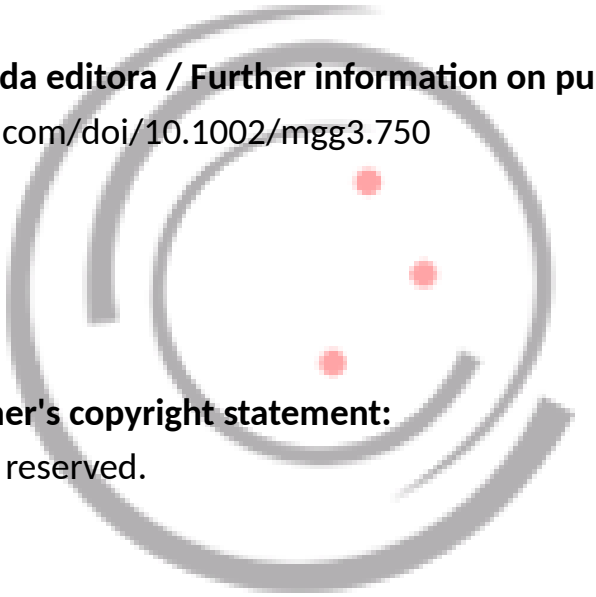

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ORIGINAL ARTICLE

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Copy number alterations associated with clinical features in an underrepresented population with breast cancer

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Abstract

Background: As the most incident tumor among women worldwide, breast cancer is a heterogeneous disease. Tremendous efforts have been made to understand how tumor characteristics as histological type, molecular subtype, and tumor microenvironment collectively influence disease diagnosis to treatment, which impact outcomes. Differences between populations and environmental and cultural factors have impacts on the origin and evolution of the disease, as well as the therapeutic challenges that arise due to these factors. We, then, compared copy number variations (CNVs) in mucinous and nonmucinous luminal breast tumors from a Brazilian cohort to investigate major CNV imbalances in mucinous tumors versus non-mucinous luminal tumors, taking into account their clinical and pathological features.

Methods: 48 breast tumor samples and 48 matched control blood samples from Brazilian women were assessed for CNVs by chromosome microarray. Logistic regression and random forest models were used in order to assess CNVs in chromosomal regions from tumors.

Results: CNVs that were identified in chromosomes 1, 5, 8, 17, 19, and 21 classify tumors according to their histological type, ethnicity, disease stage, and familial history.

Conclusion: Copy number alterations described in this study provide a better understanding of the landscape of genomic aberrations in mucinous breast cancers that are associated with clinical features.

KEYWORDS

breast cancer, copy number alteration, ethnicity, family history, mucinous, stage

1 | INTRODUCTION

As the most incident tumor among women worldwide, breast cancer also causes the highest number of deaths in the female population, especially in developing countries where the diagnosis of late-stage disease is made in most cases (World Health Organization, 2018). Breast cancer is also a heterogeneous disease, where the individual's genetics in combination with the influence of tumor histological type, molecular subtype, and tumor microenvironment contribute to disease progression. A better understanding of these factors in relation to early diagnosis and disease treatment impacting overall survival is critical (Cecilio et al., 2015). In addition, differences between populations and also environmental and cultural factors significantly affect the origin and evolution of the disease, and therefore bring additional therapeutic challenges (IARC, 2014).

Ductal carcinomas account for more than 70% of breast tumors and include all histological types that cannot be classified into defined types. Their prognosis depends mainly on the molecular subtype and other features such as stage that includes tumor size, affected lymph nodes, and the presence of metastasis (IARC, 2014). Among the histological types of breast tumors, mucinous carcinomas of the breast are rare and comprise 1%–6% of all breast tumor cases, especially in women over 75 years of age (Ha, Deleon, & Deleon, 2013). Genomic studies involving this type of tumor are understudied, in part because of its low incidence. A portion of the cases that did not respond well to standard-of-care treatments were characterized as presenting positivity for *ERBB2* and *P53*, with a higher probability of metastasis. Cases that present the mucinous histological type in less than 90% of the tumor or, in association with invasive ductal tumors, also tend to be more aggressive (Lacroix-Triki et al., 2010). In addition, chromosome analysis in pure mucinous tumors in conjunction with other histological types showed gains in 1q and 16p arms and losses in the 16q and 22q arms, despite lower genetic instability compared to invasive ductal tumors. Studies have shown that a number of genes such as *ERBB2*, *FGFR1*, *CCND1*, *FGF3*, *FGF4*, *FGF19*, *PIK3CA*, *BRCA1*, *TSC2*, *STK11*, *AKT3,* and *ESR1*, among others, present changes in tumors of this type (Lei, Yu, Chen, Chen, & Wang, 2016; Ross et al., 2016). Hence, a better understanding is needed of altered genomic landscape in aggressive, treatment-refractory mucinous breast tumors.

Majority of defined breast cancer molecular subtypes were derived from ductal invasive breast tumors, and largely lacked profiling from other histological types of breast tumors (Dieci, Orvieto, Dominici, Conte, & Guarneri, 2014; Perou et al., 2000; The Cancer Genome Atlas [TCGA], 2012). Few studies have described how molecular features from different histological types may influence treatment response (Caldarella et al., 2013; Weigelt et al., 2008). Mucinous tumors are often described as Luminal A, and recent studies have shown that this subtype tended to have worse responses to cytotoxic agents and develop resistance to chemotherapy compared earlier to other histological subtypes (Araki & Miyoshi, 2018; Martelotto, Ng, Piscuoglio, Weigelt, & Reis-Filho, 2014).

Although breast cancer comes in many histological forms, the mucinous histological type remains understudied, in part due to its low incidence. In addition, the Brazilian population of breast cancer patients is understudied regardless of the tumor phenotype. Current demographic data shows that the Brazilian population is composed of mixed ethnicities (Instituto Brasileiro de Geografia e Estatística [IBGE], 2018). Since Brazil is a genetically underrepresented population, studies that include Brazilian cohorts may uncover previously unknown genetic drivers of therapeutic resistance and lead to the discovery of new biomarkers. The genetic composition of tumors in the Brazilian population is also dissimilar from that of populations living in other regions of the globe, even in neighboring Latin America countries, since the patterns of colonization and intrinsic miscegenation between colonizers and the native populations vary markedly across these countries (Giolo et al., 2012; Popejoy & Fullerton, 2016).

In this study, we compare the genomic features in terms of copy number variations (CNVs) in mucinous and nonmucinous luminal breast tumors of a Brazilian cohort. With this methodological approach, we were able to describe major CNV imbalances in mucinous tumors versus ordinary luminal A/B tumors in association with clinical and pathological features.

2 | SUBJECTS AND METHODS

The procedures for obtaining the samples used in this study, as well as the informed consent form signed by all the women participating in this study, followed the recommendations

of the Declaration of Helsinki and were approved by the Research Committee of CAISM—Women's Hospital/UNICAMP (approved project n.° 082/2013) on 12/12/2013 and by the Research Ethics Committee of UNICAMP and CONEP—National Research Committee (approved project n.° 1.166.843) on 7/30/2015. Tumor and blood samples of women who agreed to participate in the study and signed the consent form for this purpose were collected by the Division of Gynecological Oncology and Breast Pathology of CAISM—Women's Hospital/UNICAMP. Medical records were reviewed to obtain women clinical and epidemiological data. For this study, only ductal and mucinous tumors with or without other minor components were selected after the histopathological characterization of the biopsy. A skilled pathologist selected tumor and normal areas for microdissection. Tumor areas were used to obtain 10μm fragments from which DNA extraction using phenol/chloroform protocol was performed. A similar protocol was used for DNA retrieval from blood samples.

DNA was verified in agarose gel and considered adequate only when hosting >80% of integrity. DNA was then diluted at concentrations between 40 and 60 ng/μl, which were verified by the Epoch spectrophotometer (Biotek®, Winooski, VT). These concentrations are suitable for use with Affymetrix® Cytoscan™ HD Array assay kits (Thermo Fisher Scientific Inc., Santa Clara, CA). The protocol was performed as per manufacturer recommendations, comprising the steps of preparing the genomic DNA, digestion, ligation, PCR, purification, quantification, fragmentation, labeling, hybridization, washing, staining, and chip scanning. After scanning, data was processed by Affymetrix Molecular Diagnostic Software (AMDS) and quality control was generated by ChAS analysis software (Chromosome Analysis Suite, Affymetrix®). About 48 chips were hybridized for the tumor samples and 48 chips for the blood samples of the same woman, the latter being used as control of constitutive CNVs.

For CNV analysis, data were normalized via the ASCRMA and raw copy algorithms. Then, the normalized data was segmented using the Parent-specific circular binding segmentation (Olshen et al., 2011), copynumber, GADA, and CBS protocols. Only alterations contemplating at least 25 microarray probes for deletions or 50 probes for amplifications were considered, along with fragments of 100kb with low-rank representation (LRR) ≤ -0.3 for deletions and LRR ≥ 0.3 for amplifications. The data were also evaluated by the intersection of methods performed and described above: only samples with CNVs present in three or more of the methods were considered as altered for the variation of interest. Afterward, two statistical tests were applied to rank the most relevant CNVs by comparing between ductal and mucinous samples and also to evaluate the most relevant CNVs in relation to the clinical and pathological characteristics. Functional pathways associated with these CNVs were searched using DAVID 6.8 (The Database for Annotation, Visualization and Integrated Discovery, p-value ≤ 0.05) (Huang, Sherman, & Lempicki, 2009) and UCSC Table Browser was used to retrieve information on variants already described that are in association with the verified CNVs.

3 | RESULTS

Table 1 shows the clinical and epidemiological features of the women included in the study, per tumor histological type. The majority of the women were above 45 years of age and were postmenopausal. Disease stage was predominantly I or II. About 81% of the women were Caucasian versus 19% Afro-descendants. Fourteen women reported one or more cases of breast cancer in their families. Majority of the cases ($n = 35$) were classified as Luminal A, 11 Luminal B and 2 Luminal B/HER2 enriched.

The frequencies of CNVs, by chromosome, in relation to clinical/pathological data are shown in Table 2. Interestingly, the altered chromosomes that relate both to later disease stage as to the presence of family history were found to be associated with CNVs on the same chromosomes (chr 5, 19 and 21),

TABLE 1 Description of the clinical and epidemiological features of the women included in the study

	Mucinous Samples		Ductal Samples	
	n	%	*n*	%
Age at diagnosis				
35–45	0	0	3	6
>45	10	21	35	73
Ethnicity				
Caucasian	9	19	30	62
Afro-descendant	1	2	8	17
Menopausal status				
Post	9	19	28	58
Pre	1	2	10	21
Disease stage				
I/II	9	19	27	57
III	1	2	11	22
Familial history—breast cancer				
Yes	1	2	13	27
No	9	19	25	52
Molecular subtype				
Luminal A	7	15	28	58
Luminal B	1	2	10	21
Luminal B/*HER2*	2	4	0	0

TABLE 2 Percentage of CNVs found, by chromosome, including association with clinical and pathological features

	Chromosome	Percentage
Histological type	chr8	27.81
	chr1	21.16
	chr15	8.80
	chr16	7.00
	chr14	6.67
	chr12	4.82
	chr11	4.80
	chr18	4.32
	chr17	4.09
	chr19	3.16
	chr6	2.50
	chr13	2.50
	chr20	1.77
	chr22	1.54
	chr3	1.47
	chr9	1.37
	chr21	1.23
	chr7	0.95
	chr4	0.90
	chr2	0.62
	chr10	0.35
	chr5	0.10
Ethnicity	chr1	17.85
	chr17	13.23
	chr10	12.15
	chr19	12.12
	chr8	8.71
	chr16	7.88
	chr11	5.83
	chr14	5.51
	chr20	2.61
	chr13	2.59
	chr6	2.11
	chr12	1.82
	chr21	1.54%
	chr3	1.51
	chr5	1.14
	chr22	0.87
	chr2	0.71
	chr4	0.70
	chr7	0.52
	chr9	0.29
	chr18	0.21
Disease stage	chr19	46.27
	chr21	35.07
	chr5	18.66
Familial history	chr21	49.42
	chr19	28.79
	chr5	21.79

(Continues)

TABLE 2 (Continued)

although higher levels of CNVs in chromosome 19 (46%) were associated with late stage and chromosome 21 (49%) for family history presence. For histological type, comparing ductal to mucinous breast carcinomas, CNVs in chromosomes 8 and 1 account for almost 49% of all alterations found in the mucinous tumors analyzed. Similarly, CNVs in chromosome 19 sum to 46.27% of alterations related to later disease stage, alterations in chromosome 21 sum to 49.42% for familial history presence and chromosomes 1 and 17 sum to 31.08% for ethnicity (Caucasian).

Table 3 describes the genes related to CNVs in each chromosome, according to the features they were most associated with. Logistic Regressions and Random Forests models were used to assess these regions, comparing the genomic profiles of the samples, in which a power of discrimination (AUC) of 73% was obtained. The CNVs ranking data distinguishing between histological types and other clinical/pathological tumors' characteristics were assessed to evaluate how these alterations contributed to the separation between considered groups.

Table 4 summarizes the annotation findings in terms of functional pathways closely associated to the CNV-related genes found in the most altered chromosomes, depending on the analyzed trait. Pathways involved with alternative splicing and polymorphisms were mainly associated with most of the altered regions.

Supplementary Table S1 shows the variants already described associated with the CNVs found in this study. The information of cancer-related phenotypes, genes, and clinical status was assessed in order to better describe variants and their clinical interpretation. It is worth noting that all variants have been previously linked to breast or other forms of human neoplasms and roughly 60% of the CNVs found are of uncertain significance or have conflict of interpretation. Our observations add up to this data to be part of a more accurate interpretation in the future.

4 | DISCUSSION

The results shown describe altered chromosome regions that better classify tumors according to their histological type,

TABLE 3 Description of chromosomes containing most alterations per feature and related genes, verified by logistic regression/random forests

	Histological type			Familial history	Disease stage					Ethnicity	
Chromosome	1		8	21	19					1	17
Percentage	21.16%		27.81%	49.42%	46.27%					17.85%	13.23%
Genes	*FNDC5*	*NBPF13P*	*TATDN1*	*SAMSN1*	*FKRP*	*C19orf70*	*C19orf24*	*SYNGR4*	*CENPBD1P1*	*RORC*	*MEIS3P2*
	PHBP12	*CC2D1B*	*RNF139-AS1*	*SLC19A1*	*ZNF257*	*CRX*	*SF3A2*	*BSPH1*	*CTBP2P7*	*EMBP1*	*DDX42*
	STXBP3	*ZC3H11A*	*LYN*	*RAD23BLP*	*ZNF573*	*ZNF439*	*UHRF1*	*GCDH*	*ZNF155*	*SLC2A1-AS1*	*CRLF3*
	DIRAS3	*PGBD2*	*DLGAP2*	*PRDM15*	*ZNF468*	*ZNF700*	*PLEKHA4*	*ZNF814*	*SEMA6B*	*C1orf131*	*NXN*
	MYCL	*POLR3C*	*DMTN*	*PCBP3*	*ZSCAN5A*	*KLK8*	*SNORD23*	*TMEM143*	*DOT1L*	*RFWD2*	*APOH*
	FKSG48	*TRIM58*	*ZNF250*	*ERG*	*MIR3940*	*KLK15*	*OR7A10*	*CYP4F2*	*LMTK3*	*HHAT*	*ATAD5*
	LMO4	*HHIPL2*	*ANK1*	*LINC00320*	*ZNF725P*	*RNU6-902P*	*DBP*	*PCGF7P*	*RPL23AP2*	*RGL1*	*CCDC144CP*
	PPIE	*CFL1P2*	*RNF139*	*RPL31P1*	*SLC27A5*	*SAFB*	*KCNN1*	*RN7SL513P*	*TTYH1*	*RNU2-12P*	*PSMD7P1*
	VAV3	*BMP8B*	*LINC01109*	*RPL34P3*	*ZFP30*	*ZNF606*	*SPPL2B*	*SSC5D*	*ZNF793*	*GPATCH2*	*CTNS*
	ZZZ3	*EIF4G3*	*COL22A1*	*ITGB2*	*ZNF222*	*ZIM2*	*ZNF780B*	*EHD2*	*SIGLEC7*	*FMO4*	*MYO18A*
	LRRC7	*SYDE2*	*PXDNL*	*DIP2A*	*ZNF121*	*SNRPEP4*	*NTF4*	*LENG8*	*ZNF432*	*ZBTB41*	*TRIM16L*
	AK5	*AK2*	*TTPA*	*LINC00159*	*CHMP2A*	*OSCAR*	*MIR3189*	*BIRC8*	*LAIR1*	*CYCSP4*	*CCDC47*
	BRINP2	*PBX1*	*FAM66A*	*RPL23AP4*	*ZNF69*	*DHDH*	*CYTH2*	*GYS1*	*SIGLEC6*	*LAMB3*	*RAI1-AS1*
	PIGK	*SF3B4*	*IKBKB*	*SNX19P1*	*UQCR11*	*MAN2B1*	*RNA5SP468*	*ZNF285*	*ZNF135*	*PLD5*	*SREBF1*
	C1orf185	*MACF1*	*CSMD1*	*C21orf91*	*ZNF737*	*TPM3P6*	*RFX2*	*CALR*	*SAFB2*	*ARID4B*	*MAP2K3*
	GCLM	*S100PBP*	*LRRC69*	*OR4K11P*	*CTU1*	*ZNF813*	*SPHK2*	*SIPA1L3*	*MEGF8*	*RGS7*	*SCPEP1*
	COL24A1	*TFAP2E*	*NPM1P6*	*BACH1*	*SIGLEC5*	*ZNF446*	*RASIP1*	*ZNF571-AS1*	*ZNF433*	*C1orf100*	*ATP2A3*
	S100A16	*SMYD3*	*PKHD1L1*	*TTC3*	*SLC5A5*	*ZNF675*	*CLPP*	*ZNF780A*	*RPL23AP80*	*ESRRG*	*SNORD3C*
	ABL2	*DISP1*	*CLVS1*	*PRMT2*	*CACNG8*	*RNU6-1337P*	*ZNF324*	*ZNF254*	*RFXANK*	*OPTC*	*SMCR5*
	RNF115	*ZMPSTE24*	*LYPLA1*	*SLC37A1*	*GALP*	*MIR517C*	*ZNF473*	*ZNF726*	*PTPRS*	*WDR64*	*ZSWIM5P2*
	MRPS6P2	*MIR4423*	*PRKDC*	*TTC3-AS1*	*ZNF221*	*WDR87*	*ZNF878*	*SYDE1*	*CD70*	*DENND1B*	*RAI1*
	THBS3	*CFHR2*	*MFHAS1*	*PKNOX1*	*POU2F2*	*MIR520H*	*KLKP1*	*KIR3DP1*	*RNU6-751P*	*CD1A*	*MIR33B*
	GNG12-AS1	*RPS15AP6*	*FAM66B*	*CHODL-AS1*	*C5AR2*	*MIR521-1*	*KCNJ14*	*MYO9B*	*NPAS1*	*PPP1R12B*	*CDRT15L2*
	OXCT2	*SMAP2*	*RAB2A*	*HSF2BP*	*MEF2B*	*FUT2*	*RNA5SP465*	*KHSRP*	*GRIK5*	*ZP4*	*BRIP1*
	TUBB8P6	*USP33*	*ASPH*	*LSS*	*ELSPBP1*	*MIR522*	*RNA5SP464*	*CCDC130*	*FPR1*	*GNPAT*	
	HENMT1	*TRIT1*	*MYOM2*	*SNORD74*	*KDELR1*	*ZNF571*	*LSM4*	*CYP4F3*		*FCGR1A*	
	STRIP1	*CCNT2P1*	*CYCSP22*	*TIAM1*	*POLR2E*	*FUT1*	*MED25*	*CACNA1A*		*HNRNPA1P59*	
	YARS	*ASTN1*	*TRMT12*	*RNU4-45P*	*ZNF628*	*ZNF582*	*MAU2*	*TMEM145*		*FLVCR1*	
	PLD5	*RLF*	*ELP3*	*GRIK1-AS2*	*MZF1*	*MIR518A2*	*ZNF235*	*CA11*		*IBA57*	

(Continues)

TABLE 3 (Continued)

	Histological type			Familial history	Disease stage				Ethnicity
	ROR1	*MTX1*	*SGCZ*	*YBEY*	*ZNF43*	*FTL*	*ZNF611*	*GDF15*	*COLGALT2*
	CHRM3	*MUC1*	*SNORD112*	*GTF2IP2*	*C19orf18*	*CSNK1G2-AS1*	*LINC00662*	*PRR19*	*SLC35F3*
	SPATA17	*GIPC2*	*EBAG9*	*LINC00314*	*ZNF45*	*FAM90A28P*	*TUBB4A*	*SYT3*	*PBX1*
	DAB1	*TMEM56*	*THAP1*	*C21orf58*	*TNFSF9*	*OR1AB1P*	*MIR4321*	*SULT2A1*	*MDM4*
	RGS7	*FUBP1*	*FUT10*	*SCAF4*	*SNRNP70*	*ZNF420*	*TMEM161A*	*ZNF283*	*TTC13*
	RN7SL854P	*MIR1256*	*TRPS1*	*LINC00315*	*MIR1227*	*MIR519A2*	*KLK5*	*SULT2B1*	*LHX4*
	EEF1A1P14	*CFHR1*	*FER1L6-AS2*	*TIMM9P2*	*IGSF23*	*MIR516A2*	*TMEM160*	*LYPD5*	*CDC73*
	RNU6-877P	*RNF19B*	*FGFR1*	*KCNE2*	*TNFAIP8L1*	*MIR7-3*	*BAX*	*GTF2F1*	*CDC42BPA*
	AKT3	*HPCAL4*	*FBXO32*	*RPS26P5*	*SIGLEC9*	*MIR516A1*	*MIR4323*	*ALKBH7*	*COL11A1*
	ST6GALNAC5	*MIR4421*	*SNTG1*	*DSTNP1*	*KIR3DL3*	*MIR527*	*LGALS14*	*PRR12*	*CFHR2*
	RN7SL370P	*LPGAT1*	*LPL*	*H2AFZP1*	*ZNF578*	*MIR519A1*	*KCNA7*	*TPRX1*	*HMGN1P5*
	RNF11	*FMN2*	*NRG1*	*DYRK1A*	*ZNF350*	*BTBD2*	*OR7C2*	*EPN1*	*HIST2H3D*
	GJA5	*FNDC7*	*LINC01111*	*HMGN1P2*	*CABP5*	*THEG*	*OR7A5*	*ZNF490*	*SLC2A1*
	CLCA4	*DNAJB4*	*POLB*	*MIRLET7C*	*JSRP1*	*SAE1*	*JUND*	*RNU6-982P*	*TRMT1L*
	ARL5AP3	*KIF14*	*SLC10A5*	*CYP4F29P*	*URI1*	*ZNF566*	*BCL3*	*MAMSTR*	*GNG4*
	DTL	*TRAF5*	*FER1L6*	*FAM207A*	*SPACA4*	*RPS9*	*FAM83E*	*IZUMO1*	*PTPN14*
	NSRP1P1	*RCOR3*	*GSR*	*LIPI*	*ZNF28*	*ASF1B*	*KIAA1683*	*RPL39P38*	*CFHR1*
	ACOT11	*LIN9*	*ENPP2*	*UBASH3A*	*ZNF709*	*SUGP2*	*RN7SL693P*	*PRRG2*	*KLHL12*
	PLA2G12AP1	*DDX59*	*C8orf22*	*APP*	*LRRC25*	*ZNF702P*	*CYP4F8*	*RN7SL121P*	*CSRP1*
	TAF1A	*KIAA1522*	*ZNF705G*	*LINC00205*	*PSPN*	*TRIM28*	*SLC25A42*	*KLK9*	*MROH9*
	HMCN1	*TRIM46*	*IMPA1*	*ANKRD30BP1*	*ERCC1*	*SEC1P*	*RPL7P51*	*NAT14*	*CD46*
	NME7	*RNA5SP52*	*MIR4662A*	*MIR3156-3*	*AP3D1*	*CEP89*	*NOSIP*	*SIGLECL1*	*HIST2H2BF*
	SLC35F3	*TMEM54*	*DPY19L4*	*PDE9A*	*ZNF470*	*ZNF546*	*RN7SL708P*	*ZNF841*	*KDM5B*
	MIR92B	*FAM129A*	*RNF170*	*SAMSN1-AS1*	*ZNF761*	*PPP1R14A*	*SIGLEC18P*	*ACSBG2*	*BRINP3*
	CDC42BPA	*C8B*	*WISP1*	*MCM3AP-AS1*	*CRB3*	*DENND1C*	*PGPEP1*	*SPINT2*	*CRB1*
	CDKN2C	*ZNF672*	*DECR1*	*NCAM2*	*PPP1R13L*	*ZBTB45*	*ZNF676*	*KLK6*	*PDE4B*
	EVI5	*GBAP1*	*RPS3AP30*	*NRIP1*	*ZNF808*	*NDUFA3P1*	*GLTSCR1*	*KLK10*	
	FAM102B	*RNA5SP44*	*FABP5*	*TRAPPC10*	*ZNF233*	*ZNF835*	*GLTSCR2*	*KLK7*	
	SRGAP2	*TPR*	*RPL5P23*	*COL18A1*	*RUVBL2*	*RPL28*	*ZSCAN5C*	*ZNF763*	
	MRPS21	*NOTCH2*	*PCM1*	*POTED*	*CEACAM22P*	*ATP1A3*	*LONP1*	*LRG1*	

(Continues)

TABLE 3 (Continued)

Histological type			Familial history	Disease stage			Ethnicity
OSBPL9	*TTC39A*	*XKR6*	*CRYAA*	*CEACAM16*	*PLIN3*	*SLC25A41*	*VN1R85P*
WDR63	*USP25*	*RNU6-756P*	*MRPL51P2*	*KLK12*	*ZNF443*	*MIR7-3HG*	*VN1R84P*
HSPE1P25	*CSMD2*	*DEFB109P1B*	*MCM3AP*	*KLK14*	*DYRK1B*	*TCF3*	*LRRC4B*
HPCA		*SYBU*	*BRWD1-IT1*	*NR2C2AP*	*NTN5*	*ISOC2*	*HOOK2*
LINC01057		*CHD7*	*WDR4*	*UBE2S*	*ZNF415*	*TPRX2P*	*ZFP82*
NFASC		*MCM4*	*MIR125B2*	*LGALS17A*	*CGB5*	*ZNF100*	*CGB7*
RAVER2			*RNU1-98P*	*FBL*	*ARHGEF1*	*LGALS16*	*DPP9*
DDAH1			*PTTG1IP*	*RDH13*	*ZNF563*	*PAFAH1B3*	*KLK13*
OR2W3			*SIK1*	*CIRBP*	*SLC25A23*	*ZNF665*	*ZFP28*
GLMN			*ERLEC1P1*	*HDGFRP2*	*SMIM7*	*RPL18*	*CCDC9*
RN7SKP98			*CBS*	*MIDN*	*RNU6-1028P*	*TTC9B*	*ZNF225*
NEXN-AS1			*DSCAM*	*TM6SF2*	*KLK11*	*RPL18A*	*ZNF226*
NEXN			*TMPRSS15*	*PRKACA*	*RNU6-1041P*	*SEPT7P8*	*ZNF320*
DPYD			*RNU6-1326P*	*HAPLN4*	*PLIN4*	*ZNF816*	*ZNF227*
JAK1			*LINC00308*	*CYP4F22*	*MLLT1*	*ZNF540*	*ZNF112*
PSMB2			*PPIAP1*	*FEM1A*	*NCAN*	*ZNF92P2*	*RABAC1*
PIAS3			*PCNT*	*CLC*	*MAP3K10*	*SNORD112*	*ZNF805*
TMCO2			*MIR99A*	*ZNF568*	*TPM3P9*	*ZNF92P3*	*ZNF230*
RN7SKP12			*RSPH1*	*MAST3*	*MIER2*	*HKR1*	*KLK4*
PDE4B			*PCP4*	*RNU6-165P*	*NLRP8*	*LENG8-AS1*	*HMGN1P32*
RNA5SP21			*PSMG1*	*KDM4B*	*GRWD1*	*TICAM1*	*RPL36*
TMEM56-RWDD3			*MIR1283-2*	*TPM4*	*ZNF83*	*TINCR*	*ZNF564*
RNA5SP20			*LINC00322*	*LSM7*	*ABCA7*	*BRD4*	*CD33*
WLS			*MIR5692B*	*ZNF234*	*CSNK1G2*	*ARRDC5*	*ZNF223*
SV2A			*LINC00307*	*HSD11B1L*	*ONECUT3*	*SNORA68*	*ZNF224*
CACHD1			*RUNX1*	*ZNF321P*	*RPL32P34*	*ZNF574*	*MIR3188*
RNU7-121P			*ADARB1*	*RPSAP58*	*KIR2DP1*	*INSR*	*PLEKHJ1*
GPATCH2			*GRIK1*	*FCGBP*	*ZSCAN5B*	*CIRBP-AS1*	*CGB8*
FAF1			*ERVH48-1*	*ARMC6*	*KIR3DL1*	*RNA5-8SP4*	*ZNF208*

(Continues)

TABLE 3 (Continued)

Histological type	Familial history	Disease stage	Ethnicity		
ORC1	*C2CD2*	*CATSPERD*	*CGB1*	*CEACAM19*	*ATP8B3*
PRPF38B	*POFUT2*	*CYP4F23P*	*MIR5684*	*ADAT3*	*FAM90A27P*
ENAH	*TPT1P1*	*CLEC11A*	*SUGP1*	*SCAMP4*	*BBC3*
ST7L	*RNU6-286P*	*SYCE2*	*KLK2*	*GATAD2A*	*SIGLEC14*
NUDT17	*CLDN14*	*ZNF799*	*CCDC124*	*LEUTX*	*ARRDC2*
EPS15	*VDAC2P1*	*GRIN2D*	*C19orf81*	*ZNRF4*	*SHISA7*
ZFYVE9	*NDUFV3*	*ACER1*	*PLIN5*	*ZNF284*	*ZC3H4*
NFIA	*BRWD1*	*AMH*	*ATP5D*	*ZNF404*	*RCN3*
PDE4DIP	*U2AF1*	*PGK1P2*	*KIR2DL1*	*C5AR1*	*DEDD2*
IRF6	*RNU6-113P*	*UBE2M*	*KIR2DL3*	*SHANK1*	*RAD23A*
	KRTAP10-3		*KIR2DL4*	*ZNF585A*	*AKT2*
				IL12RB1	*HIPK4*

ethnicity, disease stage, and familial history. For this set of tumors, almost half of the alterations were found in chromosomes 8 and 1 when considering mucinous tumors compared to ductal breast carcinomas, in chromosome 19 when considering the later disease stage when comparing to earlier stages, in chromosome 21 when comparing presence of family history to its absence and virtually 1/3 of the changes were found on chromosomes 1 and 17 when ethnicity (Caucasian X Afro-descendants) was considered. Also, genes found in CNVs regions described in this study were significantly enriched in gene sets related to alternative splicing, polymorphisms, DNA-binding, transcriptional regulation, phosphoproteins, and mutagenic sites, among others.

Polymorphisms of single nucleotides or of larger DNA fragments and all the other abovementioned pathways are widely associated with the development of cancer in general. Aberrant activation of these pathways in breast cancer is part of the oncogenic mechanisms contributing to disease progression and is the focus of many current studies, since the disruption of mechanisms affected by these pathways may lead to pathogenic events (Mocellin, Valpione, Rossri, & Pooley, 2018; Nicolini, 2017.; Ziv et al., 2017). The description of these changes is very relevant from the point of view of genetic susceptibility.

Alternative splicing has been extensively linked to activation of many tumor processes, because RNA processing is vital for the production of variant proteins that are involved in steps such as angiogenesis, invasion, and antiapoptosis. These processes are also influenced not only by genetic but also environmental factors, for example, chemical and immune responses, heat stress, and DNA damage (Anczuków & Krainer, 2016; Pai & Luca, 2018). Copy number alterations were described as having a particular association to alternative splicing, especially large ones, as seen in our study (Sebestyén et al., 2016; Singh & Eyras, 2017). Also, hereditary breast cancer was reported as enriched for splicing mutations, what often leads to loss of functions in cancer (Rhine et al., 2018).

Thus, in relation to clinical features, namely histological type, ethnicity, disease stage, and familial history, there are particularities worth pointing out. As previously stated, CNVs in chromosomes 1, 8, 17, 19, and 21 explain around half of the alterations found in these samples when associated with one of these clinical characteristics. Alterations in chromosome 1 have been described in 50%–60% of breast tumors and are associated with disease initiation, presence of amplification sites, and a large number of copy number alterations, especially in the 1q arm, which harbor many oncogenes as *MYCL1*, *JUN*, *NRAS*, *SHC1,* and *NCSTN*, for example, all verified in samples from our current study (Goh et al., 2017; Orsetti et al., 2006; Silva et al., 2015). Chromosome 8p arm CNVs are widely linked to poor prognosis and metabolic disruptions in breast cancer; moreover,

TABLE 4 Functional annotation of genes and enriched pathways associated with CNVs described (DAVID 6.8 Database)

Feature	Chr.	Pathway/function	Gene count	%	*p-value*
Histological type	1	Alternative splicing	37	57.8	0.0017
		Splice variant	29	45.3	0.0096
		Cytoplasm	20	31.2	0.015
		Mutagenesis site	11	17.2	0.041
	8	Polymorphism	87	55.1	0.021
		Alternative splicing	81	51.3	0.0056
		Phosphoprotein	69	43.7	0.0014
		Splice variant	67	42.4	0.0012
		Cytoplasm	44	27.8	0.0047
Familial history	21	Alternative splicing	40	40.8	0.0043
		Phosphoprotein	35	35.7	0.0014
		Protein binding	32	32.7	0.038
		Nucleus	28	28.6	0.0003
		Cytosol	18	18.4	0.0055
Disease stage	19	Polymorphism	224	53.8	0.013
		Nucleus	149	35.8	1E-12
		Transcription	118	28.4	4E-28
		Metal binding	117	28.1	6E-13
		DNA binding	106	25.5	1E-26
Ethinicity	1	Alternative splicing	33	60.0	0.024
		Splice variant	28	50.9	0.01
		Ubl conjugation	10	18.2	0.016
	17	Splice variant	12	54.5	0.0028

recent studies showed that loss of multiple genes in this region may create greater genomic instability, leading to different effects from loss of a single gene (Cai et al., 2016; Lebok et al., 2015). These two chromosomes are mainly associated with differentiation of ductal and mucinous types, which explain why they were found linked to histological type alterations (Afghahi et al., 2015; Lacroix-Triki et al., 2010).

Ethnicity was found to be associated with CNVs on chromosomes 1 and 17. A recent study suggests that genes near *BRCA1* in 17q are correlated with breast cancer in African Americans (Ochs-Balcom et al., 2015). However, there is a lack of studies that confirm this association, although genes related to heredity could also contribute to this finding. Interestingly, familial history presence correlated mainly to CNVs in chromosome 21. The gene *NRIP1* localized at 21q21 was described to be a susceptibility locus (Ghoussaini et al., 2012) and this region was among our identified CNVs. Also, other chromosome 21 regions were identified, containing genes as *SAMSN1*, associated with several cancer types such as multiple myeloma, lung cancer, glioblastoma, and *RUNX1*, implicated as an oncogene and tumor suppressor in breast cancer (Browne et al., 2015; Mercado-Matos, Matthew-Onabanjo, & Shaw, 2017; Noll et al., 2014; Yamada et al., 2008; Yan et al., 2013). Late disease stage was correlated to chromosome 19 copy number alterations. These regions have been described in association with high-grade breast cancers for other studies (Yu, Kanaan, Bae, Baed, & Gabrielson, 2009) and are characterized by aggressiveness and poor prognosis tumors.

Since this study focused on a Brazilian cohort, it is worth mentioning that the genetic composition of the Brazilian population is sharply mixed and is genomically underrepresented in studies that consider variants and tumor markers (Popejoy & Fullerton, 2016). There might be considerable genetic differences underlying tumor biology in these cases, so it is critical to consider understudied populations to better understand breast cancer worldwide. Despite the restricted sample size, this is the first study to evaluate breast cancer CNVs in this specific population, associating them to tumor clinical features. CNV regions identified from these samples and their correlated genes could potentially be different from non-Brazilian cohorts. In a previous study comparing Brazilian and TCGA (The Cancer Genome Atlas) data (data not shown), we found striking differences between these two cohorts, which were related to genes involved in different carcinogenic pathways, since pathways related to FGF and

Wnt were most commonly affected in the Brazilian samples, whereas those associated with cholecystokinin receptor (CCKR) signaling and inflammation mediated by chemokine and cytokine signaling pathways were most commonly affected in the TCGA samples.

We conclude that the copy number alterations described in this study provide an overview of the chromosomal regions affected by CNVs and their association with clinical and pathological features. New molecular targets can be inferred from this study and these CNV regions should be investigated in more detail, potentially driving more dedicated studies focusing on breast tumors from Brazilian cohorts.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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