Research Square

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Preimplantation genetic testing for balanced complex chromosomal rearrangement carriers by comprehensive chromosome screening

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Abstract

Background: Balanced complex rearrangements (BCCRs) are balanced chromosomal structural aberrations that involve two or more chromosomes and at least three breakpoints. It is very rare in the population. Whether the couple of BCCRs benefit from preimplantation genetic testing (PGT) need to be further explored. Here, we reported the outcome of PGT in BCCRs carriers. Results: A total of 141 oocytes were retrieved from 7 couples within 10 PGT cycles, including 116 mature oocytes (MII), and 94 (81.03%) oocytes normally fertilized after intracytoplasmic sperm injection (ICSI). Then, 47 embryos were biopsied, including 8 embryos at the cleavage stage and 39 (41.49%) blastocysts. After comprehensive chromosome analysis, the balanced or normal embryo rate was 11.36% (5), the abnormal embryo rate was 88.63% (39), and 3 failed to amplify. Among them, the balanced or normal embryo rate was 33.33% (3) and the abnormal embryo rate was 66.67% (6) in the three-way rearrangements. The balanced or normal embryo rate was 5.6% (1) and the abnormal embryo rate was 94.4% (17) in double two-way translocations. The balanced or normal embryo rate was 5.9% (1) in exceptional CCRs, and the abnormal embryo rate was 94.1% (16). There were no significant differences among the three groups (P=0.11). In the 10 PGT cycles, there were 7 cycles in which no embryo could be transplanted and 3 cycles in which balanced or normal embryos underwent frozen-thawed embryo transplantation. One of the 3 cycles was clinically pregnant, and the prenatal diagnosis of amniocytes using G-band and SNP array at 16 weeks of gestation was 46, XN, and a boy was born alive and healthy. Conclusions: BCCR carriers have a high rate of obtaining abnormal embryos, but they can also have healthy offspring. For BCCR carriers with fertility needs, PGT is recommended to have related offspring, or they can choose sperm donor or ovum donation-assisted reproduction.

Background

Balanced complex rearrangements (BCCRs) are balanced chromosomal structural aberrations that involve two or more chromosomes and at least three breakpoints. Most of them involve three or more chromosomes and three or more break points. It is very rare in the population, with about 260 cases of CCRs reported in 2014, with approximately 0.5% neonatal morbidity[1,2]. CCRs are rare but varied. According to the chromosome structure and complexity, CCRs are usually classified into three types [3-5]: three-way rearrangement, double two-way translocations, and exceptional CCRs. The first two involve translocations only, whereas exceptional CCRS often includes other structural distortions, such as translocation, inversion, insertion, and others. CCR carriers often have growth deformities, mental retardation and congenital abnormalities [6-9]. Although many researchers have tried to explain the mechanism of CCRs, it is still not clear.

Most BCCR carriers have normal phenotypes, but they have a higher risk of reproductive failure. When one of the couples is a BCCR carrier, the possibility of producing normal gametes is theoretically much lower than that of carriers with single-chromosome abnormalities. Therefore, recurrent spontaneous abortion, arrested intrauterine pregnancy (aIUP), fetal malformation and infertility often happen. In addition, male BCCRs can also be observed as oligoasthenoterazoospermia and infertile [7,10]. It has been reported that the odds of balanced or normal embryos in couples with BCCRs are <6% [1]. PGT with an embryo biopsy is conducted before embryo transplantation, and we will aspirate a small portion of cells for comprehensive chromosome screening to analyze embryos identified as balanced or normal for transplantation. The method can reduce the miscarriage rate and improve clinical outcomes [11]. However, the odds of getting normal embryos for BCCR carriers is very low. The effects of different types of BCCRs on embryonic development and clinical outcomes after PGT are rarely reported.

In our study, clinical and laboratory data on preimplantation genetic testing to assist reproduction for three different types of BCCR carriers were collected, and we analyzed the embryo results and cycle outcomes to explore the clinical outcomes of PGT-assisted reproduction in patients with balanced complex chromosome rearrangements.

Results

General conditions

Seven BCCR couples diagnosed by karyotype analysis of peripheral blood were included. They underwent 10 PGT cycles in all. All seven couples had negative reproductive history, including spontaneous abortions, artificial abortions, aIUP and odinopoeia. This study included two female BCCR carriers (28.57%) and five male BCCR carriers (71.43%). The average age of the women was 27 years, and the average age of the men was 32.14 years. There were no significant differences among the three groups in the average age of the males (F=2.927, *P*=0.17), the average age of the females (F=0.429, *P*=0.68), or the number of antral follicles (AFC) (F=0.25, *P* =0.78) (see Table 1).

COH outcome and embryo identification from PGT cycles

A total of 141 oocytes were retrieved from 7 couples with 10 PGT cycles, including 116 mature oocytes (MII), and 94 (81.03%) oocytes were observed as two-pronuclear embryos (2PN) after intracytoplasmic sperm injection (ICSI). Then, 47 embryos were biopsied, including 8 embryos at the cleavage stage and 39 (41.49%) blastocysts. There were 3 cycles in group A with a total of 35 oocytes obtained, including 29 MII oocytes. There were 22 (75.86%) 2PN after ICSI and 9 (40.9%) blastocysts biopsied. There were 2 cycles in group B, with 41 oocytes obtained, including 40 MII oocytes. There were 35 (87.5%) 2PN after ICSI, 8 embryos in the cleavage stage, and 13 (37.14%) blastocysts biopsied. There were 5 cycles in group C with 65 oocytes obtained, including 47 MII oocytes. There were 37 (78.70%) 2PN after ICSI and 17 (41.49%) blastocysts biopsied. There were no significant differences in fertility rates among the three groups (χ^2=1.76, *P*=0.45), but the rate of embryo formation at D3 was significantly different (χ^2=10.53, *P*=0.013). Further analysis indicated that compared with group B, the rate of embryo formation was statistically significantly lower in group A (χ^2=5.38, *P*=0.01), and the rate of high-quality embryos at D3 was significantly different (χ^2=16.5, *P*=0.00). Furthermore, compared with groups B and C, the rate of high-quality embryos at D3 in group A was statistically significantly lower

(χ^2=14.06, *P*=0, χ^2=6.02, P=0). There was no significant difference in the rate of blastocyst formation or the rate of high-quality blastocysts (*P*=0.42, *P*=0.40) in the three groups (Table 2).

After comprehensive chromosome analysis, the balanced or normal embryo rate was 11.36% (5), the abnormal embryo rate was 88.63% (39), and 3 failed to amplify. Among them, the balanced or normal embryo rate was 33.33% (3) and the abnormal embryo rate was 66.67% (6) in three-way rearrangements. The balanced or normal embryo rate was 5.6% (1) and the abnormal embryo rate was 94.4% (17) in double two-way translocations. The balanced or normal embryo rate was 5.9% (1) in exceptional CCRs, and the abnormal embryo rate was 94.1% (16). (Fig. 1) There were no significant differences among the three groups (Fisher exact probabilities *P* = 0.11).

Clinical outcome of PGT cycles

In the 10 PGT cycles, there were 7 cycles in which no embryo could be transplanted and 3 cycles in which balanced or normal embryos were transplanted with frozen-thawed embryo transplantation. One of the 3 cycles was clinically pregnant, and the prenatal diagnosis of amniocytes using G-band and SNP array at 16 weeks of gestation was 46, XN, and a boy was born alive and healthy.

Discussion

BCCR carriers have a high risk of recurrent spontaneous abortion and giving birth to offspring with abnormal karyotypes [11-13]. In this study, although a couple (Case No. 5) had a natural pregnancy with a healthy girl, all seven couples had negative reproductive history, including artificial abortion, spontaneous abortion, aIUP and odinopoeia. Thus, BCCR carriers are advised to maintain contraception, and natural pregnancy should be carefully considered. If natural pregnancy occurs, regular perinatal care and prenatal assessment is needed.

Our data showed that, compared with double two-way rearrangement carriers, there was a significant decline in the embryo formation rate at D3 after fertilization in three-way rearrangement carriers (97.1% vs 72.7%, respectively). Compared with double two-way rearrangement and special CCRs, three-way rearrangement had a significantly lower (67.6% vs 47.3% vs 6.3%, respectively) high-quality embryo formation rate. However, there was no significant difference in the fertilization rate, blastocyst formation rate or high-quality blastocyst formation rate among the three groups, suggesting that different types of BCCRs may have some effect on high-quality embryo formation but not on blastocyst formation. Some studies showed that compared with exceptional CCRs, there was no significant difference in three-way rearrangements in the high-quality embryo rate on D3 after fertilization, while the former was significantly lower than the latter, which was inconsistent with our results [1]. Because CCR cases are rare and the sample size is small, the effect of BCCRs on early embryonic development should be further studied with larger samples to draw a more accurate conclusion.

Our data show that the odds of obtaining a balanced or normal embryo are 11.36%. We analyzed the effect of three types of BCCRs on the embryonic molecular karyotype and found that three-way rearrangements had more balanced or normal embryos, but the difference between the three groups was not statistically significant (33.3% vs 5.6% vs 5.9%). Due to the rarity of BCCRS, we searched the PGT data from BCCRs carriers reported in PubMed through January 2019. Frumkin T et al. reported a couple in which the husband was a three-way rearrangement carrier with 1 PGT cycle, who had 2 balanced or normal embryos and 5 abnormal embryos [14]. Chan Tian et al. reported a couple in which the male partner was an exceptional CCR carrier with 1 PGT cycle, who had no balanced or normal embryos and 2 abnormal embryos [15]. E. Vanneste et al. reported a couple in which the husband was an exceptional CCR carrier with 2 PGT cycles, who had 4 balanced or normal embryos and 12 abnormal embryos [16]. Paul et al. reported 4 couples, including 3 males and 1 female three-way rearrangement carriers with 6 PGT cycles, who had 6 balanced or normal embryos and 31 abnormal embryos [10]. Hu L et al. reported 7 couples, including 5 couples with three-way rearrangement CCRs and 1 couple with double two-way translocations with 8 PGT cycles. Five couples with three-way rearrangements had 3 balanced or normal embryos and 32 abnormal embryos. One couple with a double two-way translocation had no balanced or normal embryos and 12 abnormal embryos. Based on the data above, the balanced or normal embryo rate and abnormal embryo rate were 15.9% (14) and 84.1% (73), respectively, among three-way rearrangements. The balanced or normal embryo rate was 3.33% (1) and the abnormal embryo rate was 96.67% (29) in double two-way translocations. The balanced or normal embryo rate was 14.29% (5) and the abnormal embryo rate was 85.71% (30) in exceptional CCRs (Table 3). There was no significant difference in the embryonic molecular karyotypes among the 3 groups (χ^2=3.24，P=0.20＜P＜0.05), but we should increase the sample size in the future.

The application of PGT for CCR carriers is controversial. Some scholars hold that PGT is an effective fertility treatment for CCRS carriers, while others oppose it [1,17,18]. We analyzed 7 BCCR couples with PGT, and one couple delivered a healthy boy. Although the odds of having a balanced or normal embryo are low (11.36%), PGT reduces the risk of miscarriage and is the only way to help BCCR carriers give birth to related offspring. Therefore, we suggest that BCCR carriers with reproductive needs be treated with PGT. In addition, 18 (46.15%) of the 39 abnormal embryos had new chromosome abnormalities. Therefore, it was necessary to use comprehensive chromosome analysis with the embryos.

Conclusions

Because BCCRs are extremely rare in the population, we analyzed the PGT outcomes of seven BCCRs couples and showed that the embryo formation rate and high-quality embryo rate from three-way rearrangements were low, but the blastocyst formation rate was similar. Different types of BCCRs had little effect on the embryonic molecular karyotype. Although the odds of getting normal embryos for BCCR carriers are very low, PGT can reduce the risk of miscarriage and is the only way to help BCCR carriers give birth to related offspring. Due to the limited sample, the effects of different BCCR types on early embryo development and embryo molecular karyotype need to be studied further by expanding the sample size.

Methods

Study patients

We investigated seven couples who underwent 10 cycles of preimplantation genetic testing (PGT) for BCCRs at the Clinical Center of Reproductive Medicine in the First Affiliated Hospital of Zhengzhou University from May 2011 to June 2018 and analyzed clinical and laboratory data retrospectively. In this study, we divided seven BCCR carriers into three groups. Group A was three-way rearrangements, group B was double two-way translocations, and group C was exceptional CCRs. All subjects enrolled in the study gave written formal consent to participate.

PGT procedure

The seven female patients were treated with a long luteal phase stimulation protocol for controlled ovarian stimulation (COS). Oocytes were observed closely after ICSI, and all embryos were transferred into equilibrated blastocyst medium and cultured at 37°C in a CO_2 incubator. The embryos were scored at D3 and D5/6 according to the Gardner criterion. Embryos on D3 that scored ≥ 6 C-II were considered high-quality embryos. Blastocysts on D6 that scored ≥ 4BC were considered high-quality blastocysts.

Blastomeres on day 3 or the trophoblast cells of blastocysts on day 5/6 were biopsied. Two to five cells were taken, and comprehensive gene amplification was performed. Next, these biopsied cells were assessed by single nucleotide polymorphism microarray (SNP microarray) or next generation sequencing (NGS) technology. Then, vitrification was performed, and embryos identified as balanced or normal were subjected to frozen-thawed embryo transfer.

Statistical methods

Baseline materials were analyzed by one-way ANOVA. The rates were compared by chi-square test and Fisher exact probabilities, and $P<0.05$ was considered statistically significant. Pairwise comparisons among three groups were corrected by Bonferroni post hoc tests, and $P<0.02$ was considered statistically significant.

Declarations

Abbreviations

BCCRs: Balanced complex rearrangements ; PGT: preimplantation genetic testing; ICSI: intracytoplasmic sperm injection; SNP: single nucleotide polymorphism; COS: controlled ovarian stimulation.

Ethics approval and consent to participate

All study methods were approved by Institutional Review Board and Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2011-015), and were performed in accordance with the World Medical Association Declaration of Helsinki. A written informed consent was obtained from all patients, in which the possible risk of misdiagnosis was specified and confirmatory prenatal diagnosis for any ensuring pregnancy was recommended.

Consent for publication

All subjects enrolled in the study gave written formal consent to participate and consented for publication with anonymity. This work has been approved by the Institutional Review Board (IRB) of First Affiliated Hospital of Zhengzhou University.

Availability of data and material

All data generated or analysed during this study are included in this manuscript and its supplementary information files. The authors declared that the data described in the manuscript will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

G.L. conceived and designed the experiment. Y.G. and Y.S selected and supervised suitable patients. G.L. performed comprehensive chromosome screening. W.N. and J.X. performed next generation sequencing and sequencing data analysis. Y.S. and Y.G. recruited the patients, retrieved oocytes and transferred embryos. Y.S. provided overall supervision. G.L. and W.S. drafted the manuscript. All authors reviewed this manuscript.

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Tables

Table 1. General conditions of BCCRs couples

Group	No.	Female Age(y)	Female karyotype	Female BMI （kg/m2 ）	AFC	Female AMH	Male age（y）	Male karyotype
A	1	33	46,XX	22.3	16	2.14	31	46,XY,t(1;16;4)(p22;q22;q23)
A	2	25	46,XX	19.2	4	2.05	24	46,XY,t(8;10;13)(q21;p12;q33)
B	3	37	46,XX	19.72	15	2.53	41	46,XY,t(2;4)(q21;q31), t(2;5)(p23;q35)
B	4	23	45,XX,t(6;13)(p21.1;q34), der(15;21)(q10;q10)	26.7	22	3.04	28	46,XY
C	5	37	46,XX,t(2;11)(q22;q24), inv(13)(q12q32)	21.08	8	2.64	37	46,XY
C	6	37	46,XX	24.8	9	2.73	35	46,XY,t(1;11)(p10;p10), inv(11)(q13q14)
C	7	24	46,XX	19.3	17	3.75	29	46,XY,t(1;8)(p22;p23) Ins(1;11)(p22;q23q25)

Table 2. Effects of three types of BCCRs on embryo development in PGT cycles

Group	Retrieved oocyte	MII	2PN %（n）	D3 embryo %（n）	D3 high quality embryos %（n）	D5/6 blastocyst %（n）	D5/6 high quality blastocyst %（n）
A	35	29	75.9%（22）	72.7%（16）*	6.3%（1）*	50.00%（11）	40.90%（9）
B#	41	40	87.5%（35）	97.1%（34）	67.6%（23）	51.42%（18）	37.14%（13）
C	65	47	78.7%（37）	94.6%（35）	45.7%（16）	51.35%（19）	45.95%（17）
Total	141	116	81.03%（94）	90.4%（85）	47.1%（40）	51.06%（48）	41.49%（39）

*P<0.05

#There was a cycle being excluded from the rate of blastocyst formation and the rate of high quality blastocyst in group B, for it was a biopsied blastomeres at day 3.

Table 3 Literature review

Author	Publication time	BCCR type	PGT technology	Biopsy Type	No. of cycles	Biopsied embryo	No. of Normal/ balanced embryo	No. of Abnormal embryo	Amplification failures
Frumkin T et al.	2017	three-way rearrangements	Chromosome microarray analysis	blastocyst biopsy	1	7	2	5	0
Tian C et al.	2017	exceptional CCRs	Not stated	Not stated	1	2	0	2	0
E. Vanneste et al.	2011	exceptional CCRs	FISH	Blastomere Biopsy	2	16	4	12	0
Paul et al.	2013	three-way rearrangements	FISH	blastocyst biopsy	6	37	6	31	0
Hu Let al.	2018	three-way rearrangements	NGS	blastocyst biopsy	6	35	3	31	1
		double two-way translocations	NGS	blastocyst biopsy	2	12	0	12	0
Our data		three-way rearrangements	NGS	blastocyst or blastomere biopsy	3	9	3	6	0
		double two-way translocations	NGS/SNP	blastocyst biopsy	2	21	1	17	3
		exceptional CCRs	NGS	blastocyst biopsy	5	17	1	16	0
Total					28	156	20	132	4

Table 4 The outcome of SNP/NGS-PGT for BCCRs

Case No.	Embryo ID	Embryo molecular karyotype
1	1	46,XY, +16q(q21→qter,~18M,×3)
1	2	46,XX
2	3	46,XY,-8q(q11.23→q13.3,~20M,×1,),+10p(pter→p13,~16M,×3),-13q(q21.1→qter,~56M,×1)
2	4	47,XY,-8q(q12.1→qter,~82M,×1),+10p(pter→p13,~15M,×3),+16(×3)
2	5	46,XY,-11(×1,mos,~70%)
2	6	46,XY,-8q(q12.1→q13.2,~11M,×1),+10p(pter→p13,~15M,×3),+10q(q23.1→qter,~50M,×3),-13q(q21.33→qter,~45M,×1)
2	7	47,XY,+8q(q12.1→qter,~85M,×3),+10(×3)
2	8	46,XY
2	9	46,XX
3	10	46,XX
3	11	47, XX, +22
3	12	Amplification failure
3	13	46, XY, dup(2)(q21→qter)
3	14	46, XX,dup(5)(q35→qter)
3	15	Amplification failure
3	16	46, XY, dup(2)(q21.1→qter), dup(5)(q35→qter)
3	17	Amplification failure
4	18	47,XX,+16(×3)
4	19	47,XXY,+13q(q31.1→qter,~27M,×3)
4	20	46,XX,-6(p12.3→qter,~119M,×1),-6q(q12→q13,~11M,×1),+13(pter→q33.1,~83M,×3)
4	21	46,XY,-4p(pter→p13,~40M,×1),+6p(pter→p21.1,~42M,×3),-13q(q33.1→qter,~11M,×1),-15q(q24.3→qter,~24M,×1),-16p(pter→p12.3,~20M,×
4	22	45,XY,-4(pter→q31.21,~142M,×1),+6p(pter→p12.3,~50M,×3),-13q(q33.1→qter,~11M,×1),-21(×1)
4	23	44,XY,-6p(pter→p12.3,~50M,×1),+13(pter→q33.1,~84M,×3),+13q(q32.3→qter,~13M,×4),-14(×1),-21(×1)
4	24	45,XX,+1(×3),-4q(q31.3→qter,~28M,×1),-6(p12.3→qter,~119M,×1),-6q(q22.31→q22.33,~9M,×1),-10(p11.21→q22.3,~46M,×1),+13(pter→q
4	25	46,XY,+3p(pter→p22.1,~43M,×3),-20p(pter→p12.3,~8M,×1)
4	26	46,XX,+3p(p21.1→p12.1,~31M,×3),+3q(q25.1→q27.3,~34M,×3),+6q(q14.3→qter,~84M,×3),+7p(p15.3→p12.3,~24M,×3)
4	27	47,XY,+15(pter→q23,~41M,×4),+15(pter→q15.2,~10M,×4),+15q(q21.3→q25.2,~27M,×4),+15q(q24.1→qter,~26M,×4),+21(×3)
4	28	46,XY,-4(×1),+5(p13.3→qter,~150M,×3),-6p(pter→p12.3,~50M,×1),+11(×3),+12(pter→q13.12,~50M,×3),-12q(q13.12→qter,~82M,×1)
4	29	46,XX,-6p(pter→p12.3,~50M,×1)
4	30	46,XX,-1p(p31.2→p21.1,~38M,×1),+2q(q12.1→q24.3,~61M,×3),+2q(q32.3→q36.3,~33M,×3),+3p(p14.2→p12.1,~25M,×3),-4(p15.2→q12,~
5	31	46,XX
5	32	45,XY,-3
5	33	46,XY,del(2)(q21.3→qter),dup(11)(q23.3→qter)
5	34	46,XY,dup(2)(q21.3→qter),del(11) (q23.3→qter)
5	35	45,XY,-2q(q21.1→qter,~109M,×1),-22(×1)
5	36	46,XX,-2p(pter→p16.1)
5	37	45,XY,+2q(q21.2→qter,~104M,×3),-11q(q24.1→qter,~12M,×1),-17(×1)
6	38	45,XX-1q(q21.3→qter,~96M,×1),+11q(q21→qter,~38M,×3),-21(×1)
6	39	46,XX,+3(p24.1→q23,~112M,×3),+4q(q32.2→qter,~27M,×3),-5(pter→q13.2,~69M,×1),+6(p22.3→q16.3,~82M,×3),+6q(q21→qter,~62M,×3
6	40	46,XY,-1(p35.3→q21.3,~123M,×1),+1q(q21.3→q31.1,~34M,×3),+1q(q31.3→q43,~44M,×3),-11q(q21→qter,~39M,×1)
6	41	46,XX,+1q(q21.3→qter,~96M,×3),-11q(q21→qter,~39M,×1)
6	42	47,XY,+1q(q21.3→qter,~96M,×3),-11q(q21→qter,~40M,×1),+16(×3)

6	43	45,XX,-7(×1)
7	44	Multiple chromosome aberrations
7	45	45,XY,-8(×1)
7	46	46,XX,+11q(q22.3→q24.1,~20M,×3)
7	47	46,XX,-11q(q22.3→qter,~25M,×1)

Figures

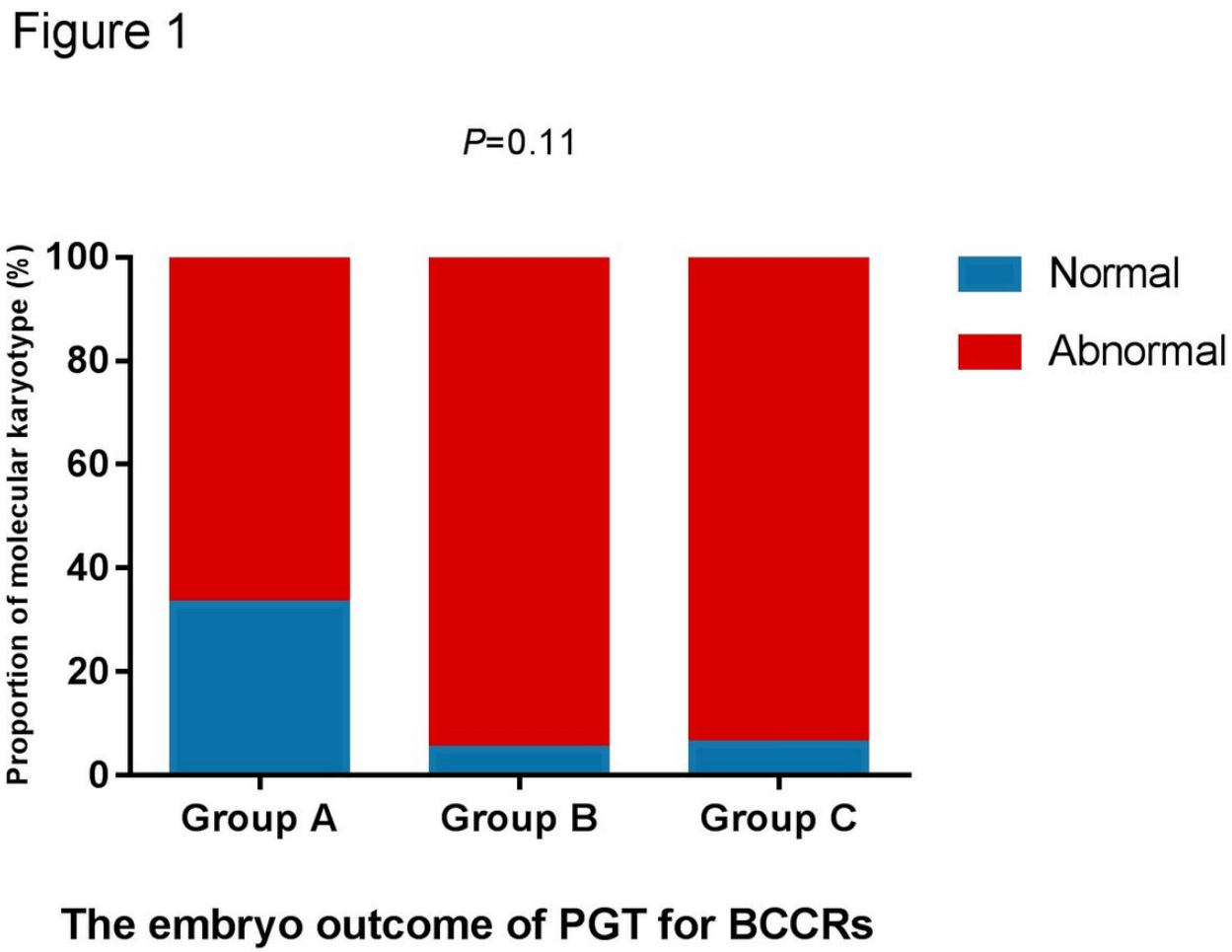


Figure 1