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Cystic Fibrosis Research News

Title:

Non-invasive prenatal diagnosis (NIPD) of Cystic Fibrosis: an optimized protocol using MEMO fluorescent PCR to detect the p.Phe508del mutation

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What was your research question?

We have developed an accurate and practical non-invasive prenatal diagnosis (NIPD) of cystic fibrosis (CF). We offer a simple assay for the detection of the paternally inherited foetal mutation p.Phe508del (the most frequent mutation in CF patients worldwide) in maternal plasma.

Why is this important?

Prenatal diagnosis of CF is available to couples in which both parents are known to be carriers of a CFTR mutation. This prenatal diagnosis is performed on foetal DNA derived from invasive procedures such as chorionic villus sampling or amniocentesis. These standard procedures are associated with a small but significant procedure-related risk of foetal loss of ~0.5–1%. However, since the discovery of circulating cell-free foetal DNA (cff-DNA) in maternal plasma, a shift towards NIPD has occurred. Unfortunately, NIPD remains very challenging because of the inherent limitations of molecular testing methods (e.g. polymerase chain reaction, PCR, based methods), the low concentration of cff-DNA in maternal plasma and its mix with large amounts of free maternal DNA.

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What did you do?

In this study, we developed and evaluated an NIPD test to detect p.Phe508del. We focused on improving the analytical sensitivity of established PCR-based methods. We proposed a simple assay combining two independent methods to determine the presence or absence of the paternally inherited foetal p.Phe508del mutation. A total of 24 plasma samples were collected and tested using our approaches. These samples were obtained from mothers (between 7 and 34 weeks of gestation) undergoing CFTR genotyping due to an increased risk of CF based on foetal ultrasound findings or familial CF history.

What did you find?

Our new assay was successfully applied to couples where fathers carried the p.Phe508del mutation and mothers carried a different CFTR mutation. All results were correlated with chorionic villus sampling or amniocentesis analyses. The new assay provided clear positive or negative results from the maternal plasma of the pregnant women. Our data show that the assay is simple and affordable for genetic labs and therefore, could be implemented into routine clinical practice. We also proposed an algorithm for diagnosis of CF by NIPD.

What does this mean and reasons for caution?

To our knowledge, this is the first study focused on the clinical validation of p.Phe508del detection by NIPD. This NIPD approach, easily set up in any clinical laboratory where prenatal diagnosis is routinely performed, offers many advantages over current methods: it is simple, rapid, and cost-effective. Despite that this approach is only applicable to compound heterozygous mutations. Nevertheless, it opens up the possibility for testing a large number of couples with offspring at risk for CF.

What's next?

This new approach offers safer, earlier, and easier antenatal testing than current standard practice. It could be applied to other small insertion or deletion mutations of the CFTR gene and also to any monogenic diseases (beta thalassemia, autosomal polycystic kidney disease...) involving the same type of mutations.

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