ZSWIM7 is associated with human female meiosis and familial primary ovarian insufficiency

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Introduction

• Primary ovarian insufficiency (POI) affects 1% of women and is associated with significant medical consequences1.
• A genetic cause for POI can be found in up to 30% of women2.
• Oogenesis is particularly critical for normal germ cell development and is dependent on meiosis.
• Pathogenic variants in several meiosis genes have already been associated with POI.

We aimed to identify the genetic mechanism underlying early-onset POI in two sisters from a consanguineous pedigree.

Methods

• Genome sequencing using an autosomal recessive model was performed in the two affected sisters and unaffected relatives.
• Quantitative reverse transcriptase PCR (qRT-PCR) was used to study the expression of ZSWIM7 during fetal gonadal development.
• Four fetal ovary and testes samples (Human Developmental Biology Resource) were included at each of five developmental stages: Carnegie Stage (CS) 22/23 weeks post conception (wpc), 9wpc, 11wpc, 15/16wpc, and 22/23 weeks. Four adult ovary and adult testes samples were also included.
• Further analysis of ZSWIM7 expression in adult tissues was performed using GTEx data (v.8), the Human Protein Atlas (v.20.1), and FANTOM5.
• The expression of ZSWIM7 and associated DNA repair genes in fetal development was studied using bulk RNA sequencing of CS22/23, 9wpc, 11wpc, and 15-16wpc tissue (five per stage).

Results

Only one homozygous variant co-segregating with the POI phenotype was found: a single nucleotide substitution in ZSWIM7, NM_001042697.2: c.173C>G; resulting in predicted loss-of-function p.(Ser58*).

qRT-PCR demonstrated higher expression of ZSWIM7 in the 15/16wpc ovary compared to testis and in the CS22/23 ovary compared to the 15/16wpc ovary, corresponding to peak meiosis in the fetal ovary; qRT-PCR analysis of adult ovary and testis showed relatively strong expression in the adult tests, where meiosis is actively occurring, but also in the adult ovary. This observation was supported following analysis of publicly available RNA expression datasets.

Conclusions

• To our knowledge, this is the first time ZSWIM7 has been associated with human POI.
• ZSWIM7 is a known DNA repair gene and has recently been associated with male infertility3.
• Zswim7/Sws1/Spw1 mutant mice reproduce the infertility phenotype, demonstrating marked meiotic abnormalities4.
• These data provide evidence for a role for ZSWIM7 in human female meiosis, implicate it in the pathogenesis of POI, and emphasize the importance of genes associated with homologous recombination and specifically meiosis prophase I in this condition.
• A broader mechanistic understanding of POI can be gained from considering meiotic genes as functional partners.

References


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