Genetic variation is higher on sperm than blood regardless male age: implications for preconceptional genetic screening

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Introduction

Advanced Paternal Age (APA) is associated with an increased risk of adverse health effects in children apparently caused by an increase in de novo mutations on spermatozoa due to the spermatogenesis process, where constant cell division occur, and mutations in the germ line that may not appear in the somatic line accumulate. Germ cell mosaicisms then are a matter of concern, of relevance on the prevention of future children's disease, since preconceptional tests are carried out on blood instead of spermatozoa, potentially causing false negatives if the mutation is present in spermatozoa but not on the analyzed tissue.

Objectives

To demonstrate the different genetic alterations in spermatozoa by showing the difference in the DNA sequence between blood and sperm and how this difference increased with age to develop a diagnostic test directed on spermatozoa for the prediction of disease in offspring.

Results

When compared the numbers of genetic variations for all patients independently of age in both tissues, we observed a statistically significant increase (0.86%) in spermatozoa (28188.76±693.76, IC95% 27063-33441) in comparison with blood (27948.28±653.60, IC95%25941-33470) (P=1.57 e-15).

Furthermore, we analyzed the number of variations considering the age of patients. In patients ≤ 30 years old we observed a statistically significant increase (0.77%) in spermatozoa (28154.94±425.44) in comparison with blood (27938.08±327.10) (P=1.44 e-7).

Equally, we observed an increase (0.93%) of number of variations in spermatozoa (28218.81±781.23) in comparison with blood (27957.35±843.59) (P=2.79 e-9) in patients ≥ 45 years old. However, when analyzed the difference of the number of genetic variations between spermatozoa and blood of patients ≤ of 30 and patients of ≥ 45 years old no statistically significant difference was observed (P=0.1).

Moreover, when we compared the genetic variations between spermatozoa and blood, there were 26996 common variants between both tissues, but interestingly we observed tissue specific variants, only presented in sperm or blood. We observed 876.96± variants only in the spermatozoa and 635.47±111.39 variants only in the blood.

Conclusions

In this study, we show that there is a major number of genetic variations in sperm than in blood. However, considering the increased numbers of genetic variations of different male's ages, there are not statistically significant differences.

Recommended reading

- *Nybo Andersen AM, Urhoj SK. Is advanced paternal age a health risk for the offspring? Fertil Steril. 2017;107(2):312-8.*
- *Brandt JS, Cruz Ithier MA, Rosen T, Ashkinadze E. Advanced paternal age, infertility, and reproductive risks: a review of the literature. Prenat Diagn. 2019;39(2):81-7.*
- *Girard SL, Bourassa CV, Lemieux Perreault LP, et al. Paternal age explains a major portion of de novo germline mutation rate variability in healthy individuals. PLoS One. 2016;11(10):e0164212.*
- *Goldmann JM, Veltman JA, Gilissen C. De novo mutations reflect development and aging of the human germline. Trends Genet. 2019;35(11):828-39.*
- *Goriely A, Wilkie AO. Paternal age effect mutations and selfish spermatogonial selection: causes and consequences for human disease. Am J Hum Genet. 2012;90(2):175-200.*