Rare autosomal aneuploidy

Fact sheet for genetic counseling

Rare autosomal aneuploidy (RAA)

These are trisomies and monosomies of chromosomes 1–12, 14–17, 19, 20 and 22 as well as monosomies of chromosomes 13, 18 and 21.

Estimated incidence per chromosomal aberration*

Trisomy 21	Trisomy 18	Trisomy 13	SCA	RAA
0.30%[1]	0.10%[1]	0.10%[1]	0.48%[2]	0.34%[3]
Incidence				
0.50%			0.48%	+ 0.34%

* for SCA and RAA the incidences of the different chromosomal aberrations are summarized

What is the test accuracy?

Sensitivity and specificity for rare autosomal aneuploidy (RAA); including known mosaics[4]

Sensitivity	Specificity
Estimate % (n/N)	
96.4% (27/28)	99.80% (2,001/2,005)
2-sided 95% CI	
82.3%, 99.4%	99.49%, 99.92%

What does a positive test result mean?

Your patient's NIPT result suggests the presence of a rare autosomal aneuploidy. You should discuss the result and the potential clinical implications with your patient. According to recommendations from international professional associations, further medical clarification, usually in the form of invasive diagnostics, is urgently recommended to validate the test result. We kindly request a response in the event of inconsistent results.

Please note:

NIPT is a screening test; false positive results can occur. The actual chance for the pregnancy to have a rare autosomal aneuploidy depends on many factors, including the patient's clinical and family history.

Chromosomal anomaly in the fetus	Confined placental mosaicism

Potential clinical outcome in the case of a positive test result
Placental insufficiency
Pre-eclampsia
Premature birth
Miscarriage
IUGR
IUFD
Fetal anomalies
No clinical findings

Clinical presentation after a positive test result is variable, and is chromosome dependent. Some cases will have no apparent clinical findings.

Literature references

Mardy A, Wapner RJ. Confined placental mosaicism and its impact on confirmation of NIPT results. Am J Med Genet C Semin Med Genet. 2016;172(2):118-22.

Kalousek DK, Barrett I. Confined placental mosaicism and stillbirth. Pediatr Pathol Januar-Februar 1994;14(1):151-9.

Kalousek DK. Confined placental mosaicism and intrauterine development. Pediatr Pathol. 1990;10(1-2):69-77.

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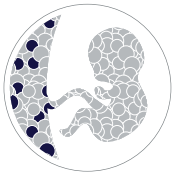
A positive NIPT result for certain autosomal trisomies is associated with an increased risk of confined placental mosaicism (CPM) associated with an increased risk of uniparental disomy (UPD).

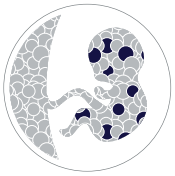
Types of chromosomal mosaicism

Certain chromosome anomalies result in confined placental mosaicism (CPM) which can be associated with an increased risk for altered placental function, leading to intrauterine growth restriction, fetal demise and risk for uniparental disomy (UPD).

Generalized mosaicism
Presence of two or more chromosomally different cell lines in both the placenta and the fetus



Confined placental mosaicism (CPM)
Presence of two or more chromosomally different cell lines in the placenta, but not the fetus



Fetal mosaicism
Presence of two or more chromosomally different cell lines which are present in the fetus, but not the placenta.

Normal cells Chromosomally abnormal cells

There are still few data about the frequency with which such feto-placental discrepancies occur. Wegner and Stumm report that in 1 – 2% of chorionic villi examined, mosaics limited to the placenta were able to be detected.[5]

Literature references

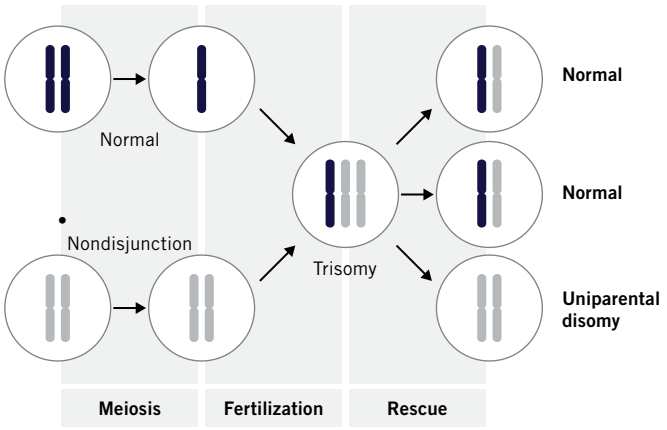
Grati FR. J Clin Med. 2014;3(3):809-837.

Van Opstal D, et al. PLoS One. 2016;11(1):e0146794.

Kalousek DK. Pediatr Pathol. 1990;10(1-2):69-77.

Uniparental disomy (UPD)

UPD refers to having two copies of a particular chromosome from the same parent, instead of one from each parent. Clinical presentation is variable. In case of confined placental mosaicism, UPD predominantly occurs due to trisomic rescue, i.e. a phenomenon in which a fertilized ovum containing three copies of a chromosome loses one of these chromosomes.



The UPD of certain imprinted chromosomes (i.e., specific methylated regions on the respective chromosomes) can lead to genetic disorders (e.g. Angelman and Prader-Willis Syndrome). For the diagnosis of an UPD additional specialized tests are required.

Literature references

Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. Am J Med Genet A 2005: 136: 287 – 305.

Shaffer LG, Agan N, Goldberg JD et al. American College of Medical Genetics statement of diagnostic testing for uniparental disomy. Genet Med 2001: 3: 206 – 211.

1 Galjaard RJ et al. Implementing NIPT as part of a national prenatal screening program: The Dutch TRIDENT studies. Prenat Diagn 2018;38(S1):8
2 Scott et al. Rare autosomal trisomies: Important and not so rare. Prenat Diagn 2018;38:765-71
3 Pertile MD Genome-wide cell-free DNA-based prenatal testing for rare autosomal trisomies and subchromosomal abnormalities. In: Nonivasive Prenatal Testing, Academic Press 2018, Eds Page-Christiaens and Klein
4 Illumina VeriSeq NIPT Solution v2 Packungsbeilage, Dokument-Nr. 1000000086774 v02 DEU, August 2019
5 Wegner und Stumm, medgen 2011; 23:457-462

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