PREVALENCE OF 22q11.2 MICRODELETION AND MICRODUPPLICATION IN OVER 9,500 PREGNANCIES

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INTRODUCTION

22q11.2 deletion (22q11.21) is included in DiGeorge (DS) and 22q11.2 microduplication (22q11.23) syndromes. Most patients (90%) have a 3Mb deletion/duplication; a subset of patients present with typical deletions/duplications within the 22q11.2 imprinted domain, with different clinical phenotypes. Abnormal epigenetic control may induce immune system remodelling and may contribute to the wide phenotypic spectrum of clinical variability. Prenatal diagnosis for 22q11.2 deletion ranges from no abnormality or mild learning disabilities to severe mental retardation (MR) with multiple congenital malformations some of which are reminiscent of the DS.8 Prenatal screening for DS currently is done by targeted FISH analysis of fetal cells in cases with congenital heart disease and/or palate anomalies at US. A recent study on DS neonates showed that neonatal hypocalcemia and seizures are significantly associated with more severe MR. The early recognition of 22q11.2 microdeletion by neonatal or prenatal screenings could prompt meaningful anticipatory care and help improve long-term outcome.7 The value of prenatal screening for copy number variations in general prenatal population by microarray is still subject to debate. However, some propose, in low-risk/general population pregnancies, in addition to karyotype, Prenatal BACs-on-Beads9 as a transitional test investigating 9 critical regions associated with dominant well characterized microdeletion syndromes, including 22q11.2.

The 22q11 deletion and duplication estimated prevalences are 1/3600–6000 and 1/1700 livebirths, respectively, by neonatal data. Estimates based on microarray prenatal study suggest an incidence of 1/1000 for deletion.2

AIM OF THE STUDY

To assess the prevalence of 22q11.21 cryptic imbalances in prenatal population, by indication for invasive procedure testing.

MATERIALS AND METHODS

- Descriptive study based on a retrospective anonymized cohort
- IRB approval: TOMI laboratory #IRB protocol 0000006
- All patients gave consent for the analyses
- 95% confidence intervals (95%CI)
- All indications for invasive prenatal diagnosis were included
- DNA extractions and PNB0s analysis were conducted as previously reported6,12
- Classification of samples:
  - 1. Classification by indication for prenatal diagnosis:
    - abnormal ultrasound (US) [subdivided into: low risk (US-LR), high risk for submicroscopic copy number abnormalities (US-SCNA) and fetal defect not reported (US-UNK)]
    - advanced maternal age (AMA)
    - increased risk for Down syndrome after maternal serum screening or sDNA testing (MSDS-DS or HR=sDNA)
    - maternal anaemia (MA)
    - miscarriage/infantile death (MD)
    - previous fetus/child with a congenital syndrome (PFA)
    - other indications (Other)
  - indication not provided (Unknown)
- 2. Subsequent division into three major groups: those with:
  - a high prior risk for CNV: PNA, PBCA, US-SCNA, MA; PTA, US-LR and Other;
  - a low a priori risk for CNV: AMA, MSDS-DS, MA, PFA, US-LR and Other;
  - undetermined risk: US-UNK and Unknown

RESULTS

In our general cohort the prevalence of 22q11.2 microdeletions and microduplications is 0.16% (95% CI: 0.102–0.277) and of microduplication is 0.14% (95% CI: 0.091–0.222). In the low-risk population it is 0.19% (95% CI: 0.124–0.265) and 0.18% (95% CI: 0.107–0.235), respectively (Table 1).

<table>
<thead>
<tr>
<th>Indication for prenatal procedure</th>
<th>22q11.2 deletion</th>
<th>22q11.2 duplication</th>
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</thead>
<tbody>
<tr>
<td>High risk</td>
<td>0.23% (95% CI)</td>
<td>0.23% (95% CI)</td>
</tr>
<tr>
<td>Low risk</td>
<td>0.15% (95% CI)</td>
<td>0.15% (95% CI)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.14% (95% CI)</td>
<td>0.14% (95% CI)</td>
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CONCLUSIONS

A prevalence – higher than previously estimated by pediatric studies was found for 22q11.2 microdeletion; duplication shows a significant prevalence in agreement with the molecular method generating these rearrangements6,11.

The maternal age independent ≥1/850, frequency of 22q11.2 deletion may be considered high, this deletion is associated with significant morbidity, its broad clinical variability may delay early diagnosis and some 22q11.2 haplosufficient infants may benefit from early therapeutic intervention. Prenatal detection of this condition by DNA testing assays and/or by tests on invasively collected products is thus likely to decrease morbidity and even neonatal mortality, with potential implications for the long-term outcomes of affected newborns11,13.

However, although still to be demonstrated by appropriately powered clinical prospective studies, the addition of smaller genomic unbalances to the panel of indications may delay early diagnosis and some 22q11 haploinsufficient infants may benefit from early therapeutic intervention.

Prenatal detection of this condition by DNA testing assays and/or by tests on invasively collected products is thus likely to decrease morbidity and even neonatal mortality, with potential implications for the long-term outcomes of affected newborns11,13.

Undetermined risk population it is 1/992 (95% CI: 1/2164–1/455) and 1/1000 (95% CI: 1/2071–1/412), respectively (Table 1).

REFERENCES