BIALLELIC PPP2R3C MUTATIONS ARE ASSOCIATED WITH PARTIAL AND COMPLETE GONADAL DYSGENESIS IN 46,XY AND 46,XX INDIVIDUALS

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INTRODUCTION

- PPP2R3C encodes the Bγ regulatory subunit of the protein phosphatase 2A (PP2A), which is a serine/threonine phosphatase involved in the phospho-regulation processes of mammalian cells.
- We have recently reported homozygous and heterozygous mutations in PPP2R3C in patients with syndromic 46,XY complete gonadal dysgenesis (MEGD syndrome) and impaired spermatogenesis, respectively (1).
- In this study, we have further investigated the role of PPP2R3C in the etiology of gonadal dysgenesis.

METHOD

- We sequenced the PPP2R3C gene in four new patients from three unrelated families.
- The clinical, laboratory and molecular characteristics were investigated.
- We have determined the requirement for Ppp2r3c in mice using CRISPR/Cas9 genome editing.

RESULTS

- We have identified a homozygous c.578T>C (p.L193S) PPP2R3C variant in one 46,XX girl with primary gonadal insufficiency, 2 girls with 46,XY complete gonadal dysgenesis, and one undervirilized boy with 46,XY partial gonadal dysgenesis.
- The patients with complete gonadal dysgenesis had low gonadal and adrenal androgens, low AMH and high FSH and LH concentrations (Table 1).
- All patients manifested characteristic features of MEGD syndrome (Figure 1).
- We then generated mice (C57BL6/N) lacking functional Ppp2r3c by using CRISPR/Cas9 genome editing to delete an 1100 bp segment encoding a critical early exon.
- Using a published single-cell RNA sequencing (scRNAseq) dataset of XX and XY mouse gonad development, we identified expression in the majority of gonadal cell lineages, including Tcf21+ gonadal progenitors at 11.5 dpc, and Sox9+ and Fst+ supporting cells in XX and XY gonads, respectively.
- Heterozygous Ppp2r3c-knockout mice appeared overly normal and fertile. (Figure 2A, D).
- Inspection of homozygous embryos at 14.5, 9.5 and 8.5 days post coitum revealed evidence of dead embryos (Figure 2C).
- We conclude that loss of function of Ppp2r3c is not compatible with viability in mice and results in embryonic death from 7.5 dpc or earlier.

CONCLUSIONS

- The 4 individuals reported here illustrate the association of PPP2R3C variants with gonadal dysgenesis spectrum phenotypes and multiple malformations in MEGD syndrome.
- In the mouse model, studies of Ppp2r3c demonstrate expression in a number of developing gonadal cell lineages important for sex determination and an essential role in development.

REFERENCES


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