Salud, Ciencia y Tecnología. 2025; 5:1043
doi: 10.56294/saludcyt20251043

ORIGINAL

Probable role of chromosomal polymorphisms in reproductive failure. Findings in the Panamanian population

Probable rol de los polimorfismos cromosómicos en las fallas reproductivas. Hallazgos en población panameña

Luis A. Sotillo-Bent[1,2], Johan Varela[3], Génesis Villarreal[3], José A. Cedeño-Escudero[1,2], Michelle Facey[1], Estela Morales- Peralta[4], Luis A. Méndez-Rosado[4]

[1]Instituto Nacional de Genética Médica y Genómica. Panamá.
[2]Facultad de Medicina, Universidad de Panamá. Panamá.
[3]Escuela de Tecnología Médica, Universidad Panamá. Panamá
[4]Centro Nacional de Genética Médica. La Habana, Cuba.

Cite as: Sotillo-Bent LA, Varela J, Villarreal G, Cedeño-Escudero JA, Facey M, Morales- Peralta E, et al. Probable role of chromosomal polymorphisms in reproductive failure. Findings in the Panamanian population. Salud, Ciencia y Tecnología. 2025; 5:1047. https://doi.org/10.56294/saludcyt20251043

Submitted: 06-03-2024 **Revised:** 15-06-2024 **Accepted:** 22-10-2024 **Published:** 01-01-2025

Editor: Prof. Dr. William Castillo-González

Corresponding author: Luis A. Méndez-Rosado

ABSTRACT

Introduction: chromosomal polymorphisms are variations in chromosomes in normal populations, generally affecting heterochromatic regions that are poor in protein-coding genes. Several international studies associate the influence of chromosomal polymorphisms with pregnancy loss.
Objective: to analyze and characterize the frequency and types of chromosomal polymorphisms found in these patients, as well as to explore possible correlations between these variations and the different reproductive disorders observed.
Method: patients with reproductive disorders who presented with a polymorphic variant of chromosomes 1, 9, 16, or Y and acrocentric chromosomes 13, 14, 15, 21, or 22 were selected. They were analyzed in different groups: recurrent pregnancy loss (I) and infertility (II).
Results: of 549 patients with reproductive disorders, chromosomal polymorphisms were detected in 61 (11 %). The most frequent polymorphisms were 1qh-, 9qh+, 21pstk+, inv 9, and 16qh+. The group with recurrent miscarriages presented 45,4 % of the most frequently found polymorphisms. Cases of infertility alone accounted for only 24,2 %. In both groups analyzed, female patients predominated over male patients.
Conclusions: the percentage of chromosomal polymorphisms found in the sample studied is consistent with international reports on this topic. An unusual chromosomal polymorphism of chromosome 1 was found with relative frequency, which could be an inherent characteristic of the population studied. Chromosomal polymorphisms on chromosome 9 are the most recurrent finding involved in reproductive disorders.

Keywords: Chromosomes; Chromosomal Polymorphisms; Heterochromatin; Infertility; Miscarriages; Panama.

RESUMEN

Introducción: los polimorfismos cromosómicos son variaciones en los cromosomas en poblaciones normales, generalmente afectan regiones heterocromáticas, pobres en genes codificantes de proteínas. Varios estudios internacionales asocian la influencia de los polimorfismos cromosómicos a las pérdidas gestacionales.
Objetivo: analizar y caracterizar la frecuencia y tipos de polimorfismos cromosómicos encontrados en estos pacientes, así como en explorar las posibles correlaciones entre estas variaciones y los diferentes trastornos

reproductivos observados.
Método: se seleccionaron pacientes con trastornos reproductivos que presentaban alguna variante polimórfica de los cromosomas 1,9,16 o Y y los acrocéntricos 13,14,15,21,22. Se analizaron en diferentes grupos, perdidas recurrentes de la gestación (I) e infertilidad (II).
Resultados: de 549 pacientes con trastornos reproductivos en 61 fueron detectados polimorfismos cromosómicos (11 %). Los polimorfismos más frecuentes fueron 1qh-, 9qh+, 21pstk+, inv 9 y 16qh+. El grupo con abortos a repetición presentó un 45,4 % de los polimorfismos más frecuentemente hallados. Los casos con infertilidad solo alcanzó el 24,2 %. En ambos grupos analizados predominaron las pacientes femeninas con respecto a los varones.
Conclusiones: el porcentaje de polimorfismos cromosómicos hallado en la muestra estudiada coincide con los reportes internacionales que abordan este tópico. Fue hallado con relativa frecuencia un polimorfismo cromosómico inusual del cromosoma 1 que podría constituir una característica inherente en la población estudiada. Los polimorfismos cromosómicos del cromosoma 9 constituyen el hallazgo más recurrente involucrado con los trastornos reproductivos.

Palabras claves: Cromosomas; Polimorfismos Cromosómicos; Heterocromatina; Infertilidad; Abortos; Panamá.

INTRODUCTION

During gestation, several genetic factors may predispose to early pregnancy loss, and 3-5 % of couples are known to experience recurrent pregnancy loss (RPL). Identifying genetic aberrations associated with PRG is a broad field of research within medical genetics.[1,2]

Chromosomal polymorphisms are chromosome variations that may exist in normal populations and usually affect heterochromatic regions that are poor in protein-coding genes. These are essentially composed of tandemly repetitive sequences of satellite DNA, which is why many authors posit that they do not affect the phenotype of carrier individuals.[3]

Nevertheless, their clinical significance is increasingly in the spotlight, with several studies assessing their influence on human reproductive diseases and disorders.[4,5]

In human karyotypes, heterochromatic repetitive DNA variants have been recognized and documented for decades to be associated, in many instances, with reproductive disorders.[6,7] In the human karyotype, the major heterochromatic regions are located at 1q12, 9q12, 13pter-q11, 14pter-q11.1, 15pter-q11.1, 16q11.2, 19p12-q12, 21pter-q11.1, 22pter-q11.1 and Yq12.[8]

Several studies associating chromosomal polymorphisms' influence on gestational losses have been reported in the Latin American region, most notably in Cuba and Colombia.[9,10] In Panama, one in six couples has infertility problems. With approximately 4,2 million inhabitants, it is the country that performs the most assisted reproduction treatments in Central America.[11] The National Institute of Medical Genetics and Genomics of the Social Security Fund has conducted an exhaustive follow-up of patients with reproductive disorders in Panama, evaluating the presence of chromosomal polymorphisms and their possible influence on reproductive health. This research analyzes and characterizes the frequency and types of chromosomal polymorphisms found in these patients and explores the potential correlations between these variations and the different reproductive disorders observed.

METHOD

An observational, analytical, cross-sectional, and retrospective study was conducted using the database of the Cytogenetics laboratory of the National Institute of Medical Genetics and Genomics from 2018-2023. Cases of patients with reproductive disorders presenting any polymorphic variant of chromosomes 1,9,16 or Y (increase, decrease, or inversion of heterochromatic region) and 13,14,15,21,22 (increased satellite size, double satellites, increased size of satellite stalks or chromosomes without satellites) were selected. This study did not include cases with numerical and structural chromosomal aberrations, even if they had chromosomal polymorphisms.

Chromosome studies were performed using the peripheral blood lymphocyte culture technique standardized in this laboratory. Chromosome analysis was performed using the GTG banding technique. The resolution of the analyzed chromosomes was in the range of 450-550 bands, so chromosomal breakpoints involved in inversions could be accurately determined.

The patients with reproductive disorders were divided into different groups for study:

- Group I- Patients with recurrent miscarriages (two or more) of the first semester of gestation.
- Group II - Patients with primary or secondary infertility (primary: couples who have not achieved pregnancy after at least one year of sexual intercourse without using contraception) (secondary: people

who have been able to get pregnant at least once but have not been able to do so again).

Ethical issues

This study was approved by the Bioethics Committee of The Panama Clinic, Code: EC CBITPC 061, Reference: RESEGIS #3757. This approval allows the publication of all the results obtained in this project. Because there was no direct contact with the patients and because of the general design of the study, informed consent was excluded; furthermore, in order to guarantee confidentiality, an identification code was used for the corresponding files.

RESULTS

Between 2018 and 2023, 549 patients were referred to the laboratory for reproductive disorders. In 61 cases, a polymorphic chromosomal variant was found in their karyogram, constituting 11 % of the sample studied by conventional cytogenetics. These variants were diagnosed in 34 females (55,7 %) and 27 males (44,2 %). They were detected 66 times, with four patients having more than one chromosomal polymorphism.

The four patients with multiple polymorphisms were: 46, XY, 16qh+, 22pstk+ associated with secondary infertility, 46, XX, 14pstk+, 22pstk- associated with primary infertility, 46, XYqh+, 22pstk+ involved in a PRG and 46, XY, 1qh-, inv(9)(p11q13), 21pstk+ presenting PRG.

Within the groups studied in this investigation, 39 patients were referred to the laboratory for recurrent pregnancy loss and 22 patients with primary or secondary infertility. The chromosomes most frequently involved with a given polymorphism in each of these groups are presented in table 1.

Table 1. Number of times the different chromosomes with polymorphisms are involved in each group of patients with reproductive disorders.

Reproductive disorder	Chromosomes with polymorphic variants									
	1	9	13	14	15	16	21	22	Y	Total
Recurrent gestational losses.	6	11		1		1	12	5	2	38
Primary infertility.	2	1	2	3		2		1	1	12
Secondary infertility.		4		1	2	3	1	3	2	16
Total (%)	8 (12)	16 (24)	2 (3)	5(7)	2(3)	6(9)	13(20)	9(14)	5(7)	66(100)

The chromosome most represented in the 61 patients with polymorphisms was chromosome 9 (16 occasions) for 24 %, followed by chromosome 21, 13 occasions, for 20 %. Chromosome 9 polymorphisms involved the inversion of the heterochromatic region with different breakpoints and the increase in size of this region. On chromosome 21, the polymorphisms found correspond to a considerable increase in the size of the stems and the size of the satellites. None of the patients had any inbreeding links that would suggest that these polymorphisms segregate in the same family.

Table 2 shows the polymorphic variants found in each group of patients with reproductive disorders.

The most frequent were 1qh- and 9qh+, with eight cases each. The first of these variants was found to be mainly associated with recurrent pregnancy losses, while the second was more homogeneously distributed between the two groups of patients analyzed.

It should be noted that polymorphic variations on chromosome 21 are strongly associated with recurrent pregnancy losses compared to the infertility variants analyzed in this study. The other acrocentric chromosome with its polymorphisms related to reproductive disorders was chromosome 22, which was reported similarly in the two groups of patients analyzed.

Table 2. Distribution of the different polymorphic variants in the two groups of patients with reproductive disorders. Percentage of occurrence concerning the 66 occasions on which it was reported in the sample

Chromosomal polymorphism	Group I	Group II			
	Recurrent miscarriages	Primary infertility	Secondary Infertility	Polymorphisms detected	%
1qh-	6		2	8	12,1
9qh+	3	1	4	8	12,1
inv (9)(p11.1q13)	5			5	7,5
inv (9)(p12q13)	1			1	1,5
inv (9)(p11.1q12)	2			2	3,0
16qh+	1	2	3	6	9,0
21pstk+	7			7	10,6
21ps+	5		1	6	9,0
22pstk+	3		2	5	7,5

22ps+	2		1	3	4,5
22ps-		1		1	1,5
13pstk+		1	1	2	3,0
14ps+		1	1	2	3,0
14pstk+	1	2		3	4,5
15ps+			1	1	1,5
15pstk+			1	1	1,5
Yqh+	2	1	2	5	7,5
Total	38	9	19	66	100

Of 36 patients studied, 22 females and 14 males were detected with polymorphisms in group I. In group II, 25 cases were reported, 12 females and 13 males.

Table 3 shows this study's most frequent polymorphic variants (70 %), distributed by each group and sex. They were much more frequent in the group of patients with recurrent miscarriages compared to patients with different infertility variants. 1qh-variants, various types of pericentric inversion of the heterochromatic block of chromosome 9, and polymorphic variations of chromosome 21 predominated within group I and were found much more frequently than in group II.

However, polymorphic variants were relatively homogeneous between the two groups: 9qh+, 22pstk+, and Yqh+. The only variant more frequent in group II than in group I was 16qh+.

In this study, females with polymorphic variants predominated over males.

Table 3. Most frequent polymorphic variants (more than five times) are distributed by group and sex of patients. Percentage of times reported in each group, concerning the 66 times polymorphisms were found in the sample

Frequent polymorphic variants	Group I			Group II		
	Women Number of times	Males Number of times	%	Women Number of times	Males Number of times	%
1qh-	3	2	7,5	1	1	3,0
inv (9)	6	1	10,6			0
9qh+	2	1	4,5	3	2	7,5
16qh+	1		1,5	4		6,0
21pstk+	4	2	9,0	2		3,0
21ps+	3	2	7,5		1	1,5
22pstk+	1	1	3,0		1	1,5
Yqh+		2	3,0		3	4,5
Total	18	12	45,4	10	6	24,2

DISCUSSION

Recurrent pregnancy losses, mainly due to miscarriages and infertility, are a frustrating experience for couples and their families; it constitutes a great challenge for the health personnel who care for these couples. The present research establishes the first study conducted in Panama on a completely unexplored topic in the context of this country.

In general, the possible relationship between chromosomal polymorphisms and reproductive disorders in humans is a very controversial topic, and there is no consensus in the scientific community that confirms or completely rules out this issue. However, the high incidence of these in international reports and their possible link to the infertile population cannot be ignored.[12,13,14]

The fact that 11 % of all patients with reproductive disorders had some chromosomal polymorphism is consistent with other studies that have reported levels ranging from 9-10 %.[5,9,12]

Despite the limited number of patients analyzed in this study, some peculiarities should be highlighted. The first example is the relatively high frequency of the 1qh-polymorphism in the patients studied. This variant is indeed rare and not frequently reported in extensive population-based studies on the subject.[4,12] The authors have no evidence of consanguinity among the patients in the sample studied; perhaps this variant constitutes a peculiarity in the Panamanian population that should be studied in depth later. It should be remembered that genome variations in Latin America have been reported by other authors from this geographic region.[15,16,17]

Another unusual finding of this study is the high frequency of polymorphic variations in chromosome 21, which has been infrequently reported in international studies.[4,18] Although it should be borne in mind that our sample size is small, which may add a bias to this finding, it may be a chance occurrence that disappears with the analysis of a larger number of cases.

However, there are significant overlaps in the present study with other international research. The most

obvious example is the polymorphisms on chromosome 9 (the pericentric inversions with different breakpoints bordering the heterochromatin block and the increase of the heterochromatic region) and their apparent relationship to reproductive disorders. Other authors consistently report this relationship.[4,5,7,12,14] However, not all agree; in a study by Kosyakova et al. taking into account 17 variants of pericentromeric heterochromatin 9, some of which are very rare, these authors found no clear evidence that infertility was linked to any of these variants.[19] Other authors report something similar.[20,21]

Limitations of the study

The present study constitutes a preliminary investigation of this vast topic in the field of reproductive disorders in Panama. With the limited number of patients analyzed, it is difficult to draw further conclusions. Still, it has been an encouraging initial result that should be continued as a line of research at this institution, so it is necessary to increase the number of patients to be analyzed.

CONCLUSIONS

The percentage of chromosomal polymorphisms found in the sample studied coincides with international reports on this topic. An unusual chromosomal polymorphism on chromosome 1 is reported relatively frequently and could be an inherent characteristic of the population studied. Chromosomal polymorphisms on chromosome 9 are the most recurrent finding involved in reproductive disorders

REFERENCES

1. Tise CG, Byers HM. Genetics of recurrent pregnancy loss: a review. Curr Opin Obstet Gynecol 2021;33:106-11. https://doi.org/10.1097/GCO.0000000000000695.

2. Barrios Martínez A, Méndez Rosado LA. Enfoque de los principales factores causales en los trastornos reproductivos. Rev Cubana Obstet Ginecol 2014;40:246-57.

3. Pires S, Jorge P, Liehr T, Oliva-Teles N. Challenges in classifying human chromosomal heteromorphisms using banding cytogenetics: From controversial guidelines to the need for a universal scoring system. Hum Genome Var 2024;11:38. https://doi.org/10.1038/s41439-024-00295-8.

4. Li Q, Chen S, Dong X, Fu S, Zhang T, Zheng W, et al. The Progress of Research on Genetic Factors of Recurrent Pregnancy Loss. Genet Res (Camb) 2023;2023:9164374. https://doi.org/10.1155/2023/9164374.

5. Álvarez Y, Barrios A, Rodríguez E, Morales-Peralta E, Domínguez N, Méndez-Rosado Luis. Inusual ganancia en 9qh y su posible influencia en los trastornos reproductivos. A propósito de un caso. Salud, Ciencia y Tecnología - Serie de Conferencias 2023;2:339. https://doi.org/10.56294/sctconf2023339.

6. Šípek AJ, Mihalová R, Panczak A, Hrčková L, Janashia M, Kaspříková N, et al. Heterochromatin variants in human karyotypes: a possible association with reproductive failure. Reprod Biomed Online 2014;29:245-50. https://doi.org/10.1016/j.rbmo.2014.04.021.

7. 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;14:422-30. https://doi.org/10.4103/jhrs.jhrs_68_21.

8. Liehr T. Benign and Pathological Chromosomal Imbalances: Microscopic and Submicroscopic Copy Number Variations (CNVs) in Genetics and Counseling. 1st ed. Cambridge, Massachusetts: Academic Press; 2013.

9. Soriano-Torres M, Morales Rodríguez E, Rojas Betancourt I, Méndez-Rosado LA. Variantes de la heterocromatina y la eucromatina en el diagnóstico prenatal citogenético. Rev Cubana Obstet Ginecol 2014;40:79-88.

10. Erazo Narváez AF. Asociación de resultados de reproducción asistida con heteromorfismos en donantes de óvulos, Risaralda 2006 – 2022. Tesis de epidemiologia. Universidad de Caldas.2022 n.d.

11. Vega Croker Dr M: Comunicación personal n.d.

12. Angelova L, Tsvetkova M, Levkova M. Chromosomal polymorphism in Bulgarian patients with

reproductive problems – one genetic centre experience. J of IMAB 2021;27:4133–8. https://doi.org/10.5272/jimab.2021274.4133.

13. Anton E, Garcia-Guixé E, Ramos-Muntada M, Godo A, Sandalinas M, Blanco J. Chromosome heteromorphisms: do they entail a reproductive risk for male carriers? Asian J Androl 2020;22:544–6. https://doi.org/10.4103/aja.aja_130_19.

14. Mottola F, Santonastaso M, Ronga V, Finelli R, Rocco L. Polymorphic Rearrangements of Human Chromosome 9 and Male Infertility: New Evidence and Impact on Spermatogenesis. Biomolecules 2023;13. https://doi.org/10.3390/biom13050729.

15. Fortes-Lima C, Bybjerg-Grauholm J, Marin-Padrón LC, Gomez-Cabezas EJ, Bækvad-Hansen M, Hansen CS, et al. Exploring Cuba's population structure and demographic history using genome-wide data. Sci Rep 2018;8:11422. https://doi.org/10.1038/s41598-018-29851-3.

16. Mao X, Bigham AW, Mei R, Gutierrez G, Weiss KM, Brutsaert TD, et al. A genomewide admixture mapping panel for Hispanic/Latino populations. Am J Hum Genet 2007;80:1171–8. https://doi.org/10.1086/518564.

17. Méndez-Rosado LA, Quiñones-Masa O, Vaglio A, Quadrelli R, Sanchez-Peñarate D, Soriano-Torres M, et al. Antenatal Diagnosis of De Novo Balanced Structural Chromosome Aberrations in Latin America. MEDICC Rev 2018;20:27–34. https://doi.org/10.37757/MR2018.V20.N4.7.

18. Mukhopadhyay S, Dasgupta S, Ghosh K, Mukherjee T. Investigating the relation between chromosomal polymorphism and recurrent pregnancy loss: A cohort study. Indian Journal of Obstetrics and Gynecology Research 2022;9:391–6. https://doi.org/10.18231/j.ijogr.2022.074.

19. Kosyakova N, Grigorian A, Liehr T, Manvelyan M, Simonyan I, Mkrtchyan H, et al. Heteromorphic variants of chromosome 9. Molecular Cytogenetics 2013;6:14. https://doi.org/10.1186/1755-8166-6-14.

20. Zhao J, Huang B, Hao J, Xu B, Li Y. Chromosomal polymorphisms have no negative effect on reproductive outcomes after IVF/ICSI-ET/FET. Sci Rep 2022;12:19052. https://doi.org/10.1038/s41598-022-20132-8.

21. Rodriguez F, Cruz M, Requena A. Impact of parental chromosomal polymorphisms on the incidence of congenital anomalies and perinatal complications in a cohort of newborns conceived after ICSI+PGT-A. Reprod Biol Endocrinol 2022;20:145. https://doi.org/10.1186/s12958-022-01012-2.

FINANCING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS' CONTRIBUTIONS

Conceptualisation: Luis A. Sotillo Bent, Luis A. Méndez-Rosado.
Data Curation: Johan Varela, Génesis Villarreal.
Formal analysis: Estela Morales Peralta.
Research: Luis A. Méndez Rosado, José Cedeño.
Methodology: Estela Morales-Peralta.
Supervision: Michelle Facey, Luis A. Méndez Rosado.
Validation: Luis A. Sotillo Bent, Luis A. Méndez-Rosado, Michelle Facey.
Visualisation: Johan Varela, Génesis Villarreal.
Original drafting and editing: Luis Alberto Méndez-Rosado, Michelle Facey.
Writing-revising and editing: Estela Morales-Peralta.