Short report

Biallelic variant in cyclin B3 is associated with failure of maternal meiosis II and recurrent digynic triploidy

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ABSTRACT

Background Triploidy is one of the most common chromosome abnormalities affecting human gestation and accounts for an important fraction of first-trimester miscarriages. Triploidy has been demonstrated in a few cases of recurrent pregnancy loss (RPL) but its molecular mechanisms are unknown. This study aims to identify the genetic cause of RPL associated with fetus triploidy.

Methods We investigated genomic imprinting, genotyped sequence-tagged site (STS) markers and performed exome sequencing in a family including two sisters with RPL. Moreover, we evaluated oocyte maturation in vivo and in vitro and the candidate protein variant in silico.

Results While features of hydatidiform mole were excluded, the presence of triploidy of maternal origin was demonstrated in the fetuses. Oocyte maturation was deficient and all the maternally inherited pericentromeric STS alleles were homozygous in the fetuses. A deleterious missense variant (p.V1251D) of the cyclin B3 gene (CCNB3) affecting a residue conserved in placental cyclins was demonstrated in the fetuses. Oocyte maturation was deficient and all the maternally inherited pericentromeric STS alleles were homozygous in the fetuses.

Conclusion Here, we report a family in which a damaging variant in cyclin B3 is associated with the failure of oocyte meiosis II and recurrent fetus triploidy, implicating a rationale for CCNB3 testing in RPL.

INTRODUCTION

Recurrent pregnancy loss (RPL) affects up to 5% of clinical pregnancies and is associated with both parental and embryonal factors including chromosomal abnormalities, endometrial changes, intrauterine abnormalities, endocrinological dysfunctions, infections and immunological abnormalities. Numerical chromosome abnormalities in the conceptus are the most common cause of early miscarriages, and triploidy accounts for about 13% of these cases. Triploid concepts can arise through three main mechanisms: (1) fertilisation of an oocyte by two spermatozoa; (2) fertilisation of an oocyte by a diploid spermatozoon; (3) fertilisation of a diploid oocyte. The last mechanism gives rise to a digynic triploid embryo and occurs more frequently as consequence of retention of the second polar body during meiosis, but can also be caused by retention of the first polar body or endoreduplication within the maternal pronucleus.

A few cases of recurrent (3+) digynic triploidy have been reported, suggesting a genetic predisposition, but no conclusive results on identification of the causal gene(s) have been achieved so far. Recurrent dispermic triploidy has also been rarely described and associated with the histopathological characteristics of partial hydatidiform mole.

RPL may also result from defective genomic imprinting. This is a mechanism causing the expression of a restricted number of genes to depend on their parental origin, due to differential epigenetic modification of the maternal and paternal alleles. Loss of function variants of proteins belonging to the subcortical maternal complex (SCMC) affect establishment of methylation of imprinted loci in oocytes and/or its maintenance in early embryos and are associated with infertility, RPL and abnormal embryo development.

Cyclins are regulatory subunits that by binding and activating their catalytic partner serine-threonine kinases (cyclin-dependent kinases, CDKs) control eukaryotic cell division and play pivotal roles in male and female meiosis. B3-cyclins contain motifs characteristics of A- and B-type cyclins, but are evolutionary distinct from the others. In placental mammals, cyclins B3 are large (about 1400 residues) because of the presence of a long sequence derived from an additional exon between the N-terminal destruction box (residues 60–68) and the C-terminal cyclin boxes (residues 1132–1375). Although not completely defined, the function of cyclin B3 appears to be distinct from that of the other cyclins. In chicken somatic cells, cyclin B3 is able to bind to both CDK1 and CDK2. Human cyclin B3 has been shown to interact with CDK2 in vitro, but the complex displays low kinase activity. Mouse cyclin B3 is able to interact with CDK1 and its inactivation leads to female infertility associated with failure of maternal meiosis I and embryonic triploidy, but has no consequence on somatic cell division and male gametogenesis. However, misexpression of the cyclin B3 gene (Ccnb3) interferes with meiosis II arrest and exit during oogenesis through interaction with CDK2.

In this study, we describe a family with RPL associated with digynic triploidy in the progeny. Genotyping of polymorphic sequence-tagged sites (STSs) and analysis of whole-exome sequencing (WES) indicate failure of maternal meiosis II associated
with a homozygous damaging variant in the cyclin B3 gene (CCNB3 [MIM: 300456]) that possibly caused the triploidy in the fetuses.

**MATERIALS AND METHODS**

A family (figure 1) including two sisters with RPL was referred to the Royan Reproductive Center (Tehran, Iran) in 2015. Peripheral blood samples were collected from the affected individuals II-6 and II-7, their partners II-5 and II-8, their parents I-3 and I-4 and their siblings II-9 and II-10. Paraffin-embedded biopsies were collected from the products of conception III-12 and III-15 derived from miscarriage pregnancies of II-7. Detailed information about karyotyping, array comparative hybridisation, histological analysis of fetal tissue, oocyte retrieval and in vitro maturation (IVM) were obtained from a controlled ovarian stimulation cycle. 24 In total, 7 were at MI stage and 3 at GV stage and no MII oocytes were observed, compared with an average of 75% MII oocytes usually obtained from a controlled ovarian stimulation cycle. 24 IVM was also deficient; all oocytes failed to mature and were discarded during IVF procedures, compared with an average of 85% oocytes reaching the MII stage during normal IVM. 25 To overcome the fertility problem, egg donation was proposed to overcome the fertility problem, egg donation was proposed to give birth to two twin boys, further supporting the hypothesis that the cause of infertility was in oocyte development.

**RESULTS**

Two sisters with RPL (II-6 and II-7, figure 1) who were born from consanguineous marriage between first-cousins (I-3 and I-4), were referred to our institute. II-6 had a history of 6 miscarriages and II-7 experienced 16 consecutive miscarriages. Clinical evaluation of uterine anatomy, and coagulation, hormonal, immunological and microbiological tests showed no sign of abnormality in either II-6 and II-7 (online supplementary table 1). All miscarriages occurred during the first 12 weeks of pregnancy in both affected sisters. The other family members did not report any history of RPL. Karyotype testing of the probands (II-6 and II-7) and their husbands (II-5 and II-8) showed normal chromosome patterns (46, XX and 46, XY) (online supplementary figure 1A-D). Also, no clinically significant chromosomal imbalance was detected by array CGH/SNPArray in both couples (II-5 and II-6, and II-7 and II-8) and a product of conception (III-12) of II-7 (online supplementary figure 1E-H). However, it must be taken into account that arrayCGH and SNP array do not detect polyploidy, balanced translocations and inversions. 25 Histological examination performed on III-12 demonstrated the presence of normal fetal chorionic villi along with central stroma covered by cytotrophoblast and syncytiotrophoblast, thus excluding any evidences of hydatidiform mole, trophoblastic proliferation, cellular atypia and central cistern formation (online supplementary figure 1J). To investigate the status of genomic imprinting in the fetuses, the methylation level of the differentially methylated regions (DMRs) of seven imprinted loci that are located on different chromosomes and whose methylation abnormalities are associated with RPL and SCMC variants 13 was determined in III-15 by bisulfite conversion and pyrosequencing. Compared with controls, we found that the PLAGL1, MEST, GRB10, KCNQ1OT1 and GNAS-AS1 DMRs that are normally methylated on the maternal chromosome were hypermethylated, and the H19/IGF2 and MEG3 DMRs that are normally methylated on the paternal chromosome were hypomethylated in III-15. These results excluded a defect of imprinting establishment or maintenance, but were consistent with the presence of genomewide digynic triploidy in this fetus (online supplementary figure 2 and online supplementary table 2).

Triploidy of maternal origin was confirmed in fetuses III-12 and III-15 by STS marker genotyping, which also excluded endoreduplication within the maternal pronucleus as cause of the triploidy (online supplementary table 3). To determine if the digynic triploidy derived from an error in meiosis I or an error in meiosis II, we evaluated the segregation of pericentromeric STSs (<10 Mbp from centromere). We found homozygosity of maternal alleles for 10/10 informative markers in III-15 and for 3/3 informative markers in III-12, consistent with failure of meiosis II in maternal oocytes (table 1).

Oocytes were retrieved from II-6 for in vitro fertilisation (IVF). Of 10 oocytes retrieved after one ovarian stimulation cycle, 7 were at MI stage and 3 at GV stage and no MII oocytes were observed, compared with an average of 85% MII oocytes usually obtained from a controlled ovarian stimulation cycle. 24 IVM was also deficient; all oocytes failed to mature and were discarded during IVF procedures, compared with an average of 80% oocytes reaching the MII stage during normal IVM. 25 To overcome the fertility problem, egg donation was proposed to II-6, as part of IVF. With egg donation, II-6 got pregnant and gave birth to two twin boys, further supporting the hypothesis that the cause of infertility was in oocyte development.
In order to determine the causal genetic variations underlying digynic triploidy, WES was performed on four individuals (I-3, I-4, II-6 and II-7) of the family. Considering the history of consanguinity, we postulated that the RPL phenotype was transmitted through a recessive pattern and the pathogenic variant was present in homozygosity in the affected individuals. After filtering and exclusion of frequent variants, two homozygous variants were found in both the probands (II-6 and II-7) (online supplementary table 4). The first of these variants consisted in an in-frame 3 bp deletion in a polymorphic CAG repeat (22 CAG, compared with a range of 11–36 and an average of 20–23 repeats in normal populations) of the androgen receptor gene.26 Thus, only the second variant affecting the X-linked cyclin-B3 (CCNB3) gene was retained as possible causal factor of RPL in this family. The homozygous missense variant g.50346749T>A (p.V1251D) (ChrX, GRCh38/hg38; SCV000886503) in exon 10 of CCNB3 was identified in II-6 and II-7 (figure 2). The variant that is present in the cyclin box—cyclin dependent kinase (CDK) binding domain of CCNB3 was not listed in gnomAD and dbSNP databases and was predicted to be deleterious by SIFT, probably damaging by PolyPhen and disease-causing by Mutation Taster prediction tools (table 2). Furthermore, V1251 is relatively conserved in placental mammals: the isosteric Val and Thr residues are present in primates and non-primates, respectively, in this position (online supplementary figure 3). Segregation of the candidate variant was investigated in 10 family members by bidirectional Sanger sequencing. The results showed that, in addition to II-6 and II-7, the variant was present in homozygosity in another sister (II-9) who had no pregnancy yet, in hemizygosity in their father (I-3) and in heterozygosity

Table 1  Segregation of pericentromeric STSs

| Marker | Chr | Cytoband | Distance from cen (bp) | II-7 | III-12 | III-15 | II-8 | MI | MII |
|--------|-----|----------|------------------------|------|--------|--------|------|----|-----|
| D4S405 | 4   | 4p14     | 9,307,605              | bc   | bbb*   | acc    | ab   | –  | III-15 |
| D4S428 | 4   | 4q12     | 2,974,289              | ab   | aab    | aab    | bb   | –  | III-12 and III-15 |
| D5S1969 | 5   | 5q13.1   | 6,389,874              | bc   | NA     | agg    | ad   | –  | III-15 |
| D5S2757 | 6   | 6p12.1   | 2,911,729              | bc   | NA     | bbd    | ad   | –  | III-15 |
| D8S532 | 8   | 8p11.2   | 3,050,515              | bd   | NA     | aab    | ac   | –  | III-15 |
| D12S1663 | 12  | 12q12    | 6,414,865              | bb   | bbb    | bbb    | ac   | –  | –     |
| D13S175 | 13  | 13q12.11 | 1,848,380              | ac   | NA     | ccd    | bd   | –  | III-15 |
| D15S128 | 15  | 15q11.2  | 5,130,705              | bc   | acc    | aab    | ac   | –  | III-15 |
| D19S414 | 19  | 19p12    | 4,232,942              | ab   | bbd    | bbd    | cd   | –  | III-12 and III-15 |
| D19S566 | 19  | 19p13.11 | 5,519,801              | bc   | ccd    | aab    | ad   | –  | III-12 and III-15 |
| DXS5991 | X   | Xp11.21  | 3,112,973              | aa   | NA     | aab    | bb   | –  | –     |

STS alleles are indicated for each individual by a letter with ‘a’ being the largest amplicon. Alleles are underlined if maternal origin is evident. The last two columns indicate if triploidy appears to be originated from meiosis I (MI) or meiosis II (MII).

* Only one type of allele is evident.

mat, maternal; NA, not assessed; STS, sequence-tagged site.

Figure 2  The g.50346749T>A (p.V1251D) (ChrX, GRCh38/hg38; SCV000886503) variant of the CCNB3 gene. (A) Schematic representation of the CCNB3 gene derived from UCSC (hg38) showing the sequences coding the destruction box (yellow) and the cyclin box domain (red) in NM_033031. Coding exons are indicated by dark blue boxes and intronic regions by blue lines. The transcription orientation is indicated with arrowheads. The g.50346749T>A is located in exon 10 (NM_033031) in the cyclin box region. (B) Example of Sanger sequencing confirming the segregation of the CCNB3 variant with the phenotype in II-6 and I-4. The variant (T4050A) is in red and showed on the forward strand.
The structure of cyclin-B3 has not been determined yet. Approximately 1000 amino acid residues at the N-terminus are classified as disordered regions and only the destruction box (residues 60–68), and cyclin boxes (1132–1257 and 1259–1375) can be aligned to the other cyclins. Thus, the segment spanning from position 1126 to 1388 of human cyclin B3 was aligned to human cyclin-B1 (CCNB1) of which structures were available, and homology models of the wild-type as well as V1251D-mutant CCNB3 were built (figure 3A–C). We analysed the amino acids in close contact with the site of mutation (<4 Å) and observed that on the basis of this model, valine 1251 was located on the protein surface making interactions with tyrosine 1192 (figure 3B). V1251D results in the replacement of the amino acids in close contact with the site of mutation (<4 Å) and observed that on the basis of this model, valine 1251 was located on the protein surface making interactions with tyrosine 1192 (figure 3B). V1251D results in the replacement of the amino acids in close contact with the site of mutation (<4 Å) and observed that on the basis of this model, valine 1251 was located on the protein surface making interactions with tyrosine 1192 (figure 3B). V1251D results in the replacement of the

| Tool                     | Prediction      | Score/value |
|--------------------------|-----------------|-------------|
| Sift                     | Deleterious     | 0.023*      |
| PolyPhen2 HDIV           | Probably damaging | 0.971†     |
| Mutation Taster          | Disease-causing | 0.954‡      |
| DynaMut                  | Destabilising   | ΔΔG=−0.947 kcal/mol |
| Normal mode analysis (ENCoM) | Destabilising | ΔΔG=−0.315 kcal/mol |
| Vibrational entropy energy (ENCoM) (mutant vs wild-type) | Increase of molecule flexibility | ΔΔS =0.394 kcal mol⁻¹ K⁻¹ |
| mCSM                     | Destabilising   | ΔΔG=−1,500 kcal mol⁻¹ |
| SDM                      | Destabilising   | ΔΔG=−0.910 kcal mol⁻¹ |
| DUET                     | Destabilising   | ΔΔG=−1,315 kcal mol⁻¹ |

*Deleterious:<=0.05; Tolerated:>=0.05.
†Probably damaging:0.957; possibly damaging:0.45<score<=0.956; benign:<=0.452.
‡Values close to 1 indicate high ‘security’ of prediction.

in their mother (I-4) and aborted fetuses (III-12 and III-15) (figure 1).

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**DISCUSSION**

In this study, we report a novel homzygous missense mutation in the CCNB3 gene as a possible causative agent of RPL associated with fetal digynic triploidy. In silico studies predicted that the variant V1251D is deleterious for CCNB3 structure and function. The mutation disrupts an intramolecular hydrophobic interaction conserved in the mouse and destabilises the protein. In addition, the position of valine 1251 in the protein structure suggests that its substitution with aspartic acid affects CCNB3-CDK interaction. Finally, segregation of STS markers in the family indicates that triploidy resulted from failure of maternal meiosis II.

Cyclin B3 has been implicated in the control of female meiosis in different organisms. Females of *D. melanogaster* lacking cyclin B3 are infertile and their oocytes are unable to complete meiosis I, but no defect is evident in their ovary structure. In addition, cyclin B3 is downregulated in the ovaries of striped bass females producing poor quality eggs. In *C. elegans* embryos, cyclin B3 promotes anaphase onset in meiosis II and mitosis through interaction with the spindle assembly checkpoint and dynein. Mouse Ccnb3 inactivation causes female infertility and failure of oocyte metaphase-anaphase transition and extrusion of the first polar body in meiosis I. Consistent with our results, fertilisation of mouse Ccnb3−/−/ oocytes by intracytoplasmic sperm injection produced triploid embryos that died before embryonic day 7.5 (equivalent to human first trimester). Studies in model organisms also indicated that CCNB3 is dispensable during male gametogenesis. Similarly, in our study, the male I-3 carrying the V1251 CCNB3 variant in hemizygosity is normally fertile. These sex-specific differences may be due to the longer duration of female meiosis I or compensation by other cyclins. Also, in both human and mouse, down-regulation of CCNB3 does not seem to have a negative impact on embryo development. In apparent contrast with our results, SNP genotyping of embryonic stem cells derived from parthenogenetic activation of mouse Ccnb3−/−/ oocytes suggested that Ccnb3 inactivation affects segregation of homologous chromosomes in maternal meiosis I. It is possible that this discrepancy is due to differences between the knockout and the V1251D variant that destabilises CCNB3 but probably does not completely abolish its function or to differences between mouse and human meiosis. On the other hand, a recent study indicates a possible role of mouse cyclin B3 in completion and exit from oocyte meiosis II that is exerted through interaction with CDK2. Consistent with this report, our study indicates that human oocytes carrying the CCNB3-V1251D variant can correctly complete recombination and chromosome segregation in meiosis I but fail to segregate sister chromatids in meiosis II after in vitro fertilisation, resulting in embryonic triploidy.

We investigated the effect of the V1251D variant on cyclin B3 structure and function by modelling the cyclin B3 box. First, we observed that the methyl group on the beta carbon of valine 1251 interacts intramolecularly with the aromatic ring of a tyrosine and that this interaction is conserved in the mouse, where threonine, an isosteric amino acid with an analogous

| Tool                     | Prediction      | Score/value |
|--------------------------|-----------------|-------------|
| Sift                     | Deleterious     | 0.023*      |
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*Deleterious:<=0.05; Tolerated:>=0.05.
†Probably damaging:0.957; possibly damaging:0.45<score<=0.956; benign:<=0.452.
‡Values close to 1 indicate high ‘security’ of prediction.
methyl group on the beta carbon, takes the place of valine. In
the mutant protein, the substitution of valine with the negatively
charged aspartic acid completely abolishes this interaction. In
addition, the predicted changes in protein dynamics indicated
that the mutant protein is less stable than the wild type; hence,
it is expected that the intracellular concentration of V1251D
CCNB3 is lower than normal. Finally, we evaluated CCNB3
interaction with either CDK1 or CDK2 by protein docking. It
is worth considering that the structures of CDK1 and CDK2 are
very similar.27 The computational results showed that Val1251 is
on the protein surface and occupies a pivotal place immediately
adjacent to two regions interacting with the kinases. We there-
fore predict that, by disturbing the concentration of cyclin B3 or
its affinity for CDK1 or CDK2, the V1251D variant affects the
correct completion of oocyte meiosis II and sister chromatids
segregation, resulting in embryonic triploidy. Another example
of how cyclin B3 can affect cell cycle regulation has been
reported in human pathology and is provided by the Ewing-like
sarcoma, in which an oncogene is formed by the fusion between
the BCOR and CCNB3 genes.33

In summary, this study highlights CCNB3 as a maternal-effect
gene possibly involved in the pathogenesis of RPL associated
with fetus triploidy and suggests to include it in future investiga-
tions on this clinical condition.

Accession number
The accession number for the variant c.T4050A reported in this
paper is [ClinVar]: [SCV000886503].

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