

CDH13 GENE WITH CERVICOVAGINAL INFECTIONS IN USERS OF A FAMILY CARE CLINIC IN NORTHERN MEXICO

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Abstract : Cervicovaginal infections (CVID) are considered the main cause of consultation in primary care, the literature indicates that they have a genetic predisposition component as a relevant susceptibility factor. Infections can occur due to various alterations in the organism, among which adhesion molecules such as cadherins may be involved, which play a fundamental role in a wide range of biological processes. Cadherins are a large group of calcium-dependent adhesion molecules, including cadherin 13, which is involved in intracellular signaling processes, as well as cell-cell adhesion. The gene that encodes this protein, *CDH13*, has a polymorphism (rs11649622) which leads to a substitution point mutation, in which the ancestral guanine (G) allele is replaced by an adenine (A), this leads to a variation in intronic region 7-8 of this gene. The objective of this study was to study the presence of the rs11649622 polymorphism of the *CDH13* gene and its relationship with the presence of CVD in users of the Family Care Clinic of Durango, Mexico. The presence of CVID was determined by vaginal culture, 206 participants were recruited after signing an informed consent; the RT-PCR method was used for the genotyping of the rs11649622 polymorphism of the *CDH13* gene using Taqman probes (Thermo Fisher Scientific). Of the recruited patients, 95 presented ICV, which represents a prevalence of 46.1% of infection; the most common was vaginosis caused by *Gardnerella vaginalis* with a frequency of 65 patients (68.4% of the women with CVID and 31.5% of the total sample). In conclusion, the rs11649622 polymorphism of the *CDH13* gene was not associated with the presence of cervicovaginal infections.

Keywords: infections of the genital system, cadherin, cervical culture.

INTRODUCTION

Cervicovaginal infections (CVI) are a group of gynecological entities characterized by the alteration of the normal vaginal microbiota with a decrease in lactobacilli and an increase in infectious agents that include viruses, bacteria, protozoa and fungi (1). These infections are considered the main cause of consultation in primary care. According to the Latin American Center for Health and Women (CELSAM) the incidence is from 7 to 20%. According to the statistics of this center, 75% of women will suffer at least one episode of this disorder in their lives and up to 50% of them will present even two episodes or more in 1 year (2). It has been observed that CVIDs not detected in a timely manner can cause serious complications in the body, especially in women who are in the reproductive stage (15 to 45 years) and/or pregnant (3). The ability of cells to adhere through specific molecular interactions plays a fundamental role in a wide range of biological processes. The lack of these interactions, or their stimulation, can lead to pathological states (4). Among the most important adhesion molecules are cadherins, which are calcium-dependent adhesion molecules, are widely distributed, including in the Central Nervous System (CNS) and are expressed during development and in adult organs (5). The gene on which the present investigation focuses is *CDH13*, which codes for the cadherin 13 protein or also called T-cadherin, it is an atypical member of the cadherin family because it lacks a common transmembrane and cytoplasmic domain (6). Some studies suggest that T-cadherin may be involved in fundamental intracellular signaling processes, as well as in cell-cell adhesion (7), a fundamental process to preserve the integrity of the epithelium, constituting the first line of defense against infections (8). in which the cervicovaginal can be included. Within this gene is the rs11649622 polymorphism, which

is a substitution point mutation, in which the ancestral guanine (G) allele is replaced by an adenine (A), this leads to a variation in the intronic region 7-8 of the gene. *CDH13* (9).

Carrying out this study will provide relevant information about the possible association of the rs11649622 polymorphism of the *CDH13* gene in patients with cervicovaginal infections.

MATERIAL AND METHODS

This research is a descriptive, comparative, cross-sectional and prospective study. The universe of study consisted of 206 women between 17 and 70 years of age, residents of the State of Durango, sexually active, who voluntarily participated in the study and expressed it by signing an informed consent letter; The participants did not present chronic degenerative diseases such as diabetes mellitus, arterial hypertension, thyroid or autoimmune disease and also met the requirements for an adequate cervical sample collection: not coming menstruating, not having applied ovules, creams, gels or vaginal douches, not having had sexual intercourse two days before attending the sampling and not taking antibiotics. Those women with a degraded or inadequate sample for processing were eliminated. The sociodemographic and gynecological -obstetric data of all the participants were collected. For the identification of cervicovaginal infection (CVI) by the clinical laboratory, three cervical sample swabs were taken for culture. From a cervical sample with 2SP medium, DNA extraction was performed by the phenol-chloroform method. Thermo Fisher Scientific TaqMan probes were used to identify the rs11649622 polymorphism, processed following the manufacturer's instructions in a StepOne Real Time PCR System from the same brand. 15% of the samples were randomly selected and processed in duplicate with a concordance of 100%.

The data capture was carried out in the Excel Windows software and its analysis in the SPSS software for Windows V20. Measures of central tendency and dispersion were determined for the quantitative variables and frequencies for the qualitative variables. univariate ; allelic and genotypic frequencies were determined by direct counting. The prevalence ratio of the rs11649622 polymorphism of the gene was calculated. *CDH13* according to the genotype in relation to the presence of cervicovaginal infection.

RESULTS

In the present study, of the 206 recruited women, 95 of them were diagnosed with cervicovaginal infection, which represents a prevalence of 46.2%. The average age of the study sample was 36 years, with 17 being the minimum and 65 the maximum; the highest percentage of the sample is 41 years old or older (36%), followed by the range of 21 to 30 years old (31%), then there is that of 41 years old or older (30%) and finally there are women with less 20 years (3%). When the ages are broken down according to the presence of infection, as observed in Table 1, the age range that predominates in women with infection are women between 31-40 years old with 36.8% (n=35), while the most frequent in women without infection was 41 years or older, which was 43.2% (n=48).

Age range	WITH INFECTION (n=95)	NO INFECTION (n=111)
under 20	2 (2.1%)	4 (3.6%)
21-30	32 (32%)	33 (29.7%)
31-40	35 (36.8%)	26 (23.4%)
41 or more	26 (27.4%)	48 (43.2)

Table 1. Frequencies of ages in patients with infection and without infection.

In the case of the occupation of the study participants, the majority of the patients are employed 59% (n=121) and followed by the

group of 82 housewives, who represent 40% of the participants. Regarding the marital status of the participants, married women predominate with 54% (n=111), followed by single women with 24% (n=50) and the group that obtained the lowest frequency were widowed women with 2% (n=3).

Table 2 shows the symptoms manifested by patients with and without infection, and in both groups it was the abnormal discharge that was reported most frequently, with a percentage of 56.8% (n=54) of the cases with infection and 48.6% of patients without infection. The symptom that occurs less frequently in both cases is inflammation with 4.3% and 5.4% of patients with and without infection, respectively. Irritation is a special case since it occurs in 21.1% (n=20) of women with infection, while in those without infection it occurs only in 8.1% (n=9).

Through laboratory identification, 95 of the participating women were diagnosed with cervicovaginal infection, which represents a prevalence of 46.1%. The microorganisms identified in the participants can be seen in Figure 1. In this study, the most frequent infection was bacterial vaginosis caused by the *Gardnerella bacterium. vaginalis* with a percentage of 65.2% (n=62), a prevalence of trichomoniasis of 7.3% (n=7) was also found.

Table 3 shows the distribution of allelic and genotypic frequencies of the rs11649622 polymorphism of the *CDH13* gene. In study participants, as well as those with cervicovaginal infection (CVI) and in healthy women. The genotypic frequencies of this polymorphism did not show deviation from the Hardy- Weinberg equilibrium; the values obtained in the total sample were 0.0044, in the group of women with ICV it was 0.15 and in healthy women it was 0.23.

	Total, of participants (n=206)	With cervicovaginal infection (CVI) (n=96)	no infection (n=110)	p-value*
allele				
TO	0.72	0.72	0.73	0.99
G.	0.28	0.28	0.27	
Genotype				
A/A	0.47	0.463	0.478	0.99
A/G	0.5	0.505	0.495	
G/G	0.03	0.032	0.027	

Table 3. Distribution of allelic and genotypic frequencies of the rs11649622 polymorphism of the *CDH13* gene.

*Pearson's Chi-square test

The prevalence ratio of the rs11649622 polymorphism of the *CDH13* gene under the codominant model is shown in Table 4. As can be seen, the presence of the G change allele does not increase the risk of CVID in the women studied, the prevalence ratio for CVID for the heterozygous A/G genotype it was 1.05 (95% CI 0.6-1.83) and for the homozygous mutated G/G genotype it was 1.2 (95% CI 0.23-6.27).

GENO-TYPE	WITH LCI	NO INFECTION	PR (95% CI)	p-value
A/A	44	53	1	0.97
BE	48	55	1.05 (0.60-1.83)	
G/G	3	3	1.20 (0.23-6.27)	

Table 4. Prevalence ratio of the rs11649622 polymorphism of the *CDH13* gene.

DISCUSSION

Cadherin 13 or T-cadherin is a non-canonical member of the cadherin superfamily, encoded by the *CDH13* gene at the 16q24 locus. *CDH13* is a mediator of CA⁺²-dependent cell-cell adhesion, which is why it is involved in epithelial integrity (8), a phenomenon considered the first line of defense against infections including cervico-vaginal infections (CVI). In this study we found a prevalence of CVID of 42.2%, with

Symptom	WITH INFECTION LCI (n=95)		NO INFECTION (n=111)	
	yes (%)	No (%)	yes (%)	No (%)
Flow	54 (56.8%)	41 (43.2%)	54 (48.6%)	57 (51.4%)
Itch	43 (45.3%)	52 (54.7%)	37 (33.3%)	74 (66.7%)
Burning	28 (29.5%)	67 (70.5%)	25 (22.5%)	86 (77.5%)
Irritation	20 (21.1%)	75 (78.9%)	9 (8.1%)	102 (91.9%)
Inflammation	4 (4.2%)	91 (95.8%)	6 (5.4%)	105 (94.6%)
Pelvic pain	15 (15.8%)	80 (84.2%)	16 (14.4%)	95 (85.6%)
pain in relationships	16 (16.8%)	79 (83.2%)	12 (10.8%)	99 (89.2%)

Table 2. Frequency of symptoms reported by patients with and without infection.

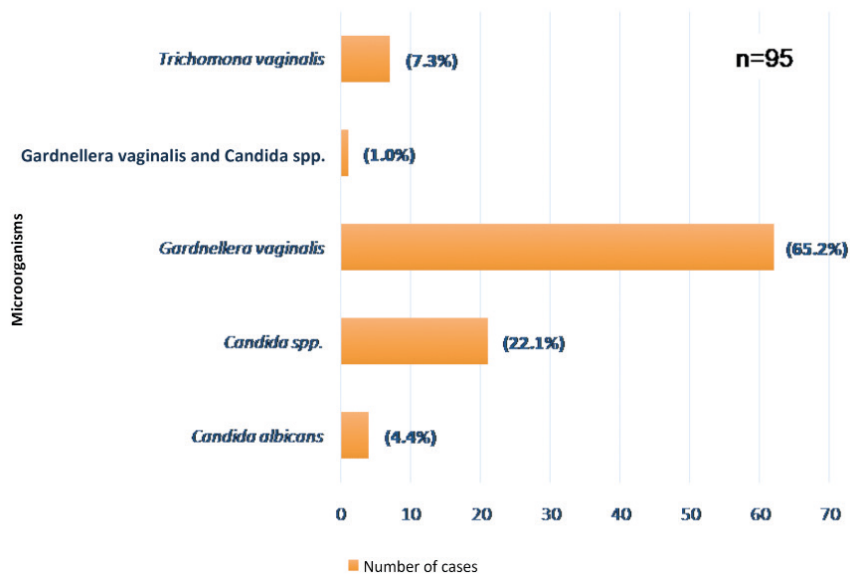


Figure 1. Frequency of microorganisms detected by culture.

bacterial vaginosis caused by *Gardnerella being the most frequently detected infection vaginalis* with a prevalence of 62.2% of all infections. In a study reported by Villaseca et al. (10) in 2015, they found a prevalence of CVI slightly higher than ours of 46.5%, data similar to that reported by Spengles et al., who report a prevalence of 49.9% (11). Regarding the presence of bacterial vaginosis, Lugo reports higher frequencies in coinfection with HPV of 76.9% in a sample of sex workers (12); however, the prevalence figures are generally lower, as is the case of Cortés (13) and Jiménez (14) who report figures of 10.4 and 12.7% respectively in the Mexican population. Regarding the presence of vulvovaginal candidiasis, our results agree with what was reported by López (15), who in the Mexican population and by molecular detection reported a prevalence of 38.8%; Lower figures have been reported by Solís (16), who reports a 12.6% prevalence, and Spengles et al. (11) found a prevalence of 18.5% in the Cuban

population. Regarding the infection caused by the *Trichomonas parasite vaginalis*, our report agrees with what was found by Jane (17) and Spengles et al. (11).

Our results reveal allelic and genotypic frequencies of the rs11649622 polymorphism of the *CDH13* gene that do not match those reported for the Mexican population (18), however in other reports the A change allele is more frequent (19), although it is important to highlight that in this study, by its nature includes only women. This polymorphism has been studied

Finally, we can affirm that in this study we did not find an increased risk of CVD determined by the genetic susceptibility of the rs11649622 polymorphism of the *CDH13* gene according to the estimated prevalence ratio. No similar reports are found in the scientific literature on the study of this polymorphism with similar infections, however epigenetic alterations of this gene have been associated with the risk of cervical cancer (20, 21).

REFERENCES

1. Picazo JJ, Prieto Prieto J. Infecciones de transmisión sexual e infecciones genitales. En: Picazo JJ, editor. Compendio de microbiología, Elsevier España, S.L.U.; 2016, p. 515–21.
2. Salinas AM, Osorio VG, PachaHerrera D, Vivanco JS, Trueba AF, Machado A. Vaginal microbiota evaluation and prevalence of key pathogens in ecuadorian women: an epidemiologic analysis. *Nature*, 2020; 10. <https://doi.org/10.1038/s41598-020-74655-z>.
3. Casabona I, Barbarà J, Alsina Gibert M, Matas Andreu L, Blanco Arévalo JL. Infecciones de transmisión sexual. En: von Domarus A, editor. Farreras Rozman. Medicina Interna, Elsevier España, S.L.U.; 2020, p. 2442–9.
4. Pratiksha G, Neha A, Anju H, Gurvinder L. Significance of bacterial vaginosis and periodontal infection as predictors of preterm labor. *Bangladesh Journal of Medical Science*, 2016;15:441–9.
5. Croatti V, Parolin C, Giordani B, Foschi C, Fedi S, Vitali B. Lactobacilli extracellular vesicles: potential postbiotics to support the vaginal microbiota homeostasis. *Microbial Cell Factories* 2022; 21. <https://doi.org/10.1186/s12934-022-01963-6>.
6. Bodegas M E, Calvo A, Megías J, Miguel TS. Especializaciones de la membrana plasmática e interacción de la célula con su entorno. En: Calvo A, editor. Biología celular biomédica, Elsevier España, S.L.U.; 2023, p. 115–38.
7. Xingyou Hu, Gaotian Shen, Tao Hu, Guoping Guan, Lu Wang. The significance of cadherin for cell–cell interactions and cell adhesions on biomaterials. *Journal of Adhesion Science and Technology*, 2015; 29:1047–59.
8. Xiao-Dong Yuan, Jing-Wen Wang, Yu Fang, Yu Qian, Shuai Gao, Yu-Chen Fan, Kai Wang. Methylation status of the T-cadherin gene promotor in peripheral blood mononuclear cells is associated with HBV-related hepatocellular carcinoma progression. *Pathology research and Practice*, 2020; 216. <https://doi.org/10.1016/j.prp.2020.152914>.
9. US National Library of Medicine NCBI. dbSNP. <https://www.ncbi.nlm.nih.gov/snp/rs11649622> (consultado el 24 de Julio de 2023).

10. Villaseca R, Ovalle A, Amaya F, Labra B, Escalona N, Lizana P, Montoya MJ, Lillo E, Martínez A. Infecciones vaginales en un Centro de Salud Familiar de la Región Metropolitana, Chile. *Revista chilena de infectología* 2015; 32. <https://doi.org/10.4067/S0716-10182015000200005>.
11. Spengler GL, Ayala RI, García RA. Infecciones cervicovaginales en exudados vaginales. *Revista Cubana de Medicina Militar* 2020; 49(3).
12. Lugo L, Jacob C, Machado A, Almeida F, Ávila L, Prata T, Padovani C, Ferreira A, Fernandes C, Tozetti I. Human papillomavirus and coinfections with *Chlamydia trachomatis*, *Gardnerella vaginalis*, and *Trichomonas vaginalis* in self-collected samples from female sex workers in the Central-Western region of Brazil. *Jornal Brasileiro de Patologia e Medicina Laboratorial*. 2018; 54(1):46–51.
13. Cortés SK, Estrada MA, Gómez CM, Alarcón RL, Flores AE, Vences VA. Prevalence and risk factors associated with bacterial vaginosis in southern México. *Sexually Transmitted Infections*. 2017;93(2):A136.
14. Jiménez FG, Flores TJ, Ruiz TA, Villagrán PC. Evaluación de los métodos utilizados para el diagnóstico de vaginosis bacteriana en el Hospital Regional ISSSTE Puebla. *Ciencia UAT*. 2020; 14(2):62–71.
15. López MA, Gómez FF, Ramos PG, Guzmán GD, Ramos LA. Codetection of *Trichomonas vaginalis* and *Candida albicans* by PCR in Urine Samples in a Low-Risk Population Attended in a Clinic First Level in Central Veracruz, Mexico. *BioMed Research International* [Internet]. 2013. Disponible en: <http://dx.doi.org/10.1155/2013/281892>
16. Solís AM, Moreno MM, Dávalos TM, Fernández MR, Díaz FO, Arenas GR. Colonización vaginal por *Candida* spp. Frecuencia y descripción de las especies aisladas en mujeres asintomáticas. *Ginecología y Obstetricia de México*. 2014; 82:1–8.
17. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, Chico RM, Smolak A, Newman L, Gottlieb S, Thwin SS, Brouteta N, Taylora MM. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* [Internet]. 2019; 97:548–62. Disponible en: <http://dx.doi.org/10.2471/BLT.18.228486>.
18. REDDIT. SNPedia 2019. <https://www.snpedia.com/index.php/Rs11649622> (consultado el 27 de julio de 2023).
19. National Center for Biotechnology Information. NIH National Library of Medicine. SNPdb 2021. <https://www.ncbi.nlm.nih.gov/snp/rs11649622> (consultado el 27 de julio de 2023).
20. Missaoui N, Hmissa S, Trabelsi A, Traoré C, Mokni M, Dante R, Frappart L. Promoter hypermethylation of CDH13, DAPK1 and TWIST1 genes in precancerous and cancerous lesions of the uterine cervix. *Pathology - Research and Practice* 2011;207:37–42.
21. Ríos-Romero M, Soto-Valladares AG, Piña-Sánchez P. Alteraciones epigenéticas en la progresión del cáncer cervicouterino. *Revista Médica del Instituto Mexicano del Seguro Social* 2015;53:S212–7.