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Expanded targeted exome sequencing in fetuses with ultrasound abnormalities reveals an important fraction of cases with associated gene defects

Konialis C, Hagnefelt B, Karapanou S, Pangalos C

1 InterGenetics SA, Center for Medical Genetics and Genomics, Athens, Greece, 2 Genomis Ltd, London, UK, 3 ClinGenics Ltd, London, UK, Athens, Greece, Greece

Objective

In the course of routine ultrasound examination of all pregnancies, 3-5% of these present with ultrasound findings, which may be related to the presence of fetal congenital abnormalities Approximately 10-15% of these cases are due to the presence of chromosomal abnormalities, while in ~85% of cases the genetic cause remains undiagnosed, leading to an inability to provide a precise diagnosis and accurate reproductive and fetal risk assessment. In order to address this important limitation and starting in early 2015, we designed and implemented an expanded exome sequencing-based test, coupled to a bioinformatics-driven prioritization algorithm, targeting gene disorders presenting with abnormal prenatal ultrasound findings. Further to the original publication in 2016, we present recent developments and discuss the latest data from the overall application of this approach (the Fetalis® test) in 50 pregnancies with ultrasound findings, which led to the diagnosis of many complex and unsuspected genetic diseases in the embryos.

Methods

Prenatal testing in all cases was preceded by consultation with the attending physician and by genetic counselling of the parents who provided the necessary informed consent. All cases involved euploid fetuses ascertained by prior prenatal aCGH. The samples consisted of either amniotic fluid (AF) or chorionic villi sampling (CVS) and parental peripheral blood samples were also collected for confirmatory analysis and/or follow-up testing. Fetal DNA was subjected to Next Generation Sequencing (NGS), followed by variant prioritization utilizing a custom analysis pipeline (Fetalis algorithm) targeting ~760 genes associated with genetic disorders which may present with abnormal fetal ultrasound findings. Variant reporting included only known pathogenic or obligatory pathogenic gene mutations, overlooking other types of variants.

Results

Exome sequencing results were typically available within 10±3 days. Overall, pathogenic mutations associated with a known genetic disorder were detected in 18 out of 50 cases (36%, 3 abortuses, 15 on-going pregnancies). No pathogenic mutations were detected in the remaining 32 cases (64%) and as far as we know in at least 18 of these cases an apparently healthy child was born. The genetic disorders diagnosed in the affected fetuses included Noonan syndrome, Nemaline myopathy, X-linked myopathy with excessive autophagy, Bartter syndrome, Congenital myasthenic syndrome, etc.

Conclusion

The expanded targeted exome sequencing-based approach described herein provides strong evidence suggesting a definite and substantial 3x increase, i. e. 38% of fetuses with troubling sonographic abnormalities and a normal chromosomal constitution. More importantly, this testing strategy overcomes many of the problems and limitations associated with clinical wide-scale WES testing in a prenatal setting, by reporting only highly confident clinically actionable results and avoiding the problems associated with the interpretation and communication of uncertain findings in the course of pregnancy.