HotSpots

A new era of non-invasive prenatal genetic diagnosis: exploiting fetal epigenetic differences

References


Fetal-specific DNA methylation ratio permits noninvasive prenatal diagnosis of trisomy 21

Papageorgiou et al. (2011)


Down syndrome (trisomy 21) is one of the most common chromosomal abnormalities, resulting in mental retardation, stunted growth and unique facial characteristics (1). Today, prenatal diagnosis of trisomy 21 and other genetic mutations is typically performed through cytogenetic or DNA analyses using invasive techniques such as amniocentesis or chorionic villus sampling (Table 1). The acquisition of fetal material through these invasive techniques, although accurate, often carries an added risk of miscarriage or fetal malformations because of the procedure, particularly with chorionic villus sampling (2). The wait time for results may also prove lengthy, depending on when testing is carried out, leaving the decisions regarding the outcome of the pregnancy to be made following the first trimester, where the emotional and physical risks are greater (2). Therefore, many research efforts in recent years have been dedicated to developing less invasive and risky procedures for prenatal genetic testing.

Non-invasive prenatal diagnosis (NIPD) techniques have been growing, and often present no associated risk for miscarriage as diagnosis depends simply on the drawing of maternal peripheral blood. These techniques are based on the existence of free fetal DNA (ffDNA) in maternal peripheral blood, in which epigenetic differences in maternal and fetal DNA can be exploited (1). Areas of the genome termed differentially methylated regions (DMRs) have been identified in various genes whereby, as its name suggests, the level of methylation differs significantly between mother and fetus. Although ffDNA can be enriched to compensate for its low presence in the maternal circulation, several barriers exist, limiting its potential as a diagnostic tool. Technologies such as bisulfite sequencing or restriction enzyme analysis possess several drawbacks including the propensity for DNA degradation and a lack of ffDNA restriction sites, respectively. The recently developed methylated DNA immunoprecipitation (MeDIP) technology is an antibody-based method, which identifies and enriches for fetal-specific hypermethylated DNA regions (3).

Using this technology, the authors are able to compare normal and trisomy 21 methylation ratios of multiple DMRs on chromosome 21, thereby increasing the accuracy of the prediction. The authors then devise a prediction equation that can be applied to each case, and the result of the test is deemed a trisomy 21 case if the value obtained is greater than zero (1). In order to test the success of their method, the methylation ratios of 80 samples (40 known samples and 40 blind samples) were assessed and were all correctly diagnosed, as confirmed subsequently by traditional karyotyping methods. Thus, this methodology yielded maximum specificity and sensitivity among the samples analyzed, and was both accurate and reproducible. Although further, large-scale studies must be conducted before this technology can be translated into the clinic, this alternative method for diagnosing trisomy 21 appears promising, given its non-invasive nature, accuracy and minimal risk over conventional methods (Table 1).

The development of a new non-invasive technique for diagnosing trisomy 21 has fundamental implications for prenatal genetic testing. This particular technique highlights the important role of epigenetics as a critical regulator of gene expression but also points to its emerging role as a potential diagnostic tool in genetic medicine. It also possesses several clear benefits as compared to the current prenatal genetic testing technologies. The non-invasive nature of such techniques greatly reduces, even abolishes, the risk for miscarriage and harm to the fetus, saving a significant number of lives as a result.

The laboratory equipment for such testing is much less elaborate and costly as quantitative polymerase chain reaction (qPCR) and MeDIP technologies require basic equipment that can be found in most standard diagnostic laboratories. This particular advantage has the potential to impact rural areas as well, as it provides distant communities the opportunity for prenatal genetic testing where it may not have been previously possible. With such advantages, it is possible that this technology could be applied to the diagnosis of other chromosomal aneuploidies.

However, as NIPD techniques such as this continue to be developed and refined for a myriad of genetic conditions, several important issues must be addressed. At the forefront of these are the potential ethical...
Table 1. Common methods for prenatal diagnosis

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<thead>
<tr>
<th></th>
<th>Amniocentesis</th>
<th>Chorionic villus sampling</th>
<th>Fetal-specific DNA methylation ratio</th>
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</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Syringe-mediated removal of amniotic fluid</td>
<td>Transcervical catheter and syringe-mediated removal of chorionic villi</td>
<td>Maternal peripheral blood draw</td>
</tr>
<tr>
<td>Invasive</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Time required for diagnosis</td>
<td>1–3 weeks</td>
<td>2–3 weeks</td>
<td>1–3 weeks</td>
</tr>
<tr>
<td>Risks</td>
<td>0.5–1% miscarriage</td>
<td>1–6% miscarriage, 1:3000 vascular limb malformation, confined placental mosaicism</td>
<td>None</td>
</tr>
<tr>
<td>Benefits</td>
<td>Highly accurate, no fetal malformation risks</td>
<td>Highly accurate</td>
<td>Highly accurate, inexpensive, maximal sensitivity and specificity, technically easier, accessible</td>
</tr>
</tbody>
</table>

implications, which include challenges for specialized informed consent as well as the potential for non-medically related prenatal genetic testing. As was the case with whole genome sequencing and other scientific technologies that have become cheaper and more accessible, there is always the possibility for uncovering controversial, unexpected results, which must be dealt with appropriately. These issues will need to be addressed before such diagnostic techniques can move from the laboratory to the clinic.

**S Ladha**
Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 980 West 28th Avenue, Vancouver, British Columbia, Canada V5Z 4H4.
e-mail: sladha@cmmt.ubc.ca