International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Fauzdar A et al. Int J Reprod Contracept Obstet Gynecol. 2024 Mar;13(3):634-642
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20240468

Original Research Article

High prevalence of D/G group acrocentric RPL chromosome polymorphisms in 1400 recurrent pregnancy losses patients, an evaluation of genetic factor and reassessing CPMs in 21st century as normal variants?

Ashish Fauzdar*, Vikas Dixit, Ritu Mavi, Tanzila Khan, Rahul Arya, Neeraj Kumar Sharma

Department of Clinical Genomics and Cytogenetics, Redcliffe Labs, Noida, Uttar Pradesh, India

Received: 04 January 2024
Revised: 05 February 2024
Accepted: 06 February 2024

***Correspondence:**
Dr Ashish Fauzdar,
E-mail: dr.ashishfauzdar@redcliffelabs.com

ABSTRACT

Background: The current burden for recurrent pregnancy losses in India is quite high and is around 7.4% and majority of them with no definitive cause for pregnancy loss even after complete RPL workup. The objective of the study was to investigate the prevalence and possible association of chromosome polymorphisms with recurrent pregnancy loss patients.
Methods: A single centre case-control retrospective study on RPL patients undergoing conventional cytogenetics culture techniques to rule out chromosome abnormalities.
Results: The prevalence of chromosome polymorphism in the study was 33.7% (471/1400) high in comparison to previous studies. The acro ps+/- polymorphisms involving D/G group of chromosomes was significantly higher in the study group observed in 23.5% (330/1400) patients and 15.8% (58/366) in the control group p <0.005. The prevalence of 22ps+ subtype polymorphism was significantly higher in the patient groups with the odd ratio OR (95% CI)- 2.35 (1.245-4.434).
Conclusions: This study substantiates the very high prevalence of CPMs and therefore should be interpreted cautiously till further strong evidence are available, until then patient should be counselled on case-to case basis. In future CPMs may play a crucial role in prognosis and management in unexplained RPL group with no other definitive cause identified after RPL workup as per recommendations from international and national guidelines.

Keywords: Chromosome abnormalities, Chromosome polymorphisms, Genetic factor, Normal variants, Polymorphisms, Recurrent pregnancy loss

INTRODUCTION

It's has been estimated that 70% of all human conceptions fails to complete full term of which 15-20% of clinically recognized pregnancies ends up as pregnancy loss or are spontaneously aborted before 20 weeks of gestation age.[1,2] Furthermore 5% of these women experiences two consecutive miscarriages and 1-2% of them report with two or more failed clinical pregnancies with diagnosis of recurrent pregnancy losses (RPL) reported worldwide.[3,4] As per official communication the current burden for recurrent miscarriages in India is quite high and is around 7.4%.[5] There are international and national recommendation for the clinical management and further evaluation of couples with clinical history of RPL based on the evidence from scientific studies.[6,7] The current established etiologies for recurrent pregnancy loss (RPL) includes antiphospholipid syndrome, endocrinal or metabolic disorders, uterine anomalies, and genetic factor

due to chromosome abnormalities. According to these guidelines, current treatment and interventions are possible in only half of the patients while another half are still categorized into idiopathic category with no major definitive diagnosis could be established as recommended after the RPL workup.[2]

The incidence of chromosome abnormalities in couples with recurrent miscarriages is 2-5% mainly contributed due to presence of balanced or Robertsonian translocation.[6,7] Though most miscarriages in first trimester are sporadic or de novo in nature with majority (~50%) of losses arising due to random numerical chromosome abnormalities including trisomy's or sex chromosome monosomy followed by polyploidies.[1] The parental karyotype is universally recommended investigation for the diagnostics evaluation and further clinical management of couples experiencing repeated pregnancy losses.[7] In addition to evaluation of whole chromosome abnormalities there are emerging evidence over the years that the variation in the short arm and nucleolar organizing (NOR) region that are commonly referred to as chromosome polymorphisms (CPMs) for a possible association in couples experiencing recurrent pregnancy loss, unexplained infertility and other reproductive failure or infertility.[8-15] There are various studies from the patients of RPL that had also reported a higher frequency of chromosomal polymorphisms i.e. between 8-15% in couple with subfertility and pregnancy losses.[16-20] The real impact of chromosomal polymorphism or normal variant in the human genetics remains controversial as they are still considered as a normal variant as a normal karyotype with no related phenotypic and functional effects. As per international system cytogenomic nomenclature, the recommendation for reporting of chromosome abnormalities suggests not to include chromosome polymorphism in reporting karyotype nomenclature but can be mentioned in the report description to avoid any misinterpretation labelling as a normal variant.[22] However, over the years it has been postulated through various scientific studies that chromatin variations can affect centromere function that could possibly impact chromosome segregation by microtubule binding through kinetochore that serve as the cohesion site between sister chromatids and chromosome biorientation that can cause difficulty in homologous chromosome paring and hence cell division during gametogenesis.[23,24] It has been further hypothesized that the heterochromatin region in the chromosome plays an essential role in spindle attachment, chromosome movement and sister chromatid cohesion.[25]

Currently there is huge dilemma in the clinical management of couples with history of recurrent pregnancy loss classified into idiopathic category as counselling of such patient is complex and challenging to the gynaecologist with no other identifiable cause even after routine RPL workup with no chromosome abnormalities being detected. In the present study we retrospectively evaluated genetic factor through by detecting chromosome abnormalities including balanced translocation in the patient with history of RPL along with the chromosome's variations in D/G group chromosomes and other normal variants. The purpose of the study was to investigate the chromosome abnormalities and possible association of chromosome polymorphism in recurrent pregnancy loss patients for further clinical management of patients.

METHODS

This was a single centre case-control retrospective study conducted between September 2021 to May 2023 on the samples received at our laboratory to rule out chromosome abnormalities in sub-fertile couples. The study group analysis included 1400 individuals with 700 couples with an established clinical diagnosis of recurrent pregnancy loss. The mean female age of 29.7 years with age range between 21-45 years while men mean age was 33.3 years and range between 21-50 years in the study population. While the control group we included 336 individuals with males age between 18-52 years and females age range between 18-55 years no history of recurrent pregnancy loss, secondary infertility, and patient sample received to rule out chromosome abnormalities during the same duration. An informed signed consent was taken from the patient to participate in the biomedical/research studies along with the test request form for getting the personal characteristics and clinical history.

The metaphase chromosome preparation was done from 72-hour peripheral blood lymphocyte stimulated culture for both the partners through conventional cytogenetics culture techniques using the standard protocols.[26] At least 20 metaphases were analysed, and five metaphases were karyotyped from each case using the bright field microscope with automated karyotype software (Olympus, Fluorescence Microscope Model BX53, Japan and Applied Spectral Imaging's, Band view Cytopower Karyotype System, Israel). The minimum banding resolution for each case was between 450-550 bands for reporting of chromosome abnormalities and polymorphic variants as per recommendation of the latest version of international system for cytogenetic nomenclature (ISCN).[21] The very clearly and distinct chromosome polymorphic variants were observed and documented in all cases in the analysed metaphases for the large variation in the length of centromeric heterochromatin on the long arm of chromosomes 1, 9, 16 (1qh+, 9qh+, 16qh+) and the distal heterochromatin region of chromosome Y (Yqh+). Also, the polymorphic variations were analysed in the acrocentric chromosomes (13, 14, 15, 21 and 22) with increase or decrease in the length of short arm of satellites and stalks were designated as ps± and pstk±. Only the most consistent and the prominent polymorphism observed in all the metaphases were classified as a polymorphism variant with at least twice the size of corresponding region on the other homologous chromosomes acting as an internal control for documentation (Figure 1).

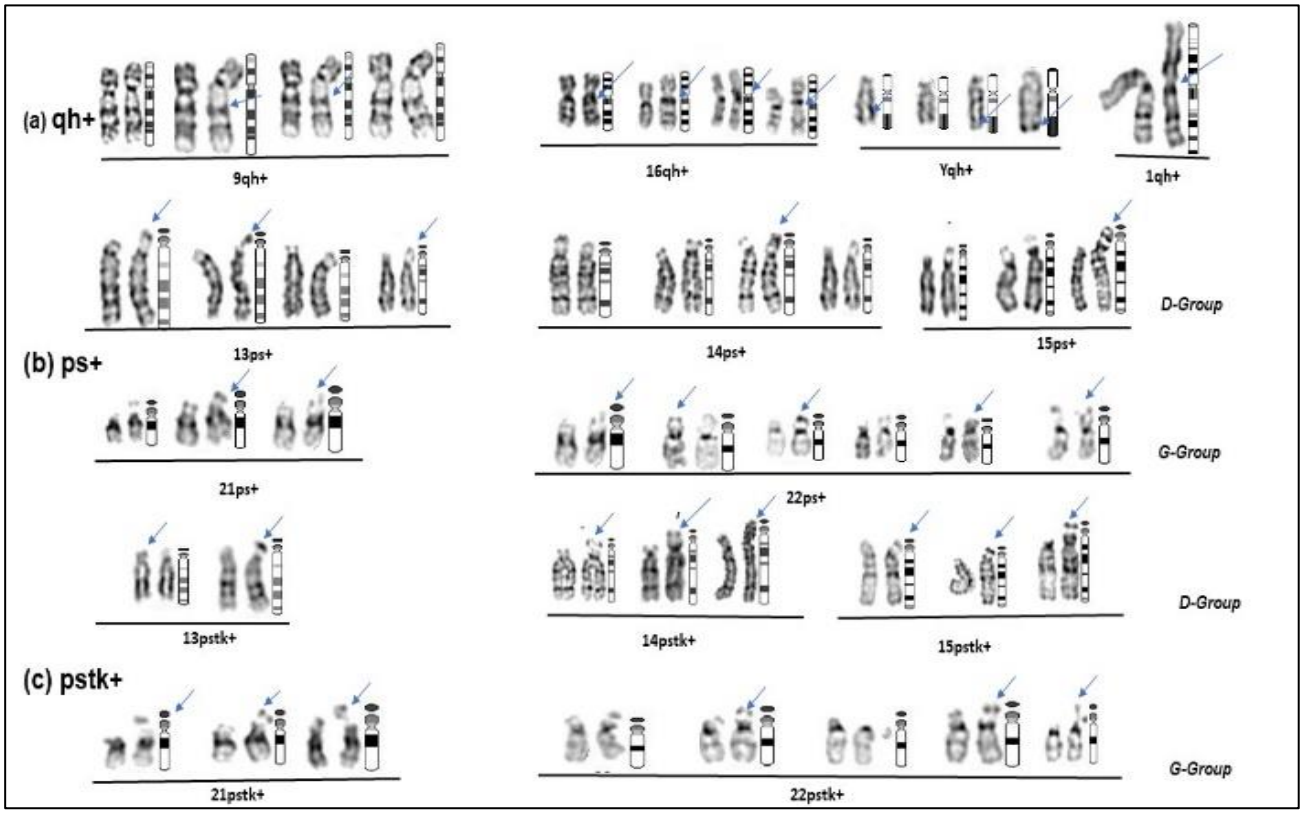

Figure 1: Some of the representative images of Chromosome Polymorphisms (CPM) observed among from RPL patients from our study indicating: (a) qh+ (1,9, 16); (b) acro ps+; (c) acro pstk+ for 13,14, 15, 21 and 22 chromosomes indicated by the arrows.

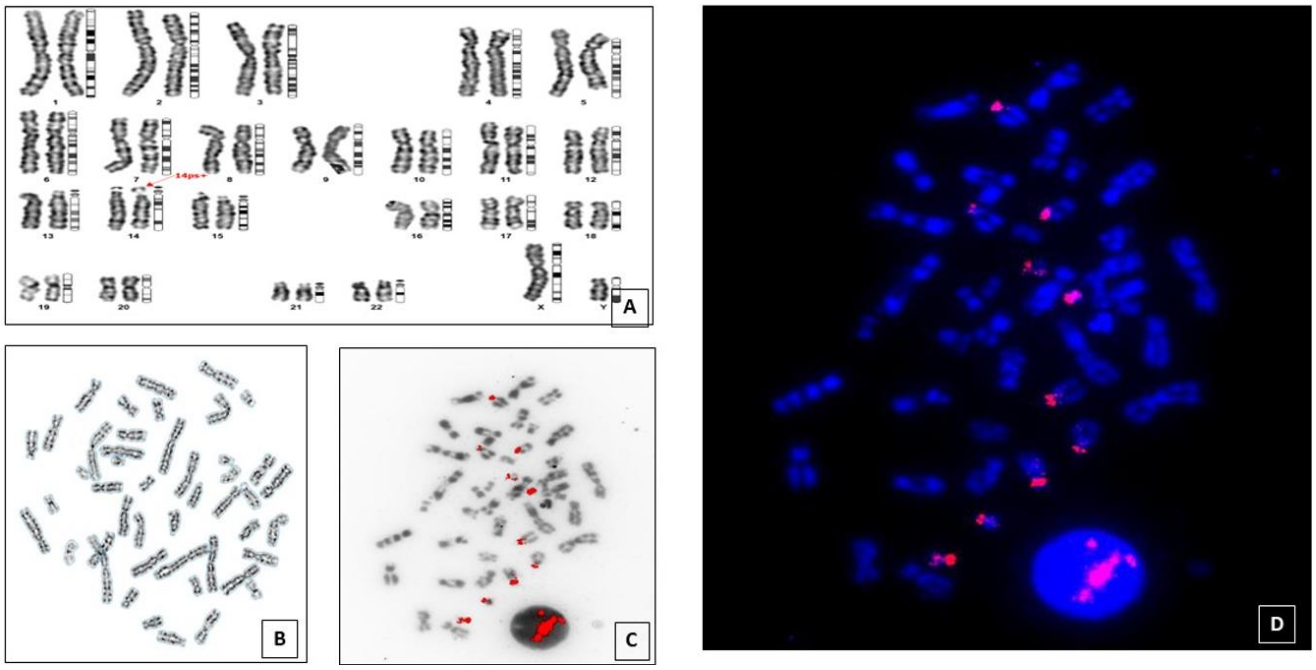

Figure 2: (A) Patient karyotype along with CPM on the NOR (acro) region on the short p-arm of the chromosome 14ps+, (B) Metaphase plate after GTG banding at 650 band resolution, (C) Inverted DAPI image with red FISH signals for the acro ps+ region of D & G group chromosomes and (D) DAPI stained chromosomes 13,14, 15, 21 & 22 along with the FISH signal for the NOR region for the acro ps+ & acro pstk+ region on the p arm of the chromosomes to rule out cryptic translocation between the chromosomes.

The pericentric inversion of chromosome 9 and Y commonly referred as inv(9) and inv(Y) and were also recorded in the study. The fluorescence in-situ hybridization (FISH) technique was applied utilizing Acro-P- Arm Probe (catalogue number LPE NOR-S) labelled with red fluorescence dye for further confirmation and presence of the NOR region specific for rRNA genes located on the short arm of the acrocentric chromosomes (13, 14, 15, 21 and 22) to rule out suspected cases of cryptic translocation processed as per the company (Cytocell, Oxford Gene Technology, Cambridge UK) recommended protocols (Figure 2).

Statistical methods

All the patient related information and variable factors were captured daily in Microsoft Excel spreadsheet, and analysis was done using the statistical package for social sciences IBM Corp. released 2012. IBM SPSS Statistics for Windows, version 28.00, IBM, Armonk, NY, United States of America. Categorical variables were presented in number and percentage (%). Categorical variables are expressed as frequencies and percentages. Different types of chromosome polymorphisms (CPM) observed and classification between the groups were analysed and compared using the χ^2 test. Fisher's exact test was used when fewer than five patients were expected. Odds ratio (OR) with 95% CI was used to determine the odds of the event occurring in study group as compared to control group. P<0.05 was considered statistically significant.

RESULTS

The overall results of the study for the different types of numerical and structural chromosome abnormalities are summarized in the Table 1. In total in 21 (1.5%) individuals chromosome abnormalities was detected and chromosome polymorphisms in 471 (33.7%) individuals. The balanced translocations were the most common structural chromosomal abnormalities including both reciprocal and robertsonian translocation in 17 (1.2%) patients, predominately observed among the females 12 (0.85%) (Table 1). During the further analysis by comparing different types of polymorphic variations observed in the study and the control group, the prevalence of acro ps+/- polymorphisms involving D/G groups of chromosomes was significantly higher. In the study group with 13ps+/-, 14ps+/-, 15ps+/-, 21ps+/-, 22ps+/- was observed in 23.5% (330/1400) patient with p<0.005 in the study group and 15.8% (58/366) individuals of the control group. Among the acro ps+/- the prevalence of 22ps+ subtype polymorphism was significantly higher with the odd ratio OR (95% CI)- 2.35 (1.245-4.434). The most prevalent CPM variant observed in the study group was 21ps+ (6.9%) and 22ps+ (6.7%) followed by increase in the heterochromatin region 9qh+ (4.5%) and variants with increase in the stalks on the short arm of acrocentric chromosomes reported as acro pstk+/- (3.7%) couples (Table 2).

Table 1: Summary of different types of chromosome abnormalities and polymorphism observed among 1400 individuals (700 sub fertile couples) with the clinical diagnosis of recurrent pregnancy losses (RPL).

Karyotype	Prevalence (%) (n=1400), 700 couples	
Normal (46, XX/ 46, XY)	908 (64.8)	
Chromosome polymorphism	471 (33.7)	
Chromosome abnormalities	21 (1.5)	
Numerical abnormalities	2 (0.14)	
Mosaic		
45, X [39]/47, XXX [11]		38/F
45, X [15]/46, XX [35]		28/F
Structural abnormalities	19 (1.4)	
Reciprocal translocation	12 (0.85)	
46, XY, t (2;4) (q37; p14)	1	35/M
46, XX, t (2;21) (q13; q22)	1	32/F
46, XX, t (3;13) (q12; q22)	1	33/F
46, XX, t (4;6) (p35: q21)	1	33/F
46, XX, t (6;19) (p21.3; p13.3)	1	24/F
46, XX, t (7;13) (q32; q14)	1	25/F
46, XY, t (7:20) (q11.2; q11.2)	1	45/M
46, XY, t (7:17) (q22; q22)	1	30/M
46, XX, t (8:20) (q22; p13)	1	29/F
46, XX, t (18:20) (q21.1: q13.1)	1	30/F
46, XX, t (X;7) (q24; q32)	1	24/F
46, XY, t (4;8) (q31; q22)	1	32/M
Robertsonian translocation	5 (0.35)	
45, XX, der (13:14) (q10; q10)	2	21/F

Continued.

Karyotype	Prevalence (%) (n=1400), 700 couples	
45, XX, der (14;21) (q10; q10)	2	23/F
45, XY der (14;22) (q10; q10)	1	35/M
Addition 46, XY, add (22) (q13)	1	33/M
Deletion 46, XY, del (22) (q12.3)	1	32/M

Table 2: Comparison and types of Chromosome polymorphic variations observed between the study group and the control group without the history of recurrent pregnancy loss.

Classification	CPM	Study group (N=1400)	Composition ratio (%)	Control group (N=366)	Composition ratio (%)	P value	OR	95% CI
qh+	1qh+	1	0.07	0	0	1.000	Ref	Ref
	9qh+	63	4.5	16	4.37	0.916	1.031	0.588-1.807
	16qh+	5	0.35	1	0.27	1.000	1.308	0.152-11.233
	Yqh+	10	0.71	3	0.81	0.739	0.871	0.238-3.180
	Total	79	5.6	20	5.5	0.895	1.035	0.625-1.714
Chromosome variation in D/G genomes								
acro ps+/-	13ps+	28	2.0	5	1.4	0.425	1.474	0.565-3.883
	14ps+	55	3.9	9	2.5	0.180	1.633	0.794-3.314
	15ps+	55	3.9	11	3.0	0.407	1.32	0.684-2.548
	21ps+	97	6.9	22	6.0	0.533	1.164	0.722-1.877
	22ps+	95	6.7	11	3.0	0.007*	2.262	1.198-4.270
	Total	330	23.5	58	15.8	0.002*	1.638	1.205-2.225
acro pstk+/-	13pstk+	2	0.14	1	0.27	0.502	0.5222	0.047-5.775
	14pstk+	7	0.5	1	0.27	1.000	1.834	0.225-5.474
	15pstk+	9	0.64	2	0.54	1.000	1.178	0.253-5.474
	21pstk+	20	1.4	7	1.9	0.502	0.743	0.312-1.772
	22pstk+	15	1.07	2	0.54	0.549	1.966	0.448-8.635
	Total	53	3.7	13	3.5	0.834	1.068	0.576-1.982
Inversions	Inv(9)	8	0.57	3	0.81	0.707	0.695	0-184-2.635
	Inv(Y)	1	0.07	2	0.54	0.111	0.130	0.012-1.439
	Total	9	0.64	5	1.4	0.165	0.467	0.156-1.403
	Grand total	471	33.6	96	26.2	0.007*	1.426	1.102-1.846

*Signifies significant p value <0.05, Test used: Chi square or Fisher's exact test (if any frequency <5).

Table 3: Details and frequency for different chromosomal polymorphic variants observed among male and females (700 couples) with the history of recurrent pregnancy losses.

Classification	CPM	No. of male (n=700)	Composition ratio (%)	No. of female (n=700)	Composition ratio (%)	Total No.	Composition ratio (%)	P value
qh+	1qh+	0	0	1	0.14	1	0.07	1.000
	9qh+	35	5	28	4	63	4.5	0.367
	16qh+	2	0.28	3	0.42	5	0.35	1.000
	Yqh+	10	1.4	0	0	10	0.71	0.002*
	Total	47	6.7	32	2.2	78	5.5	0.082
Chromosome variation in D/G genomes								
acro ps+/-	13ps+	12	1.7	16	2.2	28	2.0	0.445
	14ps+	28	4.0	27	3.84	55	3.9	0.891
	15ps+	30	4.2	25	3.5	55	3.9	0.492
	21ps+	42	6.0	55	7.8	97	6.9	0.171
	22ps+	48	6.8	47	6.6	95	6.7	0.915
	Total	160	22.8	170	24.2	330	23.5	0.529
acro pstk+/-	13pstk+	2	0.28	0	0	2	0.14	0.500
	14pstk+	3	0.42	4	0.64	7	0.5	1.000

Continued.

Classification	CPM	No. of male (n=700)	Composition ratio (%)	No. of female (n=700)	Composition ratio (%)	Total No.	Composition ratio (%)	P value
	15pstk+	5	0.71	4	0.57	9	0.64	1.000
	21pstk+	11	1.5	9	1.2	20	1.4	0.652
	22pstk+	7	4.0	8	1.14	15	1.07	0.795
	Total	28	4	25	3.5	53	3.78	0.674
Inversions	Inv(9)	6	0.85	2	0.28	8	0.57	0.288
	Inv(Y)	1	0.14	0	0	1	0.07	1.000
	Total	7	1	2	0.28	9	0.64	0.178
	Grand total	242	34.5	229	32.7	471	33.6	0.462

*Signifies significant p value <0.05, Test used: Chi square or Fisher's exact test (if any frequency <5).

The study population was further evaluated for prevalence of CPM as per the gender and was observed that the prevalence of male carriers (34.5%) was little higher compared to that of women carriers (32.7%) with no significant difference (p=0.462). In the study population acro ps+/- group chromosomes labelled as 13ps+/-, 14ps+/-, 15ps+/-, 21ps+/-, 22ps+/- were the most prevalent forms even among the female carriers (24.2%) then the male carriers (22.8%) with no clinical significance (p=0.529). In the study group the most observed normal variant among the female carriers was 21ps+ (7.8%) and 22ps+ (6.8%) in the male carriers with no significant difference p>0.005 (Table 3).

DISCUSSION

Traditionally, chromosome polymorphisms (CPM) are considered as normal variant in an individual with no phenotypic or clinical significance.[22] However, at present, there are many published studies worldwide that had hypothesized a close association of chromosomal polymorphisms to unexplained infertility, reproductive disorders, and couples with recurrent pregnancy losses. This study for the first time highlights a higher prevalence of chromosome polymorphic i.e., around 33.7% a significantly higher prevalence compared to the earlier reported studies from subcontinent from the sub-fertile couples experiencing repeated pregnancy loss and primary infertility.[8-15] Over the years there had been many reported studies worldwide that had reported a significantly high frequency of chromosomal polymorphisms between 8–22% in the sub-fertile couples in comparison to the fertile couples.[16-19] While in-contrast very few studies had reported prevalence as low as to 1.6% in couples experiencing RPL.[20]

The chromosome abnormality reported from the study is 3.0% (700 couples) that is in the lower limit range of percentile contribution of genetic factor between 2-5% as per the published guidelines for the evaluation and management of couples of recurrent pregnancy loss.[5-7] The chromosome abnormalities observed in this study are also in an agreement to other reported studies from the subcontinent.[8,15.27-30] The most common chromosome abnormality detected were for structural chromosome abnormalities that included both robertsonian and reciprocal translocations in 2.7% of couples contributing to about 90% of the total chromosome abnormalities observed from the study. Approximately, twice the number of females were seen with chromosomal rearrangements with a female to male ratio of 2:1 in the present study also in conjunction to other studies from the region.[27-30] The current study shows that the most common and significant number of polymorphic variations observed for D/G group of chromosomes for acro $ps^{+/-}$ (23.5%) labelled as $13ps^{+}$, $14ps^{+}$,$15ps^{+}$, $21ps^{+}$, $22ps^{+/}$. The prevalence of $22ps^{+}$ was significantly higher in study group as compared to the control group with odds ratio suggesting that the study group including the patient of recurrent pregnancy loss were 2.35 times more likely to have $22ps^{+}$ compared to the control group p<0.005 (Table 2).

The incidence $21ps^{+}$ chromosomal polymorphisms are reported to be higher in women (7.8%) but were not significantly high compared to men (6.0%) in the study. The aneuploidy for chromosome 21 is one of the most common chromosome abnormalities observed postnatally leading to high incidence of babies born with trisomy 21 consistent with the diagnosis of Down's syndrome (1 in 876).[31] Women with clinical history of recurrent pregnancy loss and most miscarriages in first trimester are sporadic or de novo in nature with majority (~50%) of losses arising due to random numerical chromosome abnormalities including trisomy's or sex chromosome monosomy followed by polyploidy's as discovered with the genetic testing of product of conception (poc) tissue.[1-4] Further studies have established that the chromatin variations in D/G chromosomes polymorphic variants arises due to increased heterochromatin region in the short arm of chromosome telomeres commonly known as NOR are rich in large structural rRNA (5.8S, 18S, and 28S) covering ribosomal genes. These rRNA gene are critically important for the viability of cell and represent around 0.5% of the human diploid genome clustered in the short arm or stalks attached to the centromeres and playing an important role in spindle attachment and may cause the defects in kinetochore assembly and centromere function thus affecting the homologous chromosome paring, chromosome movement, meiotic pairing and sister

chromatid cohesion that could impact cell division and can finally affect the gamete formation during gametogenesis.[11-13,25] These errors can further impact the cell cycle and chromosome abnormalities in embryos oogenesis leading to the formation of chromosomally abnormal (aneuploid) gametes.

There are now many follow-up studies on the carriers of polymorphism that had investigated the pregnancy outcomes through assisted reproductive technologies in infertile carriers of CPM. Hong et al, and few others had highlighted that the chromosomal polymorphism seems to have no adverse effects on pregnancy outcomes including implantation and clinical pregnancy rate through IVF-ICSI techniques.[32,33] In one of the recent studies as a the follow up to the female carriers of D/G chromosome polymorphisms in the embryos reported significantly lower fertilization and cleavage rate in the embryos as compared to the control patients undergoing IVF treatment.[34] Cheng et al also reported significantly low numbers of 2PN stages embryos, increased rate of spontaneous miscarriage rate and preterm birth in infertile couples undergoing assisted reproductive techniques as in comparison to the patient with normal karyotype.[13] In arising due to non-disjunction of chromosome either due to anaphase lag during the meiosis-I or non-disjunction of homologous chromosomes during meiosis II during

another study on unexplained RPL couples undergoing preimplantation genetic testing for aneuploidy analysis (PGT-A) highlighted that the male carriers had lower blastocyst rate and high aneuploidy rate with no difference in pregnancy outcomes as compared to the female carriers suggesting an adverse effect on the embryo quality only.[14] Ni et al reported that the embryo transferred rate and cumulative live birth rate of male polymorphism carriers were significantly lower than those of female carriers and normal karyotype couples in IVF/ICSI treatments. Their seems to some connection between gender and CPMs as the studies suggested that male CPMs are linked to a higher cumulative early miscarriage rate and lower live birth rate following in-vitro fertilization (IVF).[35,36] In this study also the incidence of chromosomal polymorphisms was higher in men but were not significantly different as compared to women (Table 3). The current study on analysis of CPM in sub-fertile couples showed that the prevalence of polymorphic variants is higher as compared to previous reported studies from the sub-continent (Figure 3).[8-11,16,18-20,27,28,37-39]

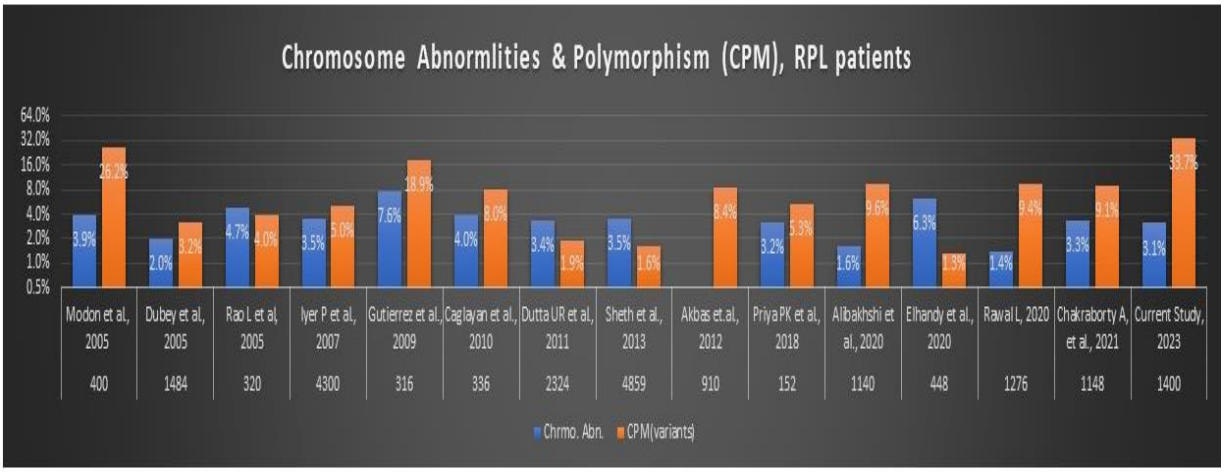

Figure 3: Review of literature for the chromosome abnormalities and polymorphism (CPM) from RPL patients reported worldwide in correlation with our study.

Even though chromosomes analysis or karyotype test is a gold standard investigation and remains an essential part of genetic workup for detecting balanced translocations for further management of patient before planning for any future pregnancies, but still the reported prevalence of chromosome abnormality is reported with low prevalence from the region. One of the reasons for the lower prevalence of chromosome abnormality from the subcontinent could be access to the quality genetic diagnostic care at an affordable cost to the patient. Further the availability of genetic testing from an accredited laboratory with experienced personals working behind the microscopes with demonstrated and proven competency to detect cryptic (small) structural chromosomal rearrangements including translocations and polymorphisms. However, other reason could be due to socio-economic reasons of patient opting out for further investigations including genetic testing after experiencing psychological distress of recurrent pregnancy loss.

CONCLUSION

In conclusion the presence of normal variant should be interpreted cautiously in the patient with recurrent

pregnancy losses and should not be further ignored as they may play a significant role in prognosis and treatment needs to be followed by on case-to-case basis till further strong evidence are available through scientific studies. In the meantime, this approach can help treating clinician in counselling and timely clinical intervention for plan for future pregnancies in couples further that are categorized as unexplained RPL. Also, there is a need for further case control follow-up studies with male female carriers of polymorphism through assisted reproductive technologies followed by preimplantation genetic screening for aneuploidy screening (PGS-A) to know the exact impact of CPM in the embryo development including blastocyst rate, aneuploidy rate followed by clinical pregnancy rate, early miscarriages, and live birth rate for further investigation of normal variant in the 21st century. The current study instigates further research to explore for the possible association of chromosome polymorphism of acro ps+ region including 21ps+ and 22ps+ regions that may be resulting in the high prevalence of chromosome 21 aneuploidies in women with advanced maternal age and with history of recurrent pregnancy losses.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Jacobs PA, Hassold T. Chromosome abnormalities: origin and etiology in abortions and livebirths. In: Vogel F, Sperling K, eds. Human genetics. Berlin: Springer-Verlag; 1987:233-244.
2. Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. Fertil Steril. 2012;98(5):1103-11.
3. Gabbe S, Niebyl J, Simpson J, Landon M, Galan H. Obstetrics Normal and problem pregnancies 6th edn. Elsevier Saunders Philadelphia: PA; 2012.
4. Stirrat GM. Recurrent miscarriage. Lancet. 1990;336(8716):673-5.
5. Standard Treatment Guidelines for Management of Recurrent Spontaneous Abortions. MoH and FW, 2017. Available from: http://clinicalestablishments.gov.in/WriteReadData/3361.pdf. Accessed on 2 December 2023.
6. Bender Atik R, Christiansen OB, Elson J, Kolte AM, Lewis S, Middeldorp S, et al. ESHRE guideline: recurrent pregnancy loss: an update in 2022. Hum Reprod Open. 2023;2023(1).
7. Society for Maternal-Fetal Medicine. Committee Opinion No. 682: Microarrays and next-generation sequencing technology: the use of advanced genetic diagnostic tools in obstetrics and gynecology. Obstet Gynecol. 2016;128(6):e262-8.
8. Madon PF, Athalye AS, Parikh FR. Polymorphic variants on chromosomes probably play a significant role in infertility. Reprod Biomed Online. 2005;11:726-32.
9. Sahin FI, Yilmaz Z, Yuregir OO, Bulakbasi T, Ozer O, Zeyneloglu HB. Chromosome heteromorphisms: an impact on infertility. J Assist Reprod Genet. 2008;25:191-5.
10. De la Fuente-Cortés BE, Cerda-Flores RM, Dávila-Rodríguez MI, García-Vielma C, De la Rosa Alvarado RM, Cortés-Gutiérrez EI. Chromosomal abnormalities and polymorphic variants in couples with repeated miscarriage in Mexico. Reprod Biomed Online. 2009;18:543-8.
11. Caglayan AO, Ozyazgan I, Demiryilmaz F, Ozgun MT. Are heterochromatin polymorphisms associated with recurrent miscarriage? J Obstet Gynaecol Res. 2010;36:774-6.
12. Dong Y, Jiang YT, Du RC, Zhang HG, Li LL, Liu RZ. Impact of chromosomal heteromorphisms on reproductive failure and analysis of 38 heteromorphic pedigrees in northeast China. J Assist Reprod Genet. 2013;30:275-81
13. Cheng R, Ma Y, Nie Y. Chromosomal polymorphisms are associated with female infertility and adverse reproductive outcomes after infertility treatment: a 7-year retrospective study. Reprod Biomed Online. 2017;35:72-80.
14. Cao M, Zhang Q, Zhou W, Zhu Y, Li H, Yan J. Analysis of aneuploidy rate and pregnancy outcomes in unexplained recurrent pregnancy loss couples with chromosome polymorphism after PGT-A. Front Med. 2022;9:803988.
15. Minocherhomji S, Athalye AS, Madon PF, Kulkarni D, Uttamchandani SA, Parikh FR. A case-control study identifying chromosomal polymorphic variations as forms of epigenetic alterations associated with the infertility phenotype. Fertil Steril. 2009;92(1):88-95
16. Akba¸s H, Isi H, Oral D, Türkyılmaz A, Kalkanlı-Ta¸s S, Sim¸sek S, et al. Chromosome heteromorphisms are more frequent in couples with recurrent abortions. Genet Mol Res. 2012;11:3847-51.
17. Wang Y, Li G, Zuo MZ, Fang JH, Li HR, Quan DD, et al. Y chromosome polymorphisms may contribute to an increased risk of male-induced unexplained recurrent miscarriage. Biosci Rep. 2017;37:BSR20160528.
18. Alibakhshi R, Nejati P, Hamani S, Mir-Ahadi N, Jalilian N. Cytogenetic analysis of 570 couples with recurrent pregnancy loss: reporting 11 years of experience. J Hum Reprod Sci. 2020;13(3):216-20.
19. Elhady GM, Kholeif S, Nazmy N. Chromosomal aberrations in 224 couples with recurrent pregnancy loss. J Hum Reprod Sci. 2020;13(4):340-8.
20. Sheth FJ, Liehr T, Kumari P, Akinde R, Sheth HJ, Sheth JJ. Chromosomal abnormalities in couples with repeated fetal loss: an Indian retrospective study. Indian J Hum Genet. 2013;19:415-22.
21. McGowan-Jordan J, Hastings RJ, Moore S. ISCN 2020: an international system for human cytogenetic nomenclature. S Karger, Basel; 2020.

22. Borgaonkar DS. Chromosomal variation in man: a catalogue of chromosomal variants and anomalies. New York: Wiley-Liss; 1997.
23. Westhorpe FG, Straight AF. Functions of the centromere and kinetochore in chromosome segregation. Curr Opin Cell Biol. 2013;;25(3):334-40.
24. Kitajima TS, Ohsugi M, Ellenberg J. Complete kinetochore tracking reveals error-prone homologous chromosome biorientation in mammalian oocytes. Cell. 2011;146(4):568-81.
25. Karpen G, Endow S. Meiosis: chromosome behaviour and spindle dynamics. In: Endow S, Glover D, eds. Frontiers in Biology. Oxford University Press, Oxford; 1998.
26. Verma R, Babu A. Human chromosomes manual of basic techniques. Pergamon Press: New York; 1989.
27. Dubey S, Chowdhury MR, Prahlad B, Kumar V, Mathur R, Hamilton S, et al. Cytogenetic causes for recurrent spontaneous abortions- an experience of 742 couples (1484 cases). Indian J Hum Genet. 2005;11(2):94-8.
28. Iyer P, Wani L, Joshi S, Lakshmi J, Dalvi R, Chavan D, et al. Cytogenetic investigations in couples with repeated miscarriages and malformed children: report of a novel insertion. Reprod Biomed Online. 2007;14(3):314-21.
29. Priya PK, Mishra VV, Roy P, Patel H. A study on balanced chromosomal translocations in couples with recurrent pregnancy loss. J Hum Reprod Sci. 2018;;11(4):337-42.
30. Rawal L, Kumar S, Mishra SR, Lal V, Bhattacharya SK. Clinical manifestations of chromosomal anomalies and polymorphic variations in patients suffering from reproductive failure. J Hum Reprod Sci. 2020;13(3):209-15.
31. Verma IC. Burden of genetic disorders in India. Indian J Pediatr. 2000;67(12):893-8.
32. Kim JJ, Rhee HS, Chung YT, Park SY, Choi SK. Prenatal detection of de novo inversion of chromosome 9 with duplicated heterochromatic region and postnatal follow-up. Exp Mol Med. 1999; 31(3):134-6
33. Hong Y, Zhou YW, Tao J, Wang SX, Zhao XM. Do polymorphic variants of chromosomes affect the outcome of in vitro fertilization and embryo transfer treatment? Hum Reprod. 2011;26:933-40.
34. Li SJ, Cheng YX, Ye-Shang, Zhou DN, Zhang Y, Yin TL, et al. Chromosomal polymorphisms associated with reproductive outcomes after IVF-ET. J Assist Reprod Genet. 2020;37(7):1703-10.
35. Ni T, Li J, Chen H, Gao Y, Gao X, Yan J, et al. Male chromosomal polymorphisms reduce cumulative live birth rate for IVF couples. J Assist Reprod Genet. 2017;34(8):1017-25
36. Ou Z, Yin M, Chen Z, Sun L. Meta-analysis of the association between chromosomal polymorphisms and outcomes of embryo transfer following in vitro fertilization and/or intracytoplasmic sperm injection. Int J Gynecol Obstet. 2019;144(2):135-42.
37. Rao L, Murthy K, Babu A, Venkata P, Deenadayal M, Singh L. Chromosome inversions and a novel chromosome insertion associated with recurrent miscarriages in South India. Arch Gynecol Obstet. 2005;272(4):273-7
38. Dutta UR, Rajitha P, Pidugu VK, Dalal AB. Cytogenetic abnormalities in 1162 couples with recurrent miscarriages in southern region of India: report and review. J Assist Reprod Genet. 2011;28(2):145-9.
39. Chakraborty A, Kar S, Mohapatra PC, Banerjee B. A case-control study identifying the frequency and spectrum of chromosomal anomalies and variants in a cohort of 1000 couples with a known history of recurrent pregnancy loss in the eastern region of India. J Hum Reprod Sci. 2021;14(4):422-30.

Cite this article as: Fauzdar A, Dixit V, Mavi R, Khan T, Arya R, Sharma NK. High prevalence of D/G group acrocentric chromosome polymorphisms in 1400 recurrent pregnancy losses patients, an evaluation of genetic factor and reassessing CPMs in 21st century as normal variants? Int J Reprod Contracept Obstet Gynecol 2024;13:634-42.