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Short communication

A novel homozygous mutation of bone morphogenetic protein 15 identified in a consanguineous marriage family with primary ovarian insufficiency

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A B S T R A C T

The aim of this study was to explore the pathogenic gene in a primary ovarian insufficiency (POI) patient from a consanguineous marriage family. The proband and her healthy mother were selected for whole-exome sequencing. By applying a strict filtering strategy, we found a novel homozygous missense mutation, c.G1070A (p.C357Y), of *BMP15* in the proband, whereas her mother was heterozygous for this mutation. The mutation was highly conserved among species and predicted to be disorder causing. This study has revealed a novel homozygous mutation of the *BMP15* gene that may be associated with POI.

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Introduction

Primary ovarian insufficiency (POI) is a severe type of female infertility characterized by premature menopause before the age of 40 years, and serum FSH concentration of more than 40 IU/L (Qin et al., 2015). Risk factors that disrupt follicle formation and development may lead to rapid depletion of ovarian follicles and insufficiency of ovarian function. It is clear that genetic components contribute greatly to this disorder (Fortuno and Labarta, 2014).

In this study, we used whole-exome sequencing (WES) to explore the pathogenic gene in a patient with POI from a consanguineous marriage family.

Materials and methods

Participants

The proband was an 18-year-old girl born to a consanguineous Chinese couple (**Figure 1A**). She attained menarche at 14 years of age, but was evaluated for secondary amenorrhoea at 17 years of age and diagnosed with POI (FSH = 103.2 IU/L; oestradiol = 63.51 pmol/l). Physical examinations showed no dysmorphic features, normal skeletal development, normal height (160 cm), and normal body mass index. Karyotypic abnormalities, autoimmune disorders and cancers were excluded. The parents were first cousins with no significant medical or surgical history. There was no family history of delayed puberty, infertility, or premature menopause. At the time of enrolment, the mother was 48 years of age with normal menstrual cycles and ovarian function. A total of 100 sporadic POI cases were used for candidate variant screening.

Whole-exome sequencing and validation

We carried out WES on the proband and her mother. All exons were captured using a SureSelect Human All Exon V4 Enrichment Kit (Agilent, Santa Clara, CA, USA) and massively parallel-sequenced on an Illumina Hiseq 2500 platform (Illumina, USA). Variants fulfilling the following criteria were kept: homozygous missense, nonsense, frameshift, or splicing variants; rare variants with minor allele frequency of less than 0.1% in 1000Genomes, ExAC and ESP6500si; variants absent from our in-house database (211 Chinese Han women without POI); and variants predicted to be deleterious to protein function and structure (PolyPhen [http://genetics.bwh.harvard.edu/pph2/], SIFT [http://sift.jcvi.org/], MutationTaster [http://www.mutationtaster.org/], and SNP&GO [http://snps.biofold.org/snps-and-go/]; predicted to be damaging by at least two programmes) and evolutionarily conserved (CLC Sequence Viewer 7, CLC bio, QIAGEN, Germany).

Ethics statement

This research was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University. The methods and experiments were carried out in accordance with approved guidelines. Informed written consent was obtained from all the participants.

Results

Most of the variants identified by WES were excluded by our stringent filtering. Among the remaining variants, a homozygous missense variant (NM_005448: c.G1070A, p.C357Y) in *BMP15*, a known

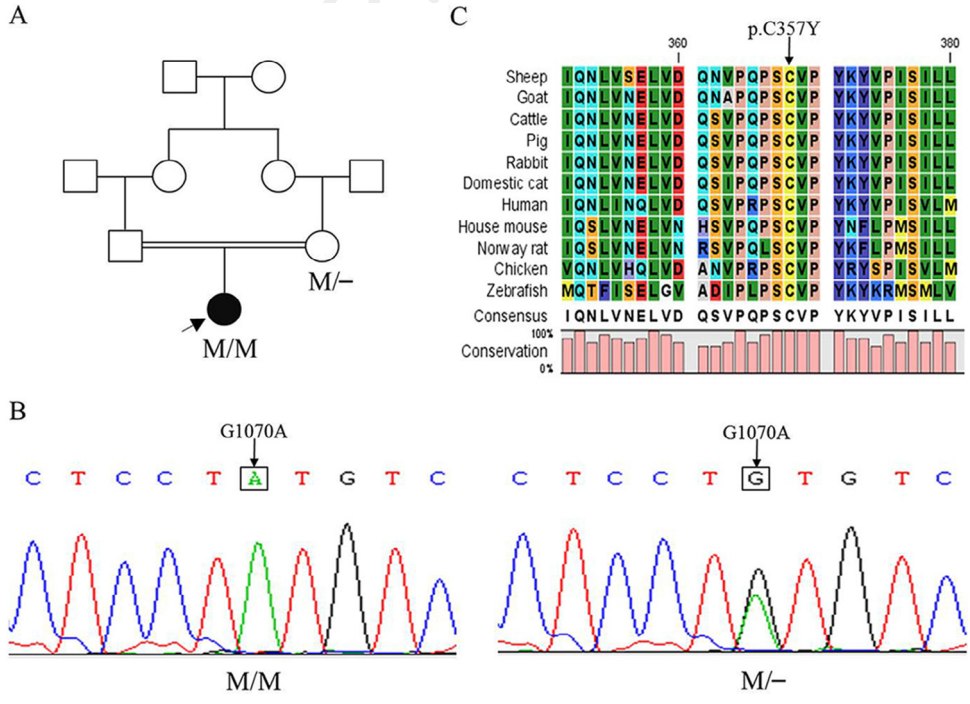

Figure 1 – (A) Pedigree structure of the consanguineous marriage family with primary ovarian insufficiency; (B) sanger sequencing confirmed the presence of the c.G1070A mutation in the proband and her mother. The proband was homozygous for the mutation, whereas her healthy mother was heterozygous; (C) alignments of the partial amino acid sequences of *BMP15* proteins among different species. The variant is evolutionarily conserved among species.

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