VCGS Leaders in Genetic Health

the partumpost

Rare autosomal trisomy & NIPT

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What are rare autosomal trisomies?

Rare autosomal trisomies (RATs) are chromosomal trisomies that are infrequently seen at birth. RATs involve all chromosomes other than 13, 18, 21 and the sex chromosomes. Most methods of NIPT report on the common trisomies and aneuploidies of the sex chromosomes, but not on rare trisomies.

RAT screening during NIPT

Several academic centres in Europe have begun to report on the clinical utility of using NIPT to screen for rare autosomal trisomies (1-3).

VCGS is also a major contributor in this area, and working closely with clinical staff, has reported over 90 RATs during the past two years of offering *percept* NIPT.

Our experience suggests the identification of RATs has significant clinical utility and is associated with an increased risk for missed or early miscarriages, true fetal mosaicism, uniparental disomy (UPD), intrauterine growth retardation (IUGR) and intrauterine fetal demise (IUFD).

Approximately 1 in 300 NIPT referrals received by VCGS is identified with a rare autosomal trisomy and of these, up to 70% have been associated with serious pregnancy complications

(VCGS data under peer review).

percept NIPT. A new beginning.

In March 2017 VCGS achieved NATA/RCPA accreditation for NIPT that includes screening for rare trisomies. Routine screening for rare trisomies will now form part of the standard *percept* NIPT and this analysis will be completed at no additional charge to the patient.

The service will be supported by our Reproductive Genetics clinical team. Our request forms, brochures, educational material and patient reports are currently being updated to reflect this change.

What is the significance of RATs?

RATs are usually lethal during pregnancy and are a frequent cause of pregnancy loss (4). Together with the common trisomies, they account for nearly 30% of all miscarriages. However, RATs may be present in mosaic form, where both trisomic and normal cells are detected in the one individual. In this situation the pregnancy may progress further.

RAT mosaicism is sometimes seen at prenatal diagnosis (amniocentesis), with or without fetal anomalies identified by ultrasound. This is called true fetal mosaicism (5).

Rarely, mosaicism may be ascertained at birth in a child with congenital anomalies (e.g. for trisomies 8, 9 and 22), or later in childhood because of mild dysmorphism and developmental delay. Body asymmetry and abnormal skin pigmentation following the lines of Blaschko can also be an indication of RAT mosaicism (6).

RAT mosaicism and the placenta

RAT mosaicism may be confined to the placenta, whereas the fetus has a normal karyotype. This is termed confined placental mosaicism (CPM).

In some situations CPM can adversely affect fetal growth. This is well documented for trisomy 2 when it involves the placental trophoblast and for trisomy 16. Both trisomies can cause severe IUGR, premature labour and in some instances, IUFD due to compromised placental function (7).

Detection of RATs during pregnancy allows for closer obstetric monitoring.

CPM involving a RAT can also suggest a trisomic conception that has corrected back to disomy. This happens through loss of one of the trisomic chromosomes during post zygotic cell division (trisomy rescue).

During this process, cells have a 1 in 3 chance of retaining two chromosomes from one parent, without having a contribution from the other parent. This leads to a situation called uniparental disomy (UPD).

Victorian Clinical Genetics Services
Murdoch Childrens Research Institute
The Royal Children's Hospital
Flemington Road, Parkville VIC 3052
P +61 3 8341 6201 W vcgs.org.au

For certain chromosomes like 7, 11, 14 and 15, UPD will lead to specific conditions such as Russell-Silver syndrome (UPD7mat), Prader-Willi syndrome (UPD15mat) or Angelman syndrome (UPD15pat) (8-10). We have identified one case of Prader-Willi syndrome caused by UPD after trisomy 15 was detected by percept NIPT (Fig. 1).

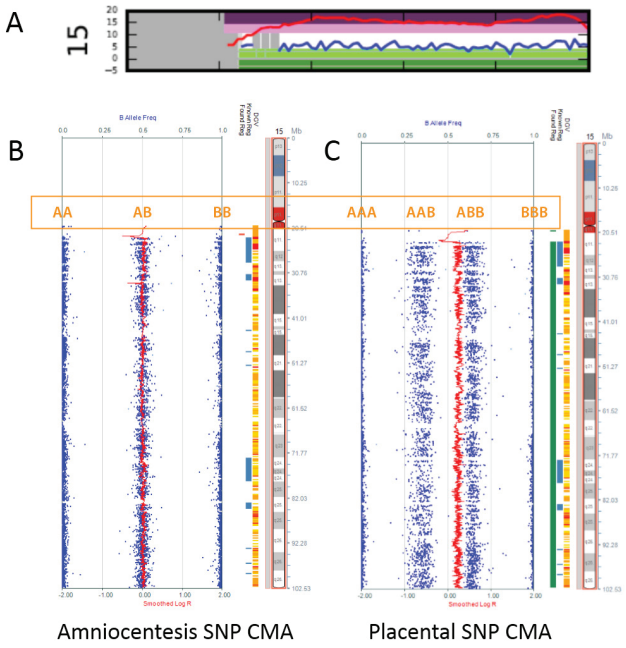

Figure 1. Prader-Willi syndrome confirmation after Trisomy 15 detection by percept NIPT. (A) An increase in chromosome 15 cfDNA sequence counts is consistent with Trisomy 15 (indicated by purple bar). (B) SNP chromosome microarray (CMA) of amniotic fluid shows a normal chromosome 15 profile (red line and blue dots). A comparison of parental and fetal DNA (not shown) indicated maternal UPD15 causing Prader-Willi syndrome (OMIM 176270). (C) Subsequent examination of chorionic villi confirmed the presence of trisomy 15 in the placenta, consistent with trisomy rescue.

How will RAT detection be reported?

RAT screening uses whole genome sequencing to enable analysis of all chromosomes. When a RAT is detected, both the fetal fraction and trisomic fraction is calculated (11). These proportions are important for helping determine the significance of the finding (VCGS data under peer review). Furthermore, the physical distribution of sequence counts across the length of the chromosome is used to help determine whether a whole chromosome trisomy is present.

Patient reports will provide a clear explanation of the possible significance of the RAT, including recommendations for follow up. This will usually include ultrasound and amniocentesis. In some instances maternal investigations or UPD studies will be recommended. VCGS can provide all cytogenomics investigations, including parental studies, conventional or molecular karyotyping and where applicable, UPD studies. Genetic counselling support is available at no charge to all patients having *percept*.

If you have any queries about the inclusion of RAT screening in the percept NIPT please direct them to perceptNIPT@vcgs.org.au

Please email vcgs@vcgs.org.au for any questions, topic suggestions or to subscribe to the partum**post**.

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