risk of producing sperm or eggs with unbalanced chromosomes.

Carriers of paracentric inversions very rarely give birth to children with abnormalities. On the other hand, carriers of pericentric inversions more frequently give birth to children with abnormalities. These children will have a partial duplication of one arm of the affected chromosome along with a partial deletion of the end of the other arm of that chromosome or vice versa. The closer the breakpoints are to the ends (telomeres) of the chromosomes, the greater the chance of the child surviving to birth. This is because the chromosome segments deleted and duplicated will be smaller.

Isochromosomes and sSMCs

Sometimes people carry an extra or supernumerary chromosome made up of parts of one or more chromosomes. They will effectively carry a duplication or triplication of the material forming this extra chromosome. If the origin of the extra chromosome is unknown, it is sometimes referred to as a small supernumerary marker chromosome (sSMC) or a marker chromosome. If the extra chromosome is made up of two copies of the same segment of a chromosome, this is called an

isochromosome. When these extra chromosomes carry two copies of the same centromere, they are called isodentric chromosomes.

Uniparental disomy (UPD)

In uniparental disomy (UPD) both chromosomes in one of the 23 pairs have come from the same parent instead of one coming from the father and the other from the mother. The result of UPD is a double presence of genes from one parent and no input from the other parent. When all the genes come from the mother, this is termed maternal UPD, sometimes shortened to mUPD or UPDmat. When all the genes come from the father, this is termed paternal UPD, sometimes shortened to pUPD or UPDpat. For most chromosomes having all the genes from one parent does not matter, but for certain chromosomes (e.g. chromosome 14) or parts of them it does make a difference.

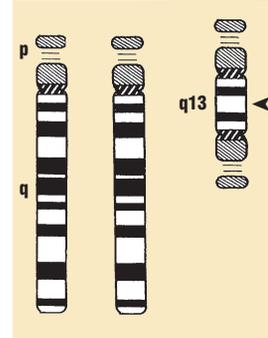


FIG. 17 Ideogram of Isodentric (idic) 15 (right) with two copies of part of a chromosome and two normal chromosomes 15 (left).

▶ denotes breakpoint

further reading and information

If you would like to read more detailed books about medical genetics (aimed at the medical or cytogenetics student or qualified doctor), find out what those incomprehensible medical and cytogenetic terms mean, keep up to date with papers published about specific rare chromosomal disorders or consult cytogenetic databases, the following may be helpful.

- “*Essential Medical Genetics*”, 6th Edition, by Edward S Tobias, Michael Connor & Malcolm FergusonSmith, John Wiley and Sons Ltd Wiley-Blackwell, ISBN10: 1405169745 ISBN13: 9781405169745
- “*Emery’s Elements of Medical Genetics*”, 14th Edition, by Peter Turnpenny & Sian Ellard, Churchill Livingstone, ISBN 9780702040436
- “*Oxford Desk Reference: Clinical Genetics*” by Helen Firth and Jane Hurst with Judith Hall (Ed), Oxford University Press, ISBN 0-19-262896-1
- “*ISCN 2013: An International System for Human Cytogenetic Nomenclature (2013)*”, Ed. Lisa G. Shaffer, Jean McGowan-Jordan & Michael Schmid, Karger, Basel, ISBN 978-3-318-02253-7
- “*Dorland’s Illustrated Medical Dictionary*”, Edition 32, Saunders, ISBN 9781416062578
- The Online Mendelian Inheritance in Man (OMIM) website www.ncbi.nlm.nih.gov/Omim
- The Medline website www.ncbi.nlm.nih.gov/PubMed (lists abstracts of papers published about medical conditions, including specific rare chromosomal disorders – updated regularly)
- Decipher database <https://decipher.sanger.ac.uk>
- Ecaruca database www.ecaruca.net

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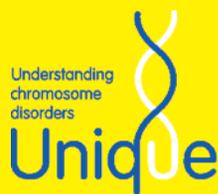
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