

the partumpost

Advanced NIPT & unbalanced translocations

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What are chromosomal translocations?

Balanced reciprocal translocations are caused by a two-way exchange of genetic material between two chromosomes. As there is no net loss or gain of genetic material this exchange usually has no effect on the phenotype of the carrier (Fig 1).

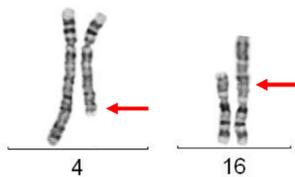


Figure 1. Balanced translocation between one chromosome 4 and one chromosome 16. The carrier has a history of recurrent miscarriage.

However, carriers of balanced translocations are at risk of passing on an unbalanced form of the chromosomal rearrangement at conception, resulting in genetic material being lost and/or gained. This can lead to sub-fertility, recurrent miscarriages, or more rarely the birth of a child with an intellectual disability and congenital malformations (1).

How common are inherited translocations?

Reciprocal translocations are carried by approximately 1 in 500 individuals (2). Each translocation is usually unique to a family. Some translocations are inherited through many generations without apparent effect, while others may severely compromise the carrier's reproductive history.

The size and genetic content of the translocated segments, as well as the position of the translocation breakpoints, are important factors that influence outcomes in these pregnancies (3, 4).

As a general rule, unbalanced translocations with large genetic imbalances are more likely to cause infertility or recurrent miscarriage, while those with small imbalances have the highest chance of live birth associated with congenital abnormalities (4).

Unbalanced translocations and prenatal diagnosis

For more than 40 years, an invasive prenatal procedure and chromosome analysis was the only way to test a pregnancy at increased risk for an unbalanced translocation. The decision for prenatal diagnosis can be a difficult one (5), especially for translocation carrier couples with a long history of infertility or pregnancy loss. The possibility of a procedure related miscarriage needs to be weighed against the chance that the pregnancy has a chromosomal imbalance arising from the translocation. This chance is not always easy to quantify.

percept NIPT provides a non-invasive option

In March 2017, VCGS gained NATA/RCPA accreditation to use NIPT in pregnancies at increased risk for unbalanced translocations, thereby providing carrier couples with a non-invasive option of prenatal testing for the very first time. *percept* is an industry-leading NIPT based on whole genome sequencing (WGS).

WGS allows screening of trisomy for all autosomes (chromosomes 1 to 22) (6), as well as screening for segmental imbalances in carriers with known translocations.

Inclusion criteria for testing

Translocation carriers who meet our inclusion criteria are eligible for screening using NIPT. An NIPT scientist trained and qualified in cytogenetics assesses each translocation for suitability for NIPT, usually on the day of the request. Most translocation carriers will meet our criteria for testing, which is based on the patient's clinical history and the size of the minimal expected chromosomal imbalance.

Once eligibility is established, blood can be collected anytime from 11 weeks of gestation. A prior ultrasound scan is required to confirm dates, confirm singleton viable pregnancy and to exclude evidence of recent co-twin demise.

Analysis is completed in 3-5 business days from sample receipt. There is no additional cost for this service and our standard NIPT fee of AUD 449.00 applies.

Translocation screening results using *percept* NIPT

To date, 50 samples have been tested by NIPT where one parent carries a balanced reciprocal translocation (32 cases) or a Robertsonian translocation (18 cases). Seven of 32 pregnancies (22%) have been identified as being at increased risk for an unbalanced reciprocal translocation.

All were confirmed as unbalanced after diagnostic testing, including one pregnancy at increased risk for Cri du chat syndrome (Fig 2). One of 18 Robertsonian translocation pregnancies (6%) has been identified at increased risk; this pregnancy also being confirmed with an unbalanced Robertsonian translocation after diagnostic testing.

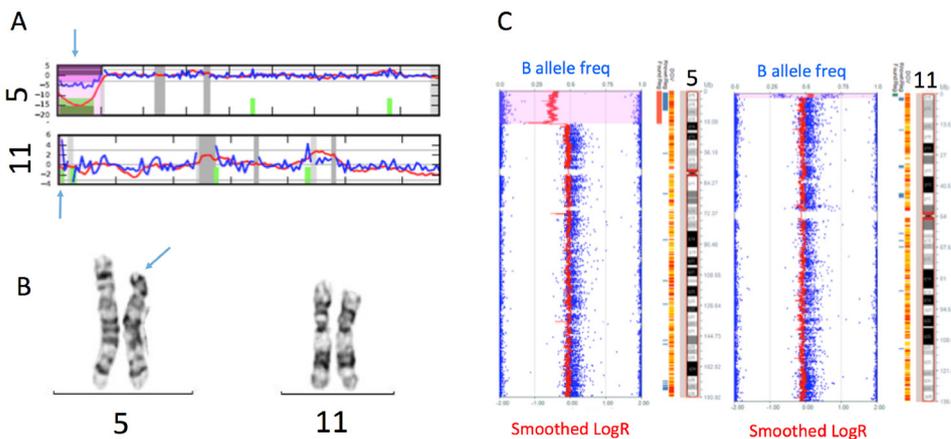


Figure 2. NIPT of an unbalanced translocation. A) WGS NIPT demonstrates a decrease in chromosome 5 sequence counts, indicating partial deletion of chromosome 5p (upper arrow and pink highlight). B) Partial karyotype of abnormal chromosome 5p (arrow) and normal chromosomes 11 seen on CVS long term culture. C) SNP microarray on DNA from chorionic villi confirms deleted 5p and sub-chromosomal duplication of 11p (pink highlight).

References

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There have been no false negative or false positive results observed to date. Based on our sample inclusion criteria and our strict sample processing quality control, we consider this application of NIPT to be near diagnostic.

Summary

Currently, treatment and testing options for balanced translocation carriers include pre-implantation genetic diagnosis (PGD) through IVF (7) or prenatal diagnostic testing using CVS or amniocentesis.

Despite the low procedural risk of miscarriage, patients with an extended history of sub-fertility or recurrent miscarriage can be particularly hesitant to agree to invasive testing (5). *percept* NIPT now provides an additional testing option for these individuals, and one which poses no procedural risk to the pregnancy.

For more information about using percept NIPT to screen pregnancies at increased risk of unbalanced translocations please contact Dr Mark Pertile on (03) 8341 6258 or email perceptNIPT@vcgs.org.au

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