REVIEW ARTICLE

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Rare autosomal trisomies detected by non-invasive prenatal testing: an overview of current knowledge

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Non-invasive prenatal testing has been introduced for the detection of Trisomy 13, 18, and 21. Using genome-wide screening also other "rare" autosomal trisomies (RATs) can be detected with a frequency about half the frequency of the common trisomies in the large population-based studies. Large prospective studies and clear clinical guidelines are lacking to provide adequate counseling and management to those who are confronted with a RAT as a healthcare professional or patient. In this review we reviewed the current knowledge of the most common RATs. We compiled clinical relevant parameters such as incidence, meiotic or mitotic origin, the risk of fetal (mosaic) aneuploidy, clinical manifestations of fetal mosaicism for a RAT, the effect of confined placental mosaicism on placental function and the risk of uniparental disomy (UPD). Finally, we identified gaps in the knowledge on RATs and highlight areas of future research. This overview may serve as a first guide for prenatal management for each of these RATs.

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INTRODUCTION

Non-invasive prenatal testing (NIPT) has been introduced for the detection of viable chromosomal aneuploidies in the fetus, trisomy 21, 18, and 13. The most commonly used methods are based on sequencing cell-free (cf) DNA in the maternal circulation during pregnancy. Sequencing-based NIPT can be either genome-wide or targeted to specific chromosomes or chromosome segments. Genome-wide sequencing can identify not only the viable, but all fetal aneuploidies [1–4]. These include rare fetal segmental chromosomal imbalances, rare autosomal monosomies (RAMs) and trisomies (RATs).

The frequency of prenatally detected RATs is related to the a priori risk of the study population. Benn et al. calculated a weighted average rate of positive results for RATs of 0.32%. This was based on data derived from a high risk obstetric population, including women with advanced maternal age, abnormal maternal serum markers, family history and abnormal ultrasound [5]. Two large NIPT studies performed in a general obstetric population showed the cumulative frequency of RATs to be respectively 0.22 and 0.18%, approximately half the frequency of the common trisomies [6, 7]. Figure 1 compares the frequency of the different RATs in the high risk and general obstetric population [5–7].

Reporting RATs detected by NIPT is controversial. First, the positive predictive value for NIPT-based RAT detection is only respectively 4.1% and 6% in the Belgium and Dutch cohorts, indicating that the majority of RATs are only present in the placenta but not in the fetus. Second, the clinical consequences of the presence of placental or fetal mosaicism for a RAT are only just beginning to emerge [8–12]. Reporting a RAT detected by NIPT and subsequent invasive testing can only be justified if there is sufficient evidence that this has the potential to improve pregnancy management and outcome. This potential benefit should be weighed against stress and anxiety that an abnormal test result may cause [13]. Currently evidence-based guidelines on how to deal with RATs detected by NIPT are limited. As a result, genetic counseling and obstetric management of a RAT is complex and inconsistent.

It is evident that the potential clinical consequences of a RAT are chromosome dependent. The aim of this article is to review the existing literature (PubMed search) regarding the most common RATs and those associated with a risk of fetal trisomy. These include chromosomes 2, 3, 7, 8, 9, 12, 14, 15, 16, 20 and 22. Taken together they represent 91% of all RATs [5–7]. We compile clinical relevant parameters such as incidence, meiotic or mitotic origin, the risk of fetal (mosaic) aneuploidy, clinical manifestations of fetal mosaicism for a RAT, the effect of confined placental mosaicism (CPM) on placental function and the risk of uniparental disomy (UPD). Finally, we identify gaps in the knowledge on RATs and highlight areas of future research. This overview may serve as a guide for prenatal management for each of these RATs.

Detailed information of the different reviewed RATs can be found in the supplementary data. In the next part of this manuscript we summarize the clinical relevant information on RATs found by NIPT.

THE ORIGIN OF RATS

In general, a RAT is only viable when present in a fraction of the fetal cells only, i.e. in a mosaic state. At the end of the first

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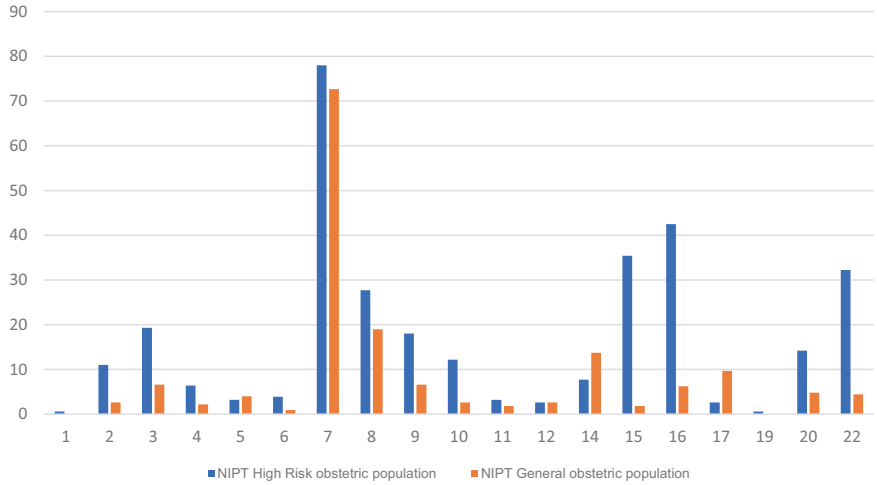

Fig. 1 Frequency of RATs detected by NIPT. Frequency of different RATs observed per 100,000 NIPTs in a high risk obstetric population (blue, data from the review by Benn et al., 2019) and the general obstetric population (amber, data from Van der Meij et al., 2019 and Van den Bogaert et al., 2021) [5–7].

trimester, when NIPT is typically performed, the vast majority of fetal RATs has been shown to be mosaic [14]. Two mechanisms may account for the development of mosaicism. First, a postzygotic mitotic non-disjunction may occur during mitosis in proliferating embryonic or placental cells. Alternatively a meiotic chromosomal segregation error leads to a trisomic zygote and subsequently a mitotic loss of the extra chromosome results in a (partial) rescue of the aneuploidy.

The stage during embryonic development and cell type involved is variable. As a consequence, the degree of mosaicism and cell lineages affected are highly variable. Mitotic errors are expected to occur more often in rapidly proliferating cells, such as the trophoblast. This is supported by the observation that in 19% of trophoblast biopsies from preimplantation embryos a mosaic aneuploidy is detected [15]. In addition, the cleavage stage is notoriously prone to acquire chromosomal imbalances [16, 17]. However, negative or possibly positive selection of aneuploid cells and their segregation within the different embryonic and extraembryonic cell lineages will ultimately determine the outcome of a mosaic aneuploidy [18–20]. Recently, the developmental potential of blastocysts with a low or medium level of mosaic aneuploidy in the trophoblast was found to be comparable to embryos without mosaicism in the trophoblast biopsy [15].

The origin of a RAT has important clinical implications. A meiotic error is likely to be present in a significant proportion of the blastomeres with a higher risk of fetal involvement. In addition, trisomy rescue has a significant risk of leading to uniparental disomy (UPD), which can result in impaired expression of genes that undergo genomic imprinting. Moreover, a meiotic origin of the RAT has been shown to correlate with a risk of intrauterine growth restriction (IUGR) [21]. In contrast, mitotic errors occur in a background of many euploid cells and therefore the risk that the fetus would be affected is lower. Also, there is virtually no increased risk of UPD in trisomies resulting from a mitotic error. Also the origin of a RAT may have implications with regard to the choice of invasive test to confirm the NIPT finding. It has been proposed that CVS (chorionic villus sampling) may be preferred for trisomies 3,7,8,9 and 20, with a predominant postzygotic origin and restricted to the trophoblast (CPM I) [22]. However, more data are needed from the general obstetric population to confirm this.

Direct evidence on the meiotic or mitotic origin of trisomies is obtained by molecular studies using polymorphic markers on material obtained from miscarriages or chorionic villus samples. Unfortunately, for the majority of chromosomes such studies are lacking or based on small series. Moreover, data from miscarriages may result in an ascertainment bias towards more severe, lethal cases with fetal involvement and thus a higher likelihood of a meiotic origin. Likewise, data from CVS studies may also be biased towards meiotic errors, since advanced maternal age and ultrasound anomalies are common indications for early invasive diagnostic procedures. Molecular studies of cases ascertained after population-based NIPT are less likely to be biased but are lacking.

Indirect evidence on the origin can be deduced from the types of confined placental mosaicism (CPM) observed for a specific RAT. CPM is the presence of a chromosomal abnormality in the extra-embryonic tissue but absent in fetal tissues.Three different types of CPM are discerned: the abnormal cell lineage can be confined to the cytotrophoblast (type I), the mesenchyme (type II) or can be present in both layers (type III). Mosaicism involving only one cell line (CPM I or II) is more likely to be mitotic, whereas CPM III is more likely to be meiotic [21, 23]. This is supported by a much higher chance of detecting fetal mosaicism (TFM) when the aneuploidy is present in both trophoblast and mesenchyme (35%), compared to an aneuploidy present in the trophoblast only (4%) or mesenchyme only (12%) [24].

Trisomies of the acrocentric chromosomes 14, 15, and 22 and chromosome 16 have a predominant maternal meiotic origin. RATs for chromosomes 2, 3, 7, and 8 are mainly mitotic in origin, whereas trisomy 12 and 20 have a variable origin. For chromosome 9, insufficient data exist. We summarized the origin in Table 1 [5–7]. Molecular studies of cases ascertained by population-based NIPT are needed to validate these data.

Additional evidence on the origin of a RAT can be obtained by comparing the frequency of a specific RAT at different stages of pregnancy and in different tissues (Table 2), including day 3 cleavage stage embryoblasts [18], day 5 trophoblast biopsies [25], early miscarriage [5], CVS trophoblast [5] and NIPT [5–7]. In apparently normal embryos, a very high incidence of aneuploidy can be detected, both in day 3 embryoblast cells (673/2119 embryos, 31.7%) [18] and in day 5 trophoblast biopsies (3920/35171 embryos, 11.1%) [25]. This is much higher than CVS trophoblast (237/57539, 0.4%) [5] and NIPT (867/282027, 0.3%) [5–7]. Not unexpectedly, the frequency of RATs is high in early miscarriages, indicating that aneuploidies are a common cause of miscarriage (564/2564, 22%) [5].

When comparing the frequency at different stages for separate chromosomes, different patterns emerge. Trisomy 1 and 19 are observed in preimplantation embryos, but are highly exceptional in later stages, suggesting that these RATs are not viable and

Table 1. Summary of characteristics of the different RAT's included in this review.

	Relative frequency (CI 95%)[a]	Absolute frequency[b]	% meiotic	Risk of fetal trisomy[c]	False negative amniocentesis	Fetal blood sampling	Consequences of CPM	Outcome fetal trisomy	Test for UPD
T2	2.4% (95% CI 1.6–3.7)	0.0059% 1/17010	NIPT: mainly mitotic	ASC: 4/11 (36%) (95% CI 11–69) GOP: 1/6 (16.7%) (95% CI 0.4-64)	not described	No data to support FBS	° increased risk IUGR ° correlated to T2M level	° 18/21 (86%) abnormal outcome ° 9/21 (46%) major malformations ° no correlation to levels of T2M	not indicated
T3	5.1% (95% CI 3.8–6.7)	0.012% 1/8151	CVS: mainly mitotic	All: 0/13 (0%) (95% CI 0–25) GOP: 0/12 (0%) (95% CI 0–26)	not described	No data to support FBS	° possible risk of IUGR	° 3/5 normal development > 1 yr ° favorable in absence of mult. malformations ° insufficient data to correlate to T3M level	not indicated
T7	30.5% (95% CI 27.8–33.5)	0.073% 1/1368	mainly mitotic	All: 2/163 (1.2%) (95% CI: 0.2–4.4) GOP: 0/137 (0%) (95% CI: 0–2.6)	not described	No data to support FBS	° elevated risk of birth weight below 2.3rd centile (RR 5) (95% CI 2.6-9.8)	° favorable outcome ° low incidence of malformations (renal) ° intellectual development normal ° no correlation to levels of T7M	1% (1/109) risk UPD7mat (Silver-Russel syndrome)
T8	9.2% (95% CI 7.4–11.2)	0.022% 1/4549	mainly mitotic	All: 3/47 (6.4%) (95% CI: 1.3–18) GOP: 3/40 (7.5%) (95% CI: 1.6–20)	° risk of false pos. T8 (maternal T8M): occult malignancy/ constitutional ° false neg. NIPT occurs	can be considered ° real risk of false negative amnioc. ° mosaicism level correlated to outcome	° increased risk of labor induction (RR 2.1) (95% CI 1.4-3.2)	° 50% normal outcome ° no correlation to levels of T8 in amniocytes, but correlated to levels of T8 in fetal blood, large overlap normal / abnormal ° favorable in absence of major malformation	not indicated
T9	4.6% (95% CI 3.3–6.1)	0.011% 1/9099	conflicting reports	All: 7/18 (39%) (95% CI: 17–64) GOP: 2/10 (20%) (95% CI: 2.5–56)	° one case of false neg. amnioc. described	° T9 has been observed in cord blood	° conflicting data, but low numbers	° very high risk of abnormal outcome (14/16) ° high incidence structural anomalies ° no correlation to levels of T9 in amniocytes	not indicated
T12	0.75% (95% CI 0.3–1.5)	0.0018% 1/55897	meiotic or mitotic	All: 2/8 (25%) (95% CI: 3.2–65) GOP: 1/6 (17%) (95% CI: 0.4–64)	not described	No data to support FBS	° no evidence for adverse effects	° 13/18 normal at birth, 5/18 major malformation ° on average higher level of T12 in congenital anomalies ° possible increased risk of high birth weight	not indicated
T14	3.2% (95% CI 2.1–4.5)	0.007% 1/13042	93% meiotic (73% mat, 20% pat) 7% mitotic	All: 1/18 (5.6%) (95% CI: 0.1–27) GOP: 0/15 (0%) (95% CI: 0–22)	not described	No data to support FBS	° no evidence for adverse effects	° 2/3rd abnormal outcome (7/11) ° 6/11 major congenital anomalies ° no correlation to levels of T14M	low risk UPD14mat or pat (none observed, 0/14)
T15	8.2% (95% CI 6.5–10.1)	0.02% 1/5081	meiotic (85% mat. 15% pat.)	All: 10/29 (35%) (95% CI: 18–54) GOP: 1/17 (5,9%) (95% CI: 0.2–29)	° a few cases of false negat. amnioc. described	No data to support FBS	° insufficient evidence for adverse effects	° 55% abnormal outcome (12/22) ° on average higher level of T15 in abnormal outcome, but overlap exists ° absence of major structural anomalies is favorable	high risk (8/21, 38%) for UPD15mat (Prader-Willi syndrome), very low risk (none reported) for UPD15pat (Angelman syndrome)
T16	11.5% (95% CI 9.5–13.7)	0.028% 1/3623	meiotic	All: 11/65 (17%) (95% CI: 8.8–28) GOP: 6/38 (16%) (95% CI: 6–32)	not described	No data to support FBS	° very high risk of placental dysfunction (preeclampsia, IUGR, prematurity, …) ° 23% heart defect ° long term outcome favorable	° 70% risk congenital malformations (mostly heart defects) ° risk malformation possibly correlated to level of mosaicism ° 80% mainstream class ° risk dev. delay correlates with level of mosaicism & multiple malformations	not indicated

Table 1. continued

	Relative frequency (CI 95%)[a]	Absolute frequency[b]	% meiotic	Risk of fetal trisomy[c]	False negative amniocentesis	Fetal blood sampling	Consequences of CPM	Outcome fetal trisomy	Test for UPD
T20	7.7% (95% CI 6.0–9.6)	0.018% 1/5434	variable	All: 0/40 (0%) (95% CI: 0–9) GOP: 0/39 (0%) (95% CI: 0–9)	not described	No data to support FBS	° increased risk of preeclampsia (RR 27.2, 95CI 8.5-86.7) and of planned cesarean section (RR 5.2) (95% CI 3.0-9.1)	° mosaicisme < 40%: 95% normal outcome ° mosaicisme > 40% 70% normal outcome ° absence major anomalies: favorable developmental outcome	low risk UPD20mat or pat after NIPT (0/5)
T22	8.1% (95% CI 6.4–10.0)	0.019% 1/5148	98% meiotic (mostly mat.)	All: 16/40 (40%) (95% CI: 25–57) GOP: 3/23 (13%) (95% CI: 2.8–34)	not described	No data to support FBS	° strong evidence that T22M is risk factor for IUGR	° high risk of miscarriage ° 60% risk of manifestations (malformations, developmental delay, IUGR)	not indicated

FBS fetal blood sampling, *CVS* chorionic villus sampling, *All* all the reported studies, *GOP* general obstetric population, *TXM* trisomy x mosaicism, *UPD* uniparental disomy, *RR* relative risk, *CI* confidence interval.
[a]Relative frequency: frequency of the RAT based on pooled data from Van der Meij et al. (2019) and Van den Bogaert et al. (2021) and studies reviewed by Benn et al. (2019) [5–7].
[b]Absolute frequency: the absolute frequency was calculated based on the reported frequency of detecting any RAT by NIPT 0.24% (Benn et al., 2019) [5].
[c]The risk of fetal trisomy is based on all the reported studies. The data for the general obstetric population (GOP) are given separately.

result in a very early demise. This is in line with the lack of reported new-borns with mosaic trisomy 1 and scarce reports of mosaic trisomy 19 in the literature. For most other trisomies, despite being frequently observed in embryos and early miscarriages, their frequency at NIPT is typically 5% or less than the frequency in day 5 trophoblast. A typical example is trisomy 16 which is likely to be of meitotic origin. There is probably a strong selection against cases with high proportions of abnormal cells explaining why the level of fetal trisomy 16 is often low [26]. A notable exception is chromosome 7. This is compatible with a predominant postzygotic origin, mainly restricted to the trophoblast, with low risk of fetal trisomy mosaicism and a low risk for UPD 7 (Table 1).

WHAT IS THE RISK OF FETAL (MOSAIC) TRISOMY

The so-called "fetal" cell-free DNA in the maternal circulation is actually derived from apoptotic trophoblast cells. Therefore, the first question is whether the detection of a RAT by genome-wide NIPT indicates only placental mosaicism or if it associated with a fetal trisomy. Since the majority of non-mosaic embryonic/fetal RATs are not viable, RATs detected at the end of the first trimester may be associated only with a mosaic fetal trisomy.

The overall positive predictive value (PPV) for detecting a RAT in the fetus when NIPT detected a RAT, was low, only 4.1% and 6% in the two reported studies in a general obstetric population (Fig. 2) [6, 7]. In high risk obstetric populations, the PPV was much higher (around 15%) [5, 27].

Large variation exists in the risk of fetal mosaicism between different chromosomes (Table 1). Since the incidence of a RAT is low for most chromosomes, we included data from both general and high risk obstetric populations. Therefore, these data need to be taken with caution, since high-risk populations, with a higher proportion of advanced maternal age, abnormal serum markers and/or ultrasound anomalies may be biased to include higher risk for fetal involvement. This is suggested by the discrepancy observed in risk of fetal mosaicism between studies in a high risk and general obstetric populations for chromosome 15 (9/12 versus 1/17, $p = 0.0002$) and for chromosome 22 (13/17 versus 3/23, $p < 0.0001$) (Table 1). But also in a low-risk population it is possible that women who receive invasive testing are biased towards those with abnormality detected by an ultrasound prior to the invasive test. High empirical risks of fetal mosaic trisomy after the detection of trisomy by NIPT are observed for chromosomes 2 (4/11), chromosome 9 (7/18), chromosome 12 (2/8), chromosome 15 (10/29), chromosome 16 (11/65) and chromosome 22 (16/40). For other chromosomes, the risk for fetal mosaicism is low (chromosomes 7 (2/163), chromosome 8 (3/47) and chromosome 14 (1/15)) or not observed (chromosome 3 (0/13) and chromosome 20 (0/40)).

Most data are based on a limited number of cases. More accurate risk figures can only be obtained by systematically analysing neonatal tissues (such as white blood cells, skin fibroblasts, buccal mucosa, …) following positive NIPT.

For RATs detected by CVS, the level of mosaicism in the trophoblast is a predictor of the risk for fetal aneuploidy. When aneuploidy is confined to the cytotrophoblast and is not found in the placental mesenchyme, non-mosaic (complete) cytotrophoblast aneuploidy is associated with a higher chance of fetal mosaicism (8.9%), whereas mosaic cytotrophoblast is associated with a lower chance of fetal mosaicism (2.9%) [24]. Several authors have reported methods to estimate the level of placental mosaicism when NIPT detected an aneuploidy [9, 14]. Pertile et al. reported an association between high rates of RAT mosaicism and an increased chance of poor pregnancy outcome, including aneuploidy associated miscarriage, true fetal mosaicism, IUGR and UPD [9]. Further independent NIPT data are needed.

Table 2. Frequency of different RATs at different stages following conception.

Chromosome	D3 embryoblast per 100,000	D5 trophoblast per 100,000	Early miscarriage per 100,000	CVS per 100,000	NIPT per 100,000	NIPT % of D5
1	1180	307	0	0	0	*0*
2	1746	321	780	21	8	*3*
3	897	293	195	52	16	*5*
4	2265	347	390	7	5	*2*
5	991	259	468	5	5	*2*
6	1038	245	468	2	3	*1*
7	1510	208	663	104	101	*49*
8	1321	341	780	37	31	*9*
9	1652	449	702	14	15	*3*
10	1085	307	351	9	9	*3*
11	1085	245	234	9	3	*1*
12	802	242	468	4	4	*1*
14	1793	282	936	17	15	*5*
15	2784	1157	3003	42	21	*2*
16	4578	2223	6240	33	28	*1*
17	944	387	429	0	9	*2*
19	2077	1120	0	2	0	*0*
20	944	284	858	38	12	*4*
22	3068	2130	5031	17	21	*1*

WHAT IF AMNIOCENTESIS REVEALS FETAL MOSAICISM FOR A SPECIFIC RAT

The prognosis for mosaicism in RATS is dependent on the chromosome involved. We focused our review on prenatally diagnosed cases to delineate the clinical manifestations that are detectable antenatally, including major and minor anomalies, fetal growth and abnormal amount of amniotic fluid. Ascertainment method of the cases was noted to evaluate potential bias towards cases with a more severe outcome. Of major concern are the limited data available on the risk for neurodevelopmental delay and intellectual disability: for most cases, long term follow-up is lacking and data on cognitive outcome remain scarce.

We also reviewed studies on postnatally diagnosed RATs, since they can help to delineate the clinical spectrum (e.g. prenatal growth, spectrum of congenital malformations and intellectual disability). However, studies on postnatally diagnosed cases are less suited to evaluate the risk of intellectual disability, since they are often ascertained due to a developmental disorder. Prospective, long-term studies of prenatally diagnosed fetal mosaicism of the different RATs are crucial to define the natural history of these cases. However for an individual patient, there will nearly always be some degree of uncertainty because the abnormalities are mosaic and the distribution of abnormal cells in different tissues may be highly variable.

Overall, this literature search demonstrates that the outcome for an individual fetus is difficult to determine antenatally.

-For chromosomes 12, 15, 16, and 20, there is some evidence for a correlation between the outcome (i.e. congenital malformations, developmental delay, growth retardation, mortality) and percentage of mosaicism (at amniocentesis). For most chromosomes such a correlation is currently lacking, which may be due to insufficient data. This might also be related to technological limitations: karyotyping may not reflect the percentage of mosaicism in the fetus, since there might be a proliferation deficit of aneuploid cells in culture. This can be overcome by more contemporary techniques of interphase FISH analysis or chromosomal microarray on uncultured amniocytes.

-Alternatively, mosaicism may result in variation in the proportion of affected cells in different tissues. There appears to be no added value of fetal blood sampling in determining the tissue distribution, perhaps with the exception of trisomy 8 [28]. The presence of multiple malformations can be predicted to be associated with higher levels of fetal trisomy in different tissues and could be a parameter of unfavorable prognosis, as observed for trisomy 16 (T16) mosaicism. The type of organ affected also indicates tissue distribution, e.g. the presence of agenesis of the corpus callosum in mosaic trisomy 8 (T8) indicates involvement of the brain and may therefore, in theory, indicate a worse developmental outcome [29]. Of interest for trisomy 16 congenital heart defects, which are observed in CPM for trisomy 16 (CPM16) as well, but at about half the frequency compared to proven fetal mosaicism for T16. It has been proposed that this might be attributable to the cell death of trisomic cells in the developing heart [26]. More speculative is a role of abnormal placentation and congenital heart defects [30].

WHAT IF AMNIOCENTESIS IS NORMAL

Given the low likelihood of fetal mosaicism for most RATs, a normal amniocentesis will be reassuring. However, low grade fetal mosaicism or mosaicism not affecting the amniocytes cannot be excluded with certainty. False negative karyotypes after amniocentesis have been reported for several chromosomes [28, 31, 32]. Therefore, in the event of a normal amniocentesis, detailed ultrasound follow-up can be advised and will allow to monitor growth and structural anomalies, to further reduce the risk of undetected fetal mosaicism. For trisomy 8, fetal blood sampling is an option [28].

The presence of a trisomic cell line in the placenta may cause placental dysfunction and result in intra-uterine growth restriction, pregnancy-induced hypertension, preterm birth and pregnancy loss [11]. CPMT16 is highly associated with an adverse pregnancy outcome. In most studies, CPM was defined as T16 detected by CVS or by NIPT and a normal amniocentesis in over 80 cases (Supplementary data chromosome 16). CPMT16 confers a very high risk of placental dysfunction, resulting in IUGR (43/81, 53%), preterm delivery (33/82, 40.2%), gestational hypertension/pre-eclampsia (23/88, 26.1%) and intrauterine death (5/82, 6.1%). In

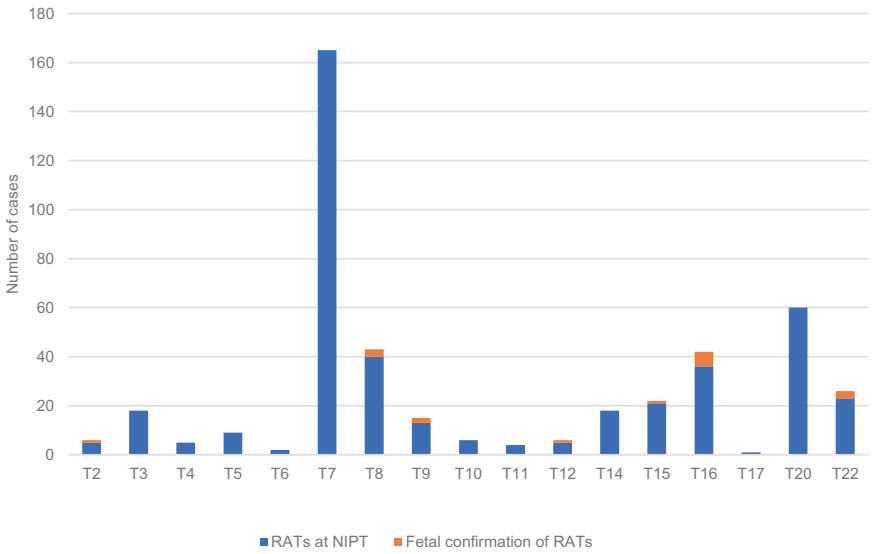

Fig. 2 Risk of fetal trisomy per RAT detected by NIPT in population-based studies. Number of cases per RAT detectected by NIPT in population-based studies are presented with in blue the cases without fetal confirmation and in amber the cases with fetal confirmation [6, 7].

16/87 (18.4%) of the cases, CPMT16 is also associated with congenital structural malformations, mostly cardiac malformations [10, 11, 33–35]. For chromosome 22, Wolstenholme et al. (1996) noted that "the behavior of trisomy 22 CPM appears very much like trisomy 16". Review of the data on 16 cases of likely CPM trisomy 22 (CPMT22) revealed IUGR in 44% of cases, strongly suggesting that CPMT22 is a risk factor for intra-uterine growth restriction as well [23]. Sifakis et al. (2010) described a significant inverse correlation between the level of mosaicism and birth weight in confined placental mosaicism in trisomy 2 [36].

Controversy exists whether CPM for other RATs is associated with adverse outcome. Different studies conflict one another. Those differences may be explained by the use of different methodologies, such as definition of adverse outcome, the inclusion of T16 or not, the inclusion of different types of CPM, the inclusion of trisomies other than RATs. All studies agree on the fact that CPM III confers a risk for IUGR [10, 37–40]. Of interest, in a cohort of 101 infants small-of-gestational-age (SGA), a 10 fold higher frequency of placental aneuploidy was detected compared to controls (11.9% versus 1.1%, $p = 0.0002$) [41]. To what extend these data can be extrapolated to RATs detected by NIPT is uncertain [42]. However in a review of five studies with reported outcome fetal growth restriction/low birth weight was observed in 14.6% (9.6–21.7) of pregnancies with a RAT diagnosed by NIPT [5] The follow-up data from the TRIDENT2 study in the Netherlands, representing the general obstetric populations, confirmed the high risk of adverse outcome of CPM for RATs, even when CPMT16 was excluded [11]. Of interest, CPMT7, the most commonly observed RAT, was found to confer an increased risk of birth weight below the 2.3rd centile, in 7/59 (11.9%) versus 2.5% in the reference population (Relative Risk of 5) (95% CI 2.6–9.8). Additional large follow-up studies are needed to investigate which RATs detected by NIPT are associated with adverse pregnancy outcome and whether the percentage of mosaicism may aid in risk stratification. This information may have practical implications, since low-dose aspirin has been shown to reduce the risk of preeclampsia in high risk pregnancies, and might also be indicated when a RAT is detected by NIPT [43].

RISK OF UNIPARENTAL DISOMY

Detecting a RAT is a risk factor for UPD. In uniparental disomy a pair of homologous chromosomes is inherited from one parent, either maternal or paternal. When an imprinted gene is located on the chromosome involved, this may result in an imprinting disorder. Different mechanisms exist, but all imply at least two errors: e.g. a meiotic error in both parents, or the combination of a meiotic event with a second event during early embryonic mitosis [44]. The main mechanism of UPD formation is trisomy rescue where in a trisomic embryo, one of the implicated chromosomes is lost, restoring the disomic state. A mosaic trisomy of postzygotic origin will not be associated with UPD.

Maternal UPD causes a phenotype if chromosome 7, 11, 14, 15, and 20 are involved. Paternal UPD is associated with a phenotype for chromosomes 6, 11, 14, 15, and 20 [45].

The risk for UPD differs amongst chromosomes. This is a consequence of the variability in meiotic and mitotic trisomies between RATs. For instance, 85% of "mosaic" trisomy 15 detected in spontaneous abortion is due to a maternal meiotic error [46]. Hence, trisomy 15 mosaicism is likely to be caused by a trisomy rescue which is expected to result in UPD15mat causing Prader-Willi syndrome in 1/3 cases. This is supported by the high risk of UPDmat when trisomy 15 is detected by NIPT in large NIPT series. (see supplementary file trisomy 15). Since trisomy 15 is rarely of paternal origin, T15 detected by NIPT has a very low risk of causing UPD15pat and Angelman syndrome. In contrast, trisomy 7 is mostly due to a mitotic error, and therefore, UPD7mat is exceptional in T7 detected by NIPT (about 1%) [5–7].

Trisomy 6 detected by NIPT is rare (representing only 0.85%) (8/939) of RATs [5–7]. In none of the cases investigated, UPD6 was detected. UPD6pat is the cause of approximately 40% of cases with transient neonatal diabetes mellitus. It is mostly due to a partial or complete isodisomy for chromosome 6 and therefore unlikely to be associated to a trisomy 6 detected by NIPT [45, 47].

Trisomy 11 is very rarely detected by NIPT, representing only 0.96% (9/939) of RAT's, and to date no instances of fetal T11 mosaicism nor UPD11 were observed, suggesting that the UPD risk is low [5–7]. Whole-chromosome UPD11pat has thus far only been observed in the context of mosaic genome-wide paternal uniparental disomy [48]. Mosaic maternal UPD11 is an extremely rare cause of Silver-Russel syndrome, with only four patients reported to date [49–51]. The occurrence of low grade mosaicism and complete or partial isodisomy of chromosome 11 indicate a postzygotic origin. Non-mosaic UPD11mat has never been observed, suggesting that this might be lethal [50]. Despite the presence of imprinted loci on chromosome 11, there is no clear

evidence to support testing for UPD11 when trisomy 11 is detected by NIPT.

The risk of UPD after detecting a trisomy by NIPT also appears to be low for chromosome 14 (0/14 cases studied, see supplementary data chromosome 14) and for chromosome 20 (0/5, see supplementary data chromosome 20), but the number of cases analysed remains very low [6]. Despite an imprinted locus on chromosome 16, there is no evidence for a recognizable UPD16(mat) phenotype. There is no difference in phenotypic expression between mosaic 16 cases with UPD16(mat) and without UPD16(mat), suggesting that the phenotype is mainly related to the T16 mosaicism and not the presence or absence of UPD16(mat) [52, 53].

Since most chromosomes do not harbor imprinted genes, UPD for these chromosomes will not give rise to a phenotype, except for the rare occasion in which UPD causes homozygosity for inherited recessive mutations resulting in an autosomal recessive disorder. The question therefore arises whether or not to evaluate, in all mosaic RAT's the presence of regions of homozygosity in the chromosome involved in the fetus, followed by exploring the presence of homozygosity for a variant causing a autosomal recessive disorder. Since the absolute risk for an autosomal recessive disorder is very low, no guidelines suggest this approach [45]. Future studies are needed to address this question.

RECOMMENDATIONS FOR FURTHER RESEARCH ON THE DIFFERENT RATS DETECTED BY NIPT

Molecular studies about the origin (meiotic/mitotic)
Assessing the risk of fetal mosaicism in low risk populations
What is the value of CVS versus amniocentesis to exclude fetal mosaicism
Is there a correlation between the level of mosaicism by NIPT and the risk of fetal involvement
Is confined placental mosaicism for each different RAT a risk factor for adverse pregnancy outcome?
Is there a correlation between the level of placental mosaicism by NIPT and adverse pregnancy outcome?
What is the long term developmental outcome of fetal mosaicism and the correlation with the level of mosaicism?
What proportion of trisomy 14,15 and 22 is due to a "inherited" Robertsonian translocation.

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All authors:—Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results. - Drafted or revised the manuscript. - Approved the final version. Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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