Telomere Length and Male Fertility

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Telomeres are evolutionary conserved, multifunctional DNA-protein complexes located at the ends of eukaryotic chromosomes. Infertility is the inability of a couple to conceive naturally after one year of regular unprotected sexual intercourse. Male infertility is a complex multifactorial pathological condition with profoundly different phenotypic presentations. Lifestyle factors, genetics, and telomeres are associated with male infertility. A moderate involvement of telomere length in male infertility and SNPs to be pleiotropic and to be involved in other regulatory mechanisms independent from telomere homeostasis, but involved in the spermatogenic process.

telomere length infertility STL LTL1

1. Introduction

Male infertility is involved in 20–70% of infertile couples [1][2][3] and it is a complex multifactorial pathological condition with profoundly different phenotypic presentations, from a complete absence of spermatozoa in semen (azoospermia) to various alterations of sperm quality [2][4]. There are several known lifestyle factors associated with male infertility, including body mass index (BMI), tobacco consumption, alcohol abuse, and peripheral vascular disease [5][6][7][8]. Several molecular and epidemiologic studies point towards a decisive role of genetics in male infertility. Structural chromosome aberrations, especially of the Y chromosome, as well as aberration and karyotype alteration, such as Klinefelter syndrome, have been frequently reported in infertile males.

Another layer of complexity in the etiology of male infertility is due to the role of telomeres, with several studies investigating sperm telomere length (STL) and leukocyte telomere length (LTL) in male infertility. A possible approach is suggested by the observation that LTL variability is under genetic control, and GWAS have identified 11 SNPs that predict LTL and therefore have been used as a surrogate for the direct measure of LTL and to evaluate the causative association between LTL and the risk of several human diseases in large epidemiologic studies. We have called teloscore the score based on genetic determinants of LTL, as previously reported. With these premises, our objective was to run a comprehensive study to investigate the role of STL and LTL in male infertility. And the secondary goal of this project was to validate the teloscore as a proxy of telomere length in sperm cells, an attempt that has never been made so far.

2. The link between Telomere Length and Male Fertility

In this large sample of male patients of Caucasian origin, we observed no associations between sperm parameters and STL nor LTL. However, among the sperm parameters, three of them (sperm motility, sperm count, sperm

morphology) were associated with 4 of the 11 candidate SNPs identified in the literature for being genetic proxies of telomere length. And telomere length in mature spermatozoa is longer compared to all other human cells, due to the delayed switching off of the telomerase activity in order to deliver intact telomeres to the future progeny, highlighting the crucial importance of telomeres in male gametes.

In our study, we investigated the association between telomere length and sperm parameters in one of the largest studies on male infertility, applying two different strategies, the direct measure of STL through RT-PCR and an indirect measure based on the teloscore. The RT-PCR analysis showed that there was no association between STL and sperm parameters. We tested, for the first time, the validity of the teloscore as a proxy of STL. We did not observe a strong association between the teloscore and STL, however two SNPs, TERT-rs2736100, and TERC-rs10936599, showed an effect on STL. Therefore, despite the different germinal cells levels of telomerase activity, we can suppose that the genetic variants TERT-rs2736100 and TERC-rs10936599 are associated with a specific telomerase regulation pathway which acts in the same way in both somatic and germinal cells. Despite the significance being weak, the effect of both SNPs is in line with what observed in studies conducted in LTL.

These are promising results, considering our sample size, and suggest that the 11 SNPs that are used in the teloscore could be considered as genetic proxies also in STL. However, it could also be possible that only TERT-rs2736100 and TERC-rs10936599 are involved in telomere length determination in both cell types, suggesting other genes and polymorphisms to determine telomere length in spermatozoa.

Considering the individual SNPs, we observed 5 statistically significant associations with sperm parameters. PXK-rs6772228 is associated with the number of spermatozoa in the ejaculate is an eQTL for the PXK gene in the human testis. This SNP and the PXK gene are associated with rheumatoid arthritis and the systemic lupus erythematosus (SLE), that are related to the male fertility.

ACYP2-rs11125529 is associated with sperm motility expressed as total motility, progressive motility, and mot_ABCD score. This SNP is an eQTL of the TSPYL6 gene and the A allele decreases the expression of the TSPYL6 gene in the testis. The TSPY genes are a superfamily that includes TSPYL1, TSPYL2, TSPYL3, TSPYL4, and TSPYL5. There are no studies reporting a biological explanation of the relationship between the TSPYL6 gene and male infertility, but two studies demonstrated that allelic variants of the TSPYL1 gene might be associated with isolated gonadal dysgenesis or anomalies of the spermatogenesis that could cause abnormal production of spermatozoa. It is possible to hypothesize that an altered spermatogenesis could also generate non-functional and less mobile spermatozoa. NAF1-rs7675998 is associated with the majority of the morphological sperm parameters, including the normal morphology of the acrosome and flagellum. This SNP is an eQTL and a sQTL for the NAF1 gene in the testis with the A allele associated with an increased expression of the gene. In our study, we observed that the A allele of rs7675998 is associated with an increased percentage of normal sperm suggesting that activation of the apoptotic process could increase the percentage of normal spermatozoa.

Finally, ZNF208-rs8105767 was associated with the percentage of spermatozoa with normal heads and with ABCD_mot score. The G allele (minor allele) of this SNP decreases the percentage of spermatozoa with normal

heads, decreases the sperm motility and decreases the expression of ZNF676 in the testis.

The authors also observed that ZNF676 is co-expressed with the ZNF678 gene, where lies a risk locus for azoospermia [9]. Our observation that ZNF208-rs8105767 is associated with sperm parameters suggests that it could be instrumental in regulating the expression of ZNF676 in human testicular tissue, although functional studies to better understand the role of ZNF676 are warranted.

3. Conclusions

Our result suggests a moderate involvement of telomere length in male infertility and we do not find a clear connection between telomere and male infertility in our analyses, four SNPs are weakly associated with sperm variables, suggesting these SNPs to be pleiotropic and to be involved in other regulatory mechanisms independent from telomere homeostasis, but involved in the spermatogenic process. We observed several associations between the SNPs and male infertility with plausible biological explanation, however we have conducted many analyses and the *p* values that we obtain are borderline and could reflect statistical fluctuation. In conclusion, the results of our study suggest the lack of direct involvement of telomere length with male infertility but the possible involvement of the selected SNPs through other mechanisms.

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