



Understanding Chromosome & Gene Disorders

Planning your next child

(for families with rare chromosome
or gene disorders)



rarechromo.org

This leaflet is designed to help families affected by rare chromosome or gene disorders who are planning to have more children. It contains information about what to consider, genetic testing and web pages that families can access for further information. The majority of this information is based on what is currently (2018) available via the NHS (national health service) in the UK and may vary in different countries.

Planning your next child

Deciding whether to have more children can be difficult even for those families who have not been affected by a genetic condition. *Unique* families have the additional challenge of having to consider the implications of having another child on their current family set up, especially if they already have children who require increased levels of care. Couples who have a child with a genetic condition often worry about the risk of their future children being similarly affected. Some couples would like to ensure that their next child is unaffected by the same condition or that they get an early diagnosis and time to prepare.

What is the risk of having another affected child?

As every child is unique it is impossible to provide a one-size-fits-all estimate for risk of recurrence. For many *Unique* children, the genetic change will have occurred in them for the first time (*de novo*) and therefore the risk for future siblings is extremely small. However, there are a proportion of families who are at risk of having more affected children. This is particularly the case in the following scenarios:

■ Where a parent carries a deletion or duplication

Many people have small deletions and/or duplications of genetic material from one or more of their chromosomes. Such chromosome alterations are commonly referred to as 'copy number variants' (CNVs), since the number of copies of specific pieces of DNA has been altered. The size of the CNV, as well as the function of the genes contained within the region, will determine the effect on the individual. Chromosome duplications and deletions can have extremely variable effects even within the same family. Other genes and individual personalities help to determine personal development, needs and achievements. If a parent is found to have the same CNV as one of their children, the possibility of having another child with this duplication or deletion is 50% in each pregnancy. If neither parent is found to have this chromosomal change, it is extremely unlikely they will have another child with the same change. Larger deletions and duplications may occur when part of a chromosome has moved to another chromosome or been turned 'upside down' (unbalanced translocations or inversions).

■ Where a parent carries a balanced translocation or inversion

Some chromosomal changes occur because one parent is an unaffected carrier of a balanced translocation (reciprocal or insertional) or inversion. This means that the parent has a change in the structure of one or more of their chromosomes but, because they have all the required genetic information, this does not cause them any problems. The problem arises during reproduction when the chromosome with the structural change does not behave as it should.

There are three potential outcomes for balanced translocation or inversion carriers who wish to have children:

- Infertility and/or multiple miscarriages
- Having a healthy child who may carry the same balanced translocation or inversion as the parent, or may have unaffected chromosomes
- Having a child who has inherited too much or too little of the genetic material from the regions of the translocation or inversion leading to variable health problems and/or learning difficulties

Structural changes in chromosomes are often unique to a family, as are the risks of having further affected children. Please see the *Unique* guides to balanced translocations or inversions for further information and speak with your genetic counsellor to discuss your specific risks.

■ **Where one parent carries an autosomal (numbered chromosome) dominant single-gene disorder**

When one parent is affected (possibly subtly or unknowingly) by a single-gene disorder (a 'spelling mistake'/mutation within a gene) that is passed on in a dominant manner (only one altered copy of the gene is needed to have an affect), the risk of having another child with the same condition can be as high as 1 in 2. The affect on each child can be extremely variable.

■ **Where both parents carry an autosomal (numbered chromosome) recessive single-gene disorder**

Where both parents are unaffected carriers of a genetic 'spelling mistake' in the same gene, the child risks inheriting both faulty copies and being affected (recessive inheritance), the risks of having an affected child is 1 in 4. (*Unique* is not currently able to provide support for families with 'autosomal recessive' disorders).

■ **Where a mother carries a genetic change on an X chromosome**

A mother usually has two X chromosomes and can carry a genetic change in one of them. In such situations, the risk of having a boy affected by the condition is 1 in 2. This is because boys usually only have one X chromosome (and a Y chromosome) and can inherit either the unaffected or affected chromosome from their mother. The risk of having a girl who carries the genetic change is also 1 in 2. Girls usually have two X chromosomes and in this situation are commonly described as carriers since they have another functional X chromosome. However, girls can show signs of X-linked disorders in certain conditions and under certain circumstances.

■ **Where a mother carries a genetic change in her mitochondria**

Mitochondrial disorders can be inherited in a number of different ways. Where the mother has a change in the DNA within her mitochondria, she risks passing this on to all her children but with hugely varying degrees of severity. (*Unique* is not able to provide support for families with mitochondrial disorders).

It is important to understand which of the above categories you fit into. This will often involve testing of both parents for the genetic change that has been found in their children. If you are unsure which situation applies to your family it is important to get in touch with your genetics team who can arrange to talk you through the risks specific to your situation. Clinical geneticists and genetics counsellors are trained to discuss the risks of recurrence specific to a family. Very rarely will a genetics clinician ever say that the risk of recurrence is zero. This is for a number of reasons, but most importantly because of a phenomenon called [germline mosaicism](#).

What is germline mosaicism?

Germline mosaicism describes the situation whereby a proportion of an individual's egg or sperm-producing cells have a genetic change which is not found in all other cells of their body (i.e. the individual shows no signs of the condition). Where such a situation exists it can mean there is a chance of them having another affected child, despite both parents testing negative for the genetic change found in their child (following a DNA test from a blood sample or cheek swab). The risk of germline mosaicism is very small. It is more frequently seen in some conditions than others (the reason for this is not fully understood). It is not currently possible to test a couple's egg and sperm cells for evidence of germline mosaicism so genetic professionals provide an 'empirical risk' of the condition based on what has been observed in other families. The risk is usually quoted to be in the region of 1-5% (but can be higher for some conditions).

How do I access reproductive genetic counselling?

Many individuals in the *Unique* group were given their diagnosis some time ago. As genetic technology advances so rapidly, if you are now thinking of extending your family, it would be worthwhile re-contacting your genetics team. If you have contact details for your genetics service, you should feel free to contact them directly and explain that you would like to discuss reproductive planning. They may be able to offer you an appointment. It is also important to discuss thoughts about growing your family with your GP. Genetics is not the only consideration for family planning and your GP will be a wealth of information about healthy pre-pregnancy life style measures, supplementation and locally available resources.

You will need to approach your GP for a referral to a genetics specialist to discuss reproductive risks under the following circumstances:

- You have moved to a new city since your last contact with your genetics team
- You are not known to a genetics service (the diagnosis was made by a doctor in a different speciality, such as a paediatrician)
- You are in the extended family of an affected individual and want to discuss your risk of having an affected child
- You are, for any reason, unable to make direct contact with the genetics team previously involved in your care

Ideally clinical geneticists and genetics counsellors like to see couples who are planning a pregnancy but have not yet conceived. This of course is not always possible and should you find yourself already pregnant then most genetics centres can arrange to see you as soon as possible.

What does a prenatal genetics consultation involve?

As with all genetics consultations you will be offered an initial appointment to discuss the genetic change in your family and your specific risk of recurrence. Some time is then spent discussing your options and how you would like to proceed.

Every parent is different in how they feel about a pregnancy. Genetic specialists see people from all walks of life and religious persuasions and have learnt that they can never predict, and certainly will not assume, that you will want to take a particular course of action.

The aim of a prenatal genetics consultation is to:

- Discuss the genetic change in your family and help you to understand it fully
- Make an estimation of the risk of recurrence (this may involve more testing)
- Discuss how you would feel about having another affected child
- Think about ways, if any, the risk of you having another affected child can be reduced
- Explain the options available with regards to making a diagnosis in a pregnancy
- Consider how you would like to proceed should you become pregnant with a child who has inherited the same genetic change

Methods to prevent passing on a genetic condition:

This applies to those couples who are not yet pregnant and where the genetic cause of the condition in a child and/or parent is firmly established.

■ **Pre-implantation Genetic Diagnosis (PGD)**

PGD is a technique employed to help families affected by a serious genetic problem to avoid passing it on. The Human Fertility and Embryology Association (HFEA) provides licenses to certain clinics to perform PGD for specific conditions which are considered serious enough to warrant this treatment. To date, over 250 conditions have been licensed by the HFEA for PGD but this is always increasing and individual applications for rare disorders can be made.

The process of PGD is complicated and varies by clinic but broadly speaking involves the following:

- A couple undergo *In-Vitro* Fertilisation (IVF). This involves the female partner taking hormones to stimulate her ovaries to produce multiple eggs simultaneously. These are then 'harvested' directly from her ovaries, usually under sedation. The male partner produces a sperm sample

- The sperm and egg cells are combined and embryos allowed to develop
- The embryos' development is continually monitored over several days and when they have divided and grown sufficiently a small amount of embryonic tissue is removed and tested for the genetic change in question
- Those embryos found not to have inherited the genetic change are kept and are available to be placed into the womb of the woman. Ideally one, good quality embryo is transferred and it may be possible to freeze any remaining embryos for future use
- Several days after the embryo transfer a pregnancy test can be undertaken to see if the embryo has implanted and the woman has become pregnant

PGD will result in a successful birth of a baby in approximately 30-40% of cycles. There are many factors that influence this, which makes it a more suitable option for some couples than others. PGD is expensive but it is available on the NHS for couples who meet strict qualifying criteria. Perhaps the most crucial criterion for NHS funding is that a couple must already have no unaffected children together. If a couple wish to privately fund PGD this will cost in the region of £10,000 or more (2018). PGD can take many months to arrange, especially for rare disorders where a new license may need to be applied for. If you think PGD may be a good option for your family it is important to ask for a referral to your local PGD clinic early in your decision-making process for a no-obligation discussion about your suitability.

Other methods to prevent passing on a genetic condition:

■ Egg, sperm or embryo donation

Where a parent is known to have a genetic change which could result in an affected child, some couples choose to use an egg or sperm donor to avoid this risk. This is usually combined with IVF. Egg and sperm donation IVF is funded differently across the UK. The best place to start would be to ask your GP what is available in your area. Your local genetics team will most likely be happy to discuss this with you and help you come to a decision about whether this is the most appropriate process for your family. They may have further information to help you get started in the process. This option may be the best solution for those couples for whom PGD is unsuitable and who would not consider terminating an affected pregnancy. The National Gamete Donation Trust is a useful resource for couples considering this option (www.ngdt.co.uk).

■ Adoption

Families with children with genetic disorders are not excluded from adopting children via the usual methods. Those couples interested in adopting children are advised to contact their local council's adoption agency. The Adoption UK charity is a useful resource for couples considering this option (www.adoptionuk.org). *Unique* also has an adoption guide for families who wish to adopt a 'Unique' child with a rare chromosome or gene disorder.

■ Mitochondrial replacement therapy

This is a technique that applies to a very small and specific subset of couples where the mother is known to be a carrier of a genetic change in her mitochondrial DNA. It is a new procedure and not yet routinely available in the UK. Mitochondrial replacement therapy is an IVF-type procedure whereby the genetic information from a fertilised embryo is placed into a donor egg with healthy mitochondria. If you have a mitochondrial disorder and you think this technique may be relevant to you please discuss this further with your local genetics service.

Prenatal Testing

The following methods of prenatal diagnosis are useful for couples who wish to conceive naturally or are already pregnant. It is important to remember that there is no such test for 'normality'. These tests are designed to exclude specific diagnoses and are no guarantee of a healthy baby.

Invasive testing:

■ Chorionic Villus Sampling (CVS)

A CVS is an invasive procedure whereby a small sample of placenta is taken and tested for the genetic change seen in the family. To obtain the sample, a small needle is usually inserted through the mother's abdominal wall into the placenta where the sample is then collected. Ultrasound scanning is used to ensure the correct position of the needle.

A CVS is usually performed between weeks 11 to 14 of pregnancy. A CVS may be undertaken at your local hospital or you may be referred to your regional Fetal Medicine service for the procedure. It can be uncomfortable but it is not usually described as painful. A CVS is associated with a small risk of miscarriage. The exact rate will vary between centres but is quoted to be in the region of 0.5-1%. This means one in every 100-500 women will miscarry as a result of the CVS procedure. It is important to remember that some women will miscarry after their CVS for reasons unrelated to the procedure. This is especially true of babies who have genetic disorders or who do not follow the expected path of development.

The CVS is a test of the placenta: the genetic make-up of the placenta is usually the same as the genetic make-up of the baby. However, there are rare occasions when this is not the case. [Confined placental mosaicism](#) describes the situation whereby the placenta has a genetic change that is not found in the baby. This is most commonly found when missing or extra whole chromosomes are found (i.e. trisomy disorders).

The genetic tests which can be undertaken on the CVS are described on page 8.

More detailed information about CVS can be found at:

www.nhs.uk/conditions/chorionic-villus-sampling

■ Amniocentesis

An amniocentesis (also known as 'amnio') is an invasive procedure whereby a small sample of the amniotic fluid surrounding the baby is taken and tested. This fluid contains cells which have been shed from the baby and is a very accurate reflection of the baby's genetic make-up. To obtain the sample, a needle is passed through the mother's abdominal wall and into the fluid-filled space around the baby. The procedure is performed under ultrasound guidance to ensure the needle is inserted into the desired location and away from the baby.

An amniocentesis can be performed after week 15 of pregnancy. An amniocentesis may be undertaken at your local hospital or you may be referred to your regional Fetal Medicine service for the procedure. It can be uncomfortable but it is not usually described as painful. An amniocentesis is associated with a small risk of miscarriage. The exact rate will vary between centres but is quoted to be in the region of 0.5-1%. This means one in every 100-500 women will miscarry as a result of the amniocentesis procedure. It is important to remember that some women will miscarry after their amniocentesis and that this will be completely unrelated to the procedure but due to their baby having a genetic alteration or unusual development.

The tests which can be performed on the sample are described below.

More detailed information about amniocentesis can be found at:

www.nhs.uk/conditions/amniocentesis

■ Other samples

Very rarely other samples can be taken from the baby including fetal blood or skin samples.

What genetic tests are undertaken on CVS, amniocentesis or other samples?

The decision about which tests to perform depends on the condition which is being tested for and the centre in which testing is being undertaken. There is currently no test available that can test for all known genetic conditions and guarantee a 'normal healthy baby'.

The following describes some of the genetic tests that may be performed.

■ Rapid aneuploidy test/ QF-PCR

Most centres will perform a rapid test to identify babies affected by three common genetic variants. This includes looking for extra copies of chromosomes 13, 18 and 21, which cause Patau, Edward and Down syndrome, respectively. It may also be used to look for alterations in the total number of sex chromosomes (X and Y). This test is often undertaken in addition to the specific test required but, as with all tests, is entirely optional and you should feel free to ask for this not to be performed. The results can often be reported in just a few days.

■ Prenatal Microarray CGH

An 'array' is a test which looks at all the chromosomes in fine detail to see if there are any missing or extra pieces (deletions and duplications). It can sometimes also provide clues about structural chromosomal rearrangements or changes in the whole number of chromosomes. This test may be useful to look for recurrences of chromosomal disorders or following an unusual finding during ultrasound. It cannot identify problems with the 'spelling' of a gene (single gene disorders).

■ Cytogenetic tests

Where the genetic alteration is known in an affected sibling and/or parent, the laboratory staff have a range of techniques they can employ to look for that specific genetic change quickly and accurately. This may include looking at the chromosomes through a light microscope (a karyotype) or staining areas of interest on the chromosomes (FISH- Fluorescent *in-situ* hybridisation).

■ Targeted gene testing

Where a causative gene change is known in a family, such as in an affected sibling, the unborn baby's DNA can be examined for that exact genetic change. This technique is also used when unusual findings identified by an ultrasound scan point towards a specific single-gene disorder diagnosis. These tests are time consuming and the time to produce a report is very much dependent on the gene in question. It can take as little as a week but is more likely to take several weeks.

■ Gene panel/Clinical exome/Whole exome sequencing

Where the diagnosis is less clear, several or almost all genes can be tested simultaneously - this can be done using a gene panel or clinical exome (also known as whole exome sequencing (WES)). These techniques are used under very specific conditions and are less relevant to *Unique* members since the genetic alteration being tested for is usually already known. These tests can take weeks or months to produce a report and may not do so before the baby's expected birth date.

■ Research tests

Prenatal genetics is a rapidly evolving field and you may be asked if you would like to be enrolled in a research study. This may include genetic testing of yourself and/or your baby. Prenatal research tests are unlikely to provide results during the course of your pregnancy, if at all, but results may help researchers further understand the consequences of genetic changes. Researchers are always very grateful to people who are prepared to take part in research projects but you should feel under no obligation to do so. It will not alter the quality of your care should you decide not to take part.

Non-invasive prenatal testing

Non-invasive prenatal testing is possible because, from relatively early in a pregnancy, the baby's (placental) DNA can be found in the mother's blood stream. This provides the opportunity to test the baby's DNA using a blood sample from the mother. This can prevent the need for an invasive test, which carries a small risk of miscarriage.

The technique has been developed over the last decade but some applications of the technique are still relatively new to the clinical setting. This type of test is not currently available for most of the rare chromosome disorders known to *Unique* families.

■ Non-invasive prenatal testing - NIPT

This technique can be used to look for changes in number of whole chromosomes in the baby. It is a highly accurate technique for identifying trisomy 13, 18 and 21, which cause Patau, Edward and Down syndrome, respectively. This is not routinely available on the NHS yet (2018) but there are many options available commercially. If a positive (abnormal) result is identified it is recommended that this is confirmed using standard invasive testing techniques (amniocentesis or CVS). This test will not identify the many chromosome changes known to affect *Unique* members.

■ Non-invasive prenatal diagnosis- NIPD

It is possible to look at the baby's DNA in the mother's blood stream to identify changes in single genes that may be affecting the baby. This technique is most well-developed for gene changes that are found in the father but not the mother. If the gene change is found in the mother's blood stream then it confirms that the baby has inherited the father's condition. This technique is currently useful for those with a risk of a single gene disorder rather than a chromosomal change. This test is increasingly being used to make a diagnosis in babies whose unusual findings on an ultrasound scan point towards a specific diagnosis that neither parent has.

More recently NIPD has been developed to identify babies who have inherited autosomal recessive conditions (inheriting a faulty gene from both parents). As long as both parents have different mutations, the DNA in the mother's blood can be examined to confirm the presence or absence of the father's specific mutation. If there is presence of the father's mutation, it can be predicted that the baby has inherited the father's faulty copy of the gene. There is then a 50:50 chance the baby has also inherited the mother's faulty copy. Couples can then make a decision about whether to have an invasive test to confirm if the baby is affected.

This technique can also be used to determine the sex of the baby. Since women usually have two X chromosomes and men usually have an X and a Y, the presence of Y chromosome material found in the mother's blood stream

indicates the baby is male. This can be helpful when considering the risk of passing on some X-linked conditions which predominantly affect males. In this situation, couples who find they are expecting a boy can choose whether to proceed to invasive testing to confirm the diagnosis.

Lastly, it is possible to perform 'bespoke NIPD'. This is of particular relevance to couples who have a child with a single gene change which is not present in either of the parents. The risk of having another affected child is small, that of germline mosaicism (see page 4). NIPD can be individually designed to look for that exact gene change in the DNA in the mother's blood stream. In the unlikely event that the gene mutation was found it would indicate that that the baby carries the single gene change. This is rarely available via the NHS.

I have found out my baby has inherited the same genetic change. What now?

The decision about how to proceed with an affected pregnancy is a very personal one. There is currently no cure for most genetic problems. The decision then becomes one of continuing or terminating an affected pregnancy. Many couples choose to continue a pregnancy in the knowledge that the child is going to be affected by a serious condition. A genetics doctor aims to give you all the information you need and support you with whatever decision you make.

Factors to consider are numerous but include:

■ **Seriousness of the condition**

It is important to remember that, whilst predictions can be made about how a genetic change will affect an individual, the effects can be very variable. Even within a family some individuals can be much more or less severely affected by the same genetic change.

■ **Family support and resources**

It is also important to consider what support you have to look after an affected child, and how having another affected child will impact on your present family set up, work, health and finances.

■ **Pregnancy choices**

Your religious, moral and ethical feelings about termination of a pregnancy are important factors in your decision making. This may be dependent on whether the diagnosis is made early or late in the pregnancy.

Your genetics doctor or counsellor will be available to talk these considerations through with you. Couples making difficult decisions about a pregnancy can find help and support from a charity called '[Antenatal Results and Choices](http://www.arc-uk.org)' (www.arc-uk.org), which offers an expert helpline and is available throughout the UK.

Inform Network Support



Understanding Chromosome & Gene Disorders

Rare Chromosome Disorder Support Group

The Stables, Station Road West, Oxted, Surrey RH8 9EE, UK
Tel: +44(0)1883 723356
info@rarechromo.org | www.rarechromo.org

Join Unique for family links, information and support

Unique is a charity without government funding, existing entirely on donations and grants. If you can, please make a donation via our website at:

www.rarechromo.org/donate

Please help us to help you!

Websites

Information about CVS:

www.nhs.uk/conditions/chorionic-villus-sampling

Information about amniocentesis

www.nhs.uk/conditions/amniocentesis

Antenatal Results and Choices charity

www.arc-uk.org

The National Gamete Donation Trust

www.ngdt.co.uk

The Adoption UK charity

www.adoptionuk.org

Translocation facebook sites:

Balanced translocations:

www.facebook.com/groups/35507179052/

Balanced translocation parents:

www.facebook.com/groups/BalancedTranslocationparents/

Robertsonian translocation:

www.facebook.com/groups/280391785397282/

Unbalanced translocation:

www.facebook.com/groups/866110093480051 <https://groups.yahoo.com/neo/groups/UBTsupport/info>

PGD/IVF/Fertility:

IVF with PGD/PGS Support Group

www.facebook.com/groups/264283357013330/

IVF buddies on facebook:

www.facebook.com/groups/117485364994394/

Fertility friends:

www.fertilityfriends.co.uk/

UK based website for people concerned with Infertility, Adoption, Parenting after infertility and Moving on

Unique mentions other organisations' message boards and websites to help families looking for information. This does not imply that we endorse their content or have any responsibility for it.

This information guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This booklet was compiled by Dr Esther Dempsey, Registrar in Clinical Genetics, South West Thames Regional Genetics Service, St George's Hospital, St. George's University Hospitals NHS foundation trust.

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