17th World Congress in Fetal Medicine

# Non-invasive prenatal test for FGFR3-related skeletal dysplasia based on next-generation sequencing and plasma cell-free DNA

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## Objective

To explore the feasibility and accuracy of non-invasive prenatal test for detection of FGFR3-related skeletal dysplasia based on next-generation sequencing (NGS) from maternal plasma cell-free DNA.

## Methods

Fragmented fetal genome DNA (gDNA) of achondroplasia (ACH) and thanatophoric dysplasia Type I (TD I) were mixed with post-delivery maternal plasma DNA to generate multiple spiked samples of different fetal fractions. Multiplex polymerase chain reaction was used to amplified the 19 FGFR3 loci and were sequenced by next-generation sequencing (NGS) to detect the fetal mutant alleles. Maternal plasma of pregnant women carrying ACH and TD I fetuses, as well as healthy controls, were tested by NGS. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the test. .

## Results

Fetal FGFR3 mutation was detected in all artificial mixtures with fetal gDNA concentration of 10%、6% and 3%. In clinical validation, our method identified all fetal FGFR3 mutant alleles from maternal plasma, with no false positive results. The sensitivity, specificity, PPV, and NPV of our method were 100% (95% CI, 54. 1% ~100%), 100% (78. 2%~100%), 100% (54. 1% ~100%) and 100% (78. 2% ~100%), respectively.

## Conclusion

The detection of fetal FGFR3 mutant alleles from maternal plasma by NGS was found to have high PPV and NPV. Our results emphasize the promising value of NGS as a non-invasive and thus favourable, prenatal test for the detection of de novo and paternal FGFR3-related skeletal dysplasia in early stage of gestation. Key words next-generation sequencing; non-invasive prenatal test; cell-free fetal DNA; achondroplasia; thanatophoric dysplasia; FGFR3.