Transcriptome profiling of fetal Klinefelter testis tissue reveals a possible involvement of long non-coding RNAs in gonocyte maturation

In humans, the most common sex chromosomal disorder is Klinefelter syndrome (KS), caused by the presence of one or more extra X-chromosomes. KS patients display a varying adult phenotype but usually present with azoospermia due to testicular degeneration, which accelerates at puberty. The timing of the germ cell loss and whether it is caused by dysgenetic fetal development of the testes is not known. We investigated 8 fetal KS testes and found a marked reduction in MAGE-A4-positive pre-spermatogonia compared to testes from 15 age-matched controls, indicating a failure of the gonocytes to differentiate into pre-spermatogonia. Transcriptome analysis by RNA-sequencing of formalin-fixed, paraffin-embedded testes originating from 4 fetal KS and 5 age-matched controls revealed 211 differentially expressed transcripts in the fetal KS testis. We found a significant enrichment of upregulated X-chromosomal transcripts and validated the expression of the pseudoautosomal region 1 (PAR1) gene, AKAP17A. Moreover, we found enrichment of long non-coding RNAs in the KS testes (e.g. LINCO1569 and RP11-485F13.1). In conclusion, our data indicates that the testicular phenotype observed among adult men with KS is initiated already in fetal life by failure of the gonocyte differentiation into pre-spermatogonia, which could be due to aberrant expression of long non-coding RNAs.