**The Frequency of the 22q11.2 Deletion and Duplication and its Implications**

Prof Peter Scambler, UCL Institute of Child Health

The opinions expressed are solely those of the author.

Chromosome 22q11.2 deletions and duplications are examples of copy number variations. Apart from most genes on the X chromosome of males, genes are represented twice in the genome. In deletions copy number is reduced to one (except in extremely rare cases where both copies are missing), and in duplications copy number is increased, almost always to three. For some genes correct dosage is very important, and too much or too little can lead to abnormal development of the fetus or post natal disease. The 22q11.2 deletion syndrome can result in a large range of birth defects with varying severity most notably heart abnormalities as well disorders of feeding, immunity, speech, learning, behavior, and psychiatric problems. Most cases occur “out of the blue”; 5-10% are inherited.

Historically, estimates of the incidence of 22q11.2 deletions have been constructed from regional clinics that tended to deal with the major presenting problems, congenital heart defect or palatal abnormality for example. Extrapolating from these studies yielded estimates that 1 in 4000 live births would be affected with the condition, but these studies were limited by their small size and restricted purview and by definition would miss cases without major abnormality.

A recent multi-centre, international study shed light on these issues (lead author: Francesca Grati)[1]. The aim of the study was to examine copy number variation across a number of chromosomes (not all) including number 22. The study examined more than 9600 pregnant mothers that came into clinic over a 3.5 year period, with 12 centres taking part. Each patient had undergone a biopsy procedure called chorionic villous sampling or amniocentesis, in other words a sampling that allows one to look at the DNA of the unborn fetus. The study then divided these pregnancies into what they called high risk and low risk categories, where risk refers to the chance that, in the authors’ opinion, the unborn baby would have a chromosome abnormality. **Therefore, when interpreting this study it is vital to consider the validity of their high vs. low risk assignments.** The high risk group was not controversial and here ~1% of unborn babies had the 22q11.2 deletion and ~0.3% the duplication. In the low risk category, which in theory should be close to population risk (see below), the deletion was present in ~0.1% and duplication detected at a similar rate.

The rationale for assignment to low risk was reasonable. However, it is possible to take a more stringent approach by being more selective in considering just the two groups for which there is reason to believe they represent the lowest risk of all. One group of mothers was referred for “anxiety” and had no other reason for the test other than an attempt to address the mother’s concern. A second group were referred for advanced maternal age. This is a group of women is known to be at risk for trisomy 21 (Down syndrome), but these pregnancies were unaffected from this point of view. A great number of studies of 22q11.2 deletion syndrome have been published worldwide and there is no evidence that maternal age is a risk factor for deletion in their children. Of course, by reducing the numbers of cases analysed in this way statistical power is lost, but 2 deletions were found in this set of 2438 cases, 0.08%. This gives us considerable confidence that the 22q11.2 deletion frequency is much greater than previously recognized. The reason is very likely to be that (by definition) no clinical problem was required to be present prior to the test being conducted. We can only speculate about the post-natal issues that will arise in these children of low-risk pregnancies that carry a deletion, but suffice to say 22q11.2 deletion syndrome presents many issues at different stages of life.

Summing the deletions and duplications of 22q11.2 found in the paper’s original low risk group we have 13/5953 abnormalities, or approximately 1 in every 460 pregnancies. This is a higher incidence figure than that of trisomy 21 (Down syndrome) (1/700), for which there is a UK-wide screening program (involving ultrasound and a serum sample, not a genetic test). It is worth emphasising that we know little about the long-term consequences of 22q11.2 duplication, as published reports have almost certainly been describing the more severely affected end of the clinical spectrum. While not in itself of any statistical significance towards the refinement of an incidence figure, it is somewhat remarkable that a case has been reported with a deletion on one chromosome 22q11.2 accompanied by a duplication on the other [2].

**Conclusion**

The frequency of 22q11.2 deletion coupled with its serious and varied clinical consequences makes a good case for including the condition in future antenatal screening programs. Moreover, it is becoming apparent that 22q11.2 duplications are just as common. While we know much less about the implications for any individual carrying a duplication it is certain that some will have clinical or educational problems. The genetic screening envisaged for 22q11.2 deletion would by its nature detect the duplication. The progress in developing a “non-invasive” test (taking a blood sample from the mother to analyse the DNA of the unborn child) removes the risk to the fetus that accompanies amniocentesis and chorionic villus sampling.

[1] Grati FR, Molina Gomes D, Ferreira JC, Dupont C, Alesi V, Gouas L, Horelli-Kuitunen N, Choy KW, García-Herrero S, de la Vega AG, Piotrowski K, Genesio R, Queipo G, Malvestiti B, Hervé B, Benzacken B, Novelli A, Vago P, Piippo K, Leung TY, Maggi F, Quibel T, Tabet AC, Simoni G, Vialard F. Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. Prenat Diagn. 2015 Aug;35(8):801-9. doi: 10.1002/pd.4613. PMID: 25962607.

[2] Molck MC, Vieira TP, Simioni M, Sgardioli IC, dos Santos AP, Xavier AC,Gil-da-Silva-Lopes VL. Distal 22q11.2 microduplication combined with typical 22q11.2 proximal deletion: a case report. Am J Med Genet A. 2015 Jan;167A(1):215-20. doi: 10.1002/ajmg.a.36809. PubMed PMID:25358462.

**Questions Asked.**

*How likely is it that the study reflects the UK experience?*

While no UK lab. was involved, most laboratories are from Europe and there is no evidence to suggest the deletion frequency differs between ethnic or national groups. Thus UK figures are likely to be similar.

*How does early diagnosis help?*

A big question to which the answer depends on the individual patient. For a severely affected baby, for instance with a congenital heart defect, the surgical team can be on hand at birth if necessary, and they will know the various factors to take into account when treating a heart defect in the context of a patient with other 22q11.2-related complications. In the less (immediately) severely affected child, the diagnosis will allow interventions that promote effective feeding, speech development, and schooling for example. Not least, the diagnosis will prevent what has been termed the “diagnostic odyssey”, where the child and family are bounced from clinic to clinic in search of a diagnosis. This is not a reflection on the clinicians, it’s more that the syndrome is so extra-ordinarily varied and can present in so many ways.

*Why was the duplication 22q11.2 more frequent in the low risk group than the high risk group?*

Generally speaking the clinical problems associated with duplication 22q11.2 are much less severe than deletions. Therefore, fetuses with the duplication are less likely to have the kind of serious abnormalities detected on ultrasound examination that led to the high risk classification in the first place. Remarkably, though, patients with a duplication can appear similar to those with a deletion, e.g. they may have heart defects, mild learning difficulty and changes to facial appearance. In fact, 22q11.2 duplications were first detected in the laboratory in patient samples sent in by clinicians expecting to find a deletion!

*Can such tests already be done outside the NHS?*

Screening tests on maternal blood samples for fetal chromosome abnormalities including trisomy 21 and 22q11.2 deletions are already available in the private sector (e.g. through Natera www.natera.com).