Genetics

This information has been compiled from various resources including the Max Appeal Consensus Document on the Diagnosis and Management of 22q11.2 deletion, and references and sources of evidence are freely available using the contact details above.

The purpose of this Information Leaflet is to inform parents, carers and the general public about the genetic basis of the 22q11.2 deletion, the diagnostic tests and prenatal examinations. It has been endorsed as 'clear and accurate' by Professor Peter Scambler at the Molecular Medicine Unit at the Institute of Child Health, University College London who is a medical advisor to Max Appeal. Also comment and input has been gratefully received from Dr Jenny Morton, Consultant Clinical Geneticist at Birmingham Women's Hospital. Review by Max Appeal parent users has been undertaken. Further comments are warmly welcomed.

What is a 22q11.2 deletion?

Genes are often referred to as a blueprint but perhaps a better analogy would be a recipe book of life. Even identical twins are subtly different individuals and that's because everyone's cooking is different! Put in a more scientific way, environmental factors are contributory.

Genes are short sections of DNA that string together to form chromosomes. Chromosomes are found in the nucleus of every cell. Chromosomes come in pairs, one from the mother and one from the father. Most people have 23 pairs of chromosomes (46 in total).

They are numbered 1 (the largest pair) to 22 (the smallest pair) and the 23rd pair are called sex chromosomes (X and Y) because they determine whether a person is male or female. Each chromosome has two sections; a 'q' arm (which is long) and a 'p' arm (which is short).

When one or more genes are lost (deleted) or extra occur (duplicated) the body's 'recipe' changes, frequently leading to problems from birth and learning differences. A person with DiGeorge syndrome/VCFS has a section of genes missing on the 'q' arm of one of their 22nd chromosomes. This is very small! Thus "22q11.2" is the genetic address of the where the genes are missing. Some people have more genes missing than others, but strangely this doesn't correlate to what problems or severity of problems that person has.

What will be the effects of 22q Deletion?

The extent to which a person is affected is extremely variable and almost impossible to predict. There are almost 200 anomalies caused by the deletion, and each individual could be affected by many (but not all!), just a few issues or have some minor problems, say, not being very good at maths at school. It truly is a "spectrum of disorders".

Many early problems make dramatic improvements in jumps and starts. It is important to note there is no pattern to the difficulties children encounter by junior school age, for example, if your child has a complex heart defect then it does not mean that they will also have other severe symptoms.

Also many issues can be linked so it can be difficult to get to the 'nub' of the problem. For instance babies with heart defects often tire very easily when feeding, but a 22q baby with or without a heart defect might have an uncoordinated swallow or a palate problem that affects or contributes to their feeding problems.

Is 22q11.2 deletion a rare genetic disorder?

It has been estimated that as many as 1 in 1,800 of the population may be affected by the 22q11.2 deletion, or it could be as few as 1:6,000. It is the most frequently occurring chromosome deletion and the second most common cause of congenital heart defects.

The frequency of diagnosis has increased enormously over the past decade or so and many individuals who are now found to have the deletion only have very mild symptoms. Also a baby may be diagnosed and then as a result of family genetic counselling a parent is also found to have the deletion but has no major symptoms.

Why did this happen to us?

For around 90% of people with the deletion it is not inherited from a parent. It's a 'new mutation' in them that occurred by chance. If you find that your child inherited the deletion from you, it is totally understandable that you will have feelings of guilt and blame yourself, but there is nothing that could have done before or during the pregnancy to have prevented the deletion from happening or could have been done that might have caused the deletion to occur. This is a defect of the human race! The chromosome deletion was present in either the egg or sperm from which the baby was conceived. In other words the baby was destined to be born with DiGeorge syndrome/Velo-Cardio-Facial Syndrome (VCFS) from the instant of conception.

It is vital to understand that this is no-ones' "fault".

The genes become duplicated or deleted during the development of sperm and egg cells. Small sections of DNA replicate (copy) by creating loops that then straighten out to form longer strands. Errors in the straightening out process mean that the loop can become lost (genes are deleted) or don't straighten out, and so become duplicated.

What are the tests to diagnose the deletion?

The usual method of chromosome analysis is called karyotyping, where the physical structure of the chromosomes is examined under a microscope. This is used for detecting large chromosomal rearrangements or deletions, or extra chromosomes like in Down's syndrome. The 22q11.2 deletion is too small to be seen by this method so other tests have been developed.

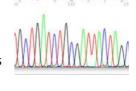
The descriptions of these tests are hugely simplistic but hopefully will give you a basic idea of what the different techniques are.

FISH (Fluorescent In Situ Hybridisation) is the oldest test and shows the deletion; tiny segments of manmade DNA are 'fired' at the 22nd chromosome and if they attach to a matching strand of DNA they 'light up'. So If there is a deletion on one of the 22nd chromosomes, the probe will have nowhere to stick to, and only one light will appear.

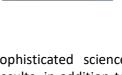
There are newer techniques that employ highly sophisticated science technologies that are cheaper and give more reliable results, in addition to providing a higher level of data about the gene defects. These are:

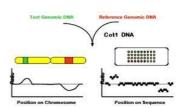
MPLA (Multiplex Ligand-dependent Probe Amplification) – again DNA replica probes are used, but here there are two sections, one that can identify the DNA at the front of the gene chain and another that can identify the one at the end. They are monitored on graphs with peaks and troughs. In this way duplications can be found and the size of deletions can be more easily identified.

Genomic Array or Array CGH test (microarraybased comparative genomic hybridisation) is the newest test now available for looking at chromosomes. It works by exploiting the ability of a DNA molecule (or strand) to bind specifically to, or hybridise to, another DNA molecule (or strand) as with the old FISH test but in this test thousands of DNA probes are used.



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Control DNA samples (of a person or group of people with no genetic abnormalities) are compared to that of the person being tested. The control sample is dyed green and the test person's sample is dyed red, and they are mixed together and scanned in a machine called a microarray scanner. Deletions show up green, duplications show up red and balanced or matched genes show as yellow. This method can identify each gene that is deleted or duplicated. It is extremely accurate.

Prenatal tests:

The above methods can be applied to samples taken during pregnancy, the samples are collected by these invasive methods, there is no non-invasive way of collecting the necessary samples; a needle is involved every time:

- **CVS** chorionic villi sampling this is carried out at 12 weeks of pregnancy and involves having a piece of placenta taken either through the cervix or the abdomen. CVS increases the risk of miscarriage by 1% but miscarriage is more likely after CVS than amniocentesis because the CVS is done in earlier pregnancy when miscarriage is more common for other reasons anyway (but gives the advantage of an early diagnosis). Occasionally (in about 1% of people having a CVS) the sample may contain tissue which is genetically different from the baby which can cause problems with interpretation of the result. In this situation, an amniocentesis may be advised to clarify the result. This is more to do with findings unrelated to the testing for the 22q deletion, such as a coincidental finding of Down syndrome or other chromosome abnormality.
- Amniocentesis this is usually carried out at 16 weeks of pregnancy, but it can be at any time if, say cardiac, palate or kidney abnormalities are spotted at a detailed scan at 20 weeks. A sample of amniotic fluid (the waters that surround the baby) is taken through the abdomen. This also carries a 1% risk of miscarriage than the earlier CVS.

NB Tests can identify whether a baby has the deletion but can not predict how severely they will be affected, they can also help a medical care plan to be put in place to prepare for the baby's arrival.

You might want to consider the "what if" scenarios before making decisions concerning invasive prenatal genetic testing. The tests both carry a 1% risk of miscarriage so the decision on which test to have isn't so much related to the risk of miscarriage, but more to do with how soon you have the result. If the test is to aid a birth plan you might well decide to have the tests later. On the other hand if you would wish to terminate the pregnancy should the test be positive then to know sooner rather than later might be best, but still bear in mind the actual risk to a potentially healthy baby. These decisions are totally personal and no-one should 'advise' you one way or another. It is a very tough call!

Prenatal examinations:

The routine 20-week ultrasound anomaly scan (risk free, painless and noninvasive) is ideal for picking up heart problems, yet detection rates are still relatively low on average across the UK (estimated to be around 30%, with widespread postcode variation). More information on prenatal heart tests and diagnoses is available at www.tinytickers.org.

These scans can also pick up many other structural issues with kidneys, palate and skeletal issues. Lots of amniotic fluid "polyhydramnios" can sometimes flag up swallowing and other problems.

When a baby is known to have the deletion, parents should offered a detailed echo-cardiogram to identify if there is a heart defect or other structural problems like kidney problems or a cleft palate, and genetic counselling, including testing to discover if either of them has the 22q11 deletion. Soon after birth a senior paediatrician should check the baby for heart problems, low blood calcium levels and also for any immune defects.

Could this happen again?

If a person doesn't have the deletion themselves, then the chance of having a further baby with the deletion is quite low (less than 1%). We are not aware of a family with two children with the deletion when neither parent has the deletion.

If a person has the deletion then they have a 50% chance of passing on the deletion to each of his or her children. The chance of having more than one child affected when the parent has the deletion is random (like the chance of tossing a coin and getting "heads" twice in a row). Also, each affected baby will almost certainly have different issues to their 22q siblings, and will almost certainly have different issues to their 22q parent.

And a final word...

A person who has 22q deletion who wishes to plan a family might want to look at the option of PGD or Pre-implantation Genetic Diagnosis. It is similar to IVF techniques where eggs from the mother are fertilised in a test tube. Then, as the cells start to multiply to form the embryo the chromosomes from one cell are tested to check for the deletion. Only those without the deletion are then implanted back in the mother. It has to be said that currently this process has had little success but techniques will improve in the future.

During pregnancy, 22q mums need to be looked after carefully, there must be good communication between her, her GP, her obstetrician, a clinical geneticist and, if she has a heart defect, her adult congenital cardiologist. She should have her endocrine system monitored especially looking at under active thyroid and hypothyroid glands. She should be offered genetic counselling and the chance for a diagnosis to be made before birth, or echocardiograph to check for heart defects. If the baby is found to have the deletion then a senior paediatrician or foetal medicine expert should carry out prenatal investigations as soon as possible, and immediately after birth arrange for expert reviews to include cardiac assessment, and assessment of calcium and immune function.

Occasionally termination of a pregnancy will be offered if the foetus has very severe organ/structural problems, also some parents will feel that termination is the best option for them for a myriad of reasons. Max Appeal will support families whatever their decision, without influencing or judging.