Should We Offer Prenatal Testing in Cases with High Paternal Age ?

From a single case to a retrospective study

AUTHORS

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Background

A maternal age of higher than 35 years is associated with a significantly increased risk for fetal chromosome abnormalities, such as trisomy 21. In the last years, noninvasive prenatal testing (NIPT) has become a standard diagnostic test for chromosomal aneuploidies in women with advanced maternal age. Besides the maternal age effect, it is known since many years that some genetic disorders are associated with advanced paternal age (e.g. Achondroplasia due to *de novo* FGFR3 mutations). Nevertheless, in most cases an advanced paternal age is not considered as an indication for invasive prenatal testing in pregnancies without ultrasound findings. In recent years, prenatal trio exome sequencing (TES) has become a powerful approach for identifying the underlying genetic cause in fetuses with ultrasound findings. During the last years, we have analyzed a cohort of >1.700 pregnancies by TES, with a solving rate of around 30%. For all these cases, the ages of both parents were available.

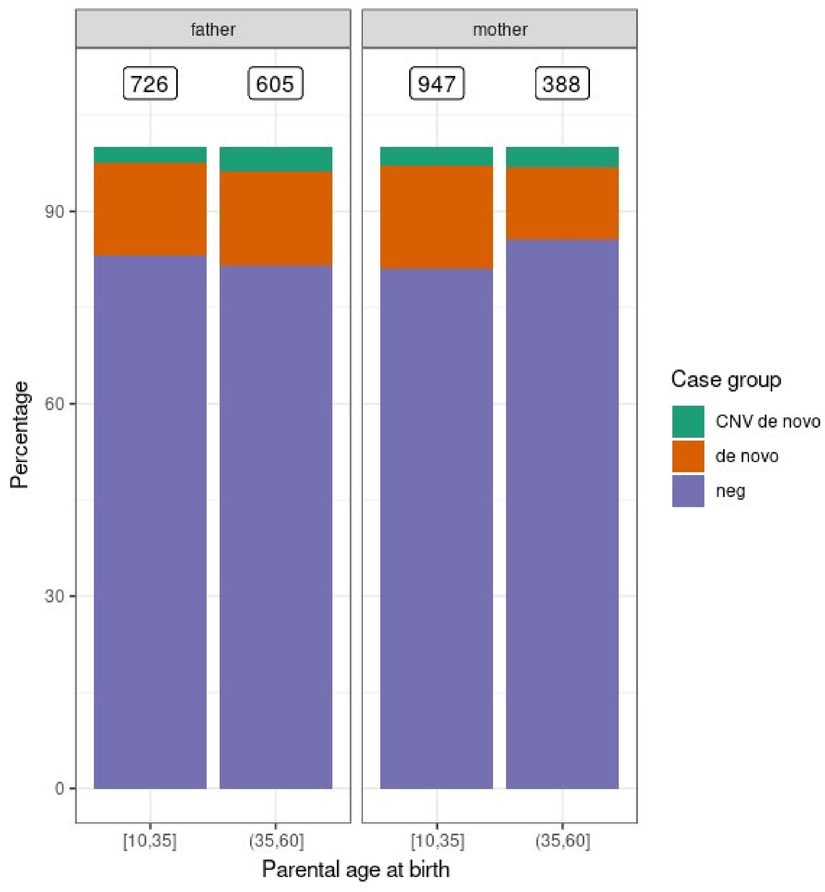
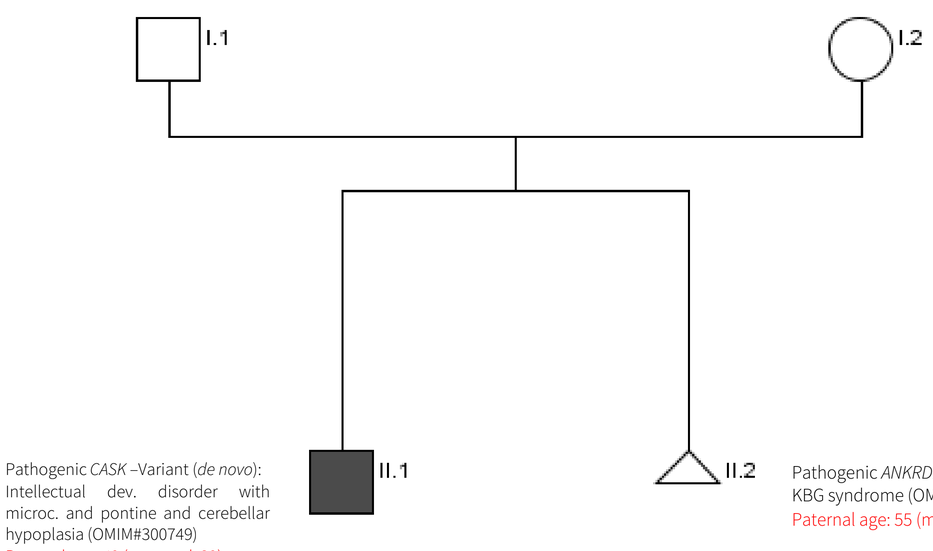


Figure 2: Different variant classes according to the age of the parents (left: age ≤35 ; right: age >35)
The only significant parental age effect could be detected for de novo CNV variants, which were more frequently found in father >35 years of age.

The Case

The starting point for the study was a case from human genetic counseling. The couple seeking counseling already had a child with a pathogenic de novo variant causative for an intellectual disability disorder. At the time of the birth of this child, the father was 49 years old. At the time of the new pregnancy, the father was 55 years old. Although no abnormalities were visible on ultrasound, the couple wanted a genetic test. A *de novo* variant was detected, which is the causative for the KBG syndrome **(figure 1).**



Pathogenic *CASK* –Variant (*de novo*): Intellectual dev. disorder with microc. and pontine and cerebellar hypoplasia (OMIM#300749)
Paternal age: 49 (maternal: 29)

Pathogenic *ANKRD11*–Variant (*de novo*): KBG syndrome (OMIM#148050)
Paternal age: 55 (maternal: 35)

Figure 1: Our Index family. Two independent pathogenic de novo variants were found

Results

Only a small, non-significant paternal age effect could be demonstrated for the occurrence of *de novo* single-nucleotide variants (SNVs) and for pathogenic CNVs. Surprisingly, we have found a significant higher number of *de novo* SNVs in mothers <35 years compared to mothers >35 years (p-Value 0.03), **(figure 1 and 2).**

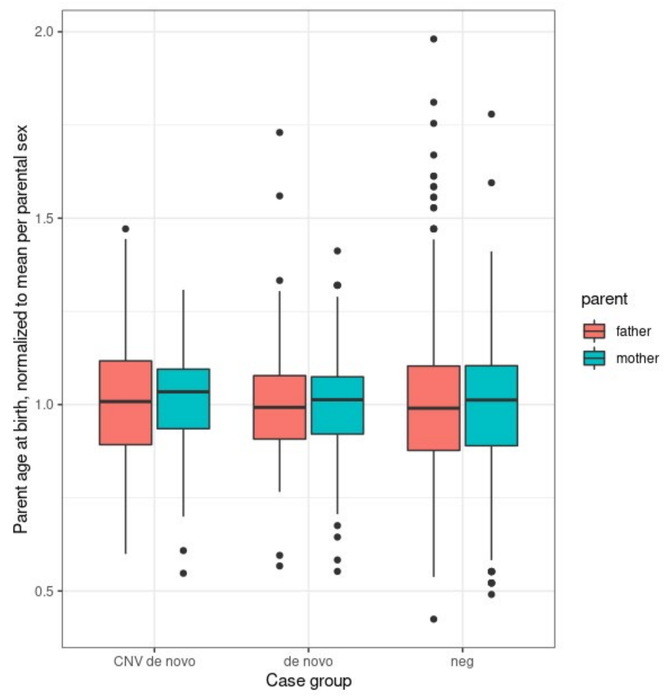


Figure 3: Parental age at birth for de novo CNV (left), de novo SNV (middle) and negative cases (right).
The data show an increased paternal age in cases with de novo CNVs (not significant)

Methods

In this retrospective study we have analysed prenatal trio exome data from >1.700 cases for maternal and paternal age effects in cases with pathogenic CNVs and pathogenic de novo variants. A statistical analysis (fisher test) was performed to test whether an advanced paternal age is a significant risk factor for *de novo* variants.

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Conclusion

In this study, we have analyzed the effect of the paternal and maternal age on the occurrence of pathogenic *de novo* SNVs and CNVs. Although the paternal age effect could not be confirmed in our cohort it is well documented at least for some, so-called "paternal-age-effect"(PAE) disorders. For these disorders it is assumed that the causative variant lead to some positive selection processes during spermatogenesis. Some studies could show that each additional year in paternal age adds 1 to 3 *de novo* variants to the genome of the offspring. Exome sequencing covers only 1-2% of the genome, therefore the number of our cohort might be too small detect such an effect in the exomic regions. Moreover, it can be speculated that *de novo* variants in some genes could lead to negative selection during spermatogenesis. Such an effect cannot be expected for the female germline. Therefore, one would expect a different kind of age effect for *de novo* SNVs in females of advanced age.