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Cancer Susceptibility for Male Breast Cancer Assessed by SNP-A Analysis and Risk Alleles of *TP*53, *MDM*2, *VEGF*, *VEGFR*1, *HIF*1*A* and *BRCA*1

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Abstract

Male Breast Cancer (MBC) has a familial component thus identification of polymorphic risk alleles of candidate genes and/or cytogenetic anomalies may help to predict the risk for the offspring of MBC patients. The conventional metaphase cytogenetics can indicate loci that are hotspots while analysis by single nucleotide polymorphism arrays (SNP-A) can identify chromosomal defects which may play a role in the etiology of cancer. A cumulative genotype risk due to each allele of candidate genes of the signaling pathways regulating *c-MYC*, *HIF*1*A*, *TP*53 and *BRCA*1 may be a factor facilitating cancer development. Cancer risk was assessed in a 35-year-old healthy son of a 60-year-old MBC patient with a family history of cancer by metaphase cytogenetics, SNP-A and analysis of 25 polymorphisms in six genes *TP*53, *MDM*2, *VEGF*, *VEGFR*1, *HIF*1*A*, and *BRCA*1. The risk genotype GG-TT of *MDM*2 309T > G and *VEGF*-417C/T polymorphisms along with chromosomal instability shown by cytogenetic analysis and SNP-A, rare *de novo* duplication Yp, deletion in 7q pericentromeric region indicate an increased risk of cancer in the healthy son of an MBC patient.

Keywords

Breast Cancer, Aneuploidy, Polymorphism, CN-LOH, SNP-A

1. Introduction

A family history of breast cancer confers a relative risk of 2.5 with 20% of men with breast cancer having a positive family history [1]. A first-degree relative of a

cancer patient may have a 2 - 3 fold higher risk of developing cancer at the same site as family members tend to share genetic background along with environment, *i.e.*, food, lifestyle, infections, pollutants [2]. Polymorphisms in both high and low penetrance genes contribute to breast tumorigenesis in combination with exogeneous (diet, pollution) and endogeneous (hormones) factors [3]. A cumulative genotype risk due to each allele may be a factor facilitating cancer development. The oncogenic changes involving non-random gene deletion, amplification or mutation in any oncogene and/or tumor suppressor genes cluster along the signalling pathways that regulate *c-MYC*, *HIF*1*A* and *TP*53. *HIF*1*A* can bind and stabilize p53, also stimulate angiogenesis and induce adaptation to hypoxia whereas p53 mediates hypoxia-induced apoptosis [4]. *MDM*2 is a negative regulator of p53. *HIF*1*A* up-regulates expression of *VEGF* during hypoxia in the majority of solid tumors [5]. *VEGF* is a potent mitogen with a vital role in normal physiological and tumor angiogenesis [6]. Angiogenesis also plays a crucial role in BRCA1/BRCA2 breast cancers [7]. *VEGF* binds to its receptor *VEGFR*1 (*FLT*1). Latter regulates *VEGF* expression as well as mediates migration of monocytes, macrophages and proliferation of endothelial cells [8]. Individuals carrying mutations in *BRCA*1/2 have a 47% - 55% probability of developing breast cancer [9] [10]. Apart from inherited mutations in *BRCA*2, in about 4% of patients *BRCA*1 tends to increase the risk of male breast cancer [11]. *HIF*1*A* expression has also been associated with male breast cancer [12].

Single Nucleotide Polymorphisms (SNPs) in the regulatory or coding regions can alter gene expression or affect protein functions and also influence different characteristics among individuals. The functional polymorphisms which alter the gene expression have been reported to be associated with the development of complex diseases like cancer [13]. Single Nucleotide Polymorphism Array (SNP-A) can identify even those chromosomal defects that are not apparent by metaphase cytogenetics, thus complementing the latter [14]. Considering the polygenic component of breast cancer, assessment of known risk-associated variants along with cytogenetic analysis can also be a useful predictor of breast cancer susceptibility.

Male breast cancer frequency is approximately 2% among breast cancer patients in India. The risk of breast cancer in a healthy male offspring of an MBC patient was estimated to be approximately 22% with a 10% chance of identifying a mutation in *BRCA*1 and *BRCA*2. In the absence of any specific tool available for assessing breast cancer risk in the Indian population, the pedigree assessment tool, the Ontario family assessment tool, Manchester scoring system available for the USA population were used to estimate the risk (https://www.uspreventiveservicestaskforce.org/apps/). Hence a multidimensional approach was used to estimate genetic risk for cancer in the healthy male offspring of Indian Male Breast Cancer (MBC) patients using classical cytogenetic analysis by G-banding, SNP-A and study of twenty-five variants in six genes (*TP*53, *MDM*2, *HIF*1*A*, *VEGF*, *VEGFR*1 and *BRCA*1) involved in proliferation, apoptosis, angiogenesis and tumor progression. The SNPs selected in the present study (**Table 1**)

Table 1. Detail of *BRCA*1, *TP*53, *VEGF*, *HIF*1*A*, *MDM2*, *VEGFR*1 variants and reaction conditions used for screening.

Gene	Variant	Location	Genotyping Method	PCR Product (bp)	Annealing Temperature, $MgCl_2$ concentration	Restriction enzyme	Restriction digestion pattern	Primers Reference
*BRCA*1	p.Pro871Leu (c.2612C > T)	Exon 10	PCR-RFLP	125	59˚C, 1.5 mM	*Hpa* II	C allele-99 and 26 T allele-125	[15]
	p.Cys64Arg (c.190T > C)	Exon 5	PCR-RFLP	193	59˚C, 1.5 mM	*SnaB* I	T allele-193 C allele-124 and 69	[16]
	130delT	Exon 11	PCR-RFLP	151	59˚C, 1.5 mM	*Dde* I	Wt-151 Mut-96 and 55	[17]
	p.G1738R (g.5331G > A)	Exon 20	PCR-RFLP	233	59˚C, 1.5 mM	*BsaX* I	G allele-112, 91, 30 A allele-233	[18]
*TP*53	p.P47S	Exon 4	PCR-RFLP	201/185*	59˚C, 1 mM	*Msp*I	S allele-201/185 P allele-156/140, 45	[19]
	p.R72P	Exon 4	PCR-RFLP	279	59˚C, 1 mM	*BstU*I	P allele 279 R allele-160 and 119	[20]
	*PIN*3 *Ins* 16 *bp*	Intron 3	PCR	-	61˚C, 1 mM		A1 allele-119 A2 allele-135	[21]
	p.R213R	Exon 6	PCR-RFLP	1621	59˚C, 1.5 mM	*Taq*I	A allele-312, 383 and 926 G allele-695 and 926	[22]
	r.13494g > a	Intron 6	PCR-RFLP	1621	59˚C, 1.5 mM	*Msp*I	G allele-356, 277, 277, 299, 168, 124 and 120 A allele-633, 299, 277, 168, 124, 120	[22]
VEGF	−2549I/D	Promoter	PCR	229/211	59˚C, 1.5 mM	-	I allele 229 D allele 211	[23]
	−2578C/A	Promoter	PCR-RFLP	459	59˚C, 1.5 mM	*Bgl*I	C allele-459 A allele-247, 212	[24]
	+936C/T	3'UTR	PCR-RFLP	207	59˚C, 1.5 mM	*Nla*III	C allele-207 T allele-122,85	[25]
	−417C/T	Promoter	Sequencing	486bp	62˚C, 1.5 mM	-	-	[26]
	−172C/A	Promoter	Sequencing			-	-	
	−165C/T	Promoter	Sequencing			-	-	
	−160C/T	Promoter	Sequencing			-	-	
	−152G/A	Promoter	Sequencing			-	-	
	−141A/C	Promoter	Sequencing			-	-	
	−116G/A	Promoter	Sequencing			-	-	
	−7C/T	5' UTR	ARMS-PCR		59˚C, 1.5 mM		Control-425 C and T allele-183	[27]
*HIF*1*A*	g.C111A	Exon 2	PCR-RFLP	187	59˚C, 1.5 mM	*Bgl*I	C allele-44, 143 A allele-187	[28]
	g.C1772T	Exon 12	PCR-RFLP	346	55˚C, 1.5 mM	*Hph*I	C allele 118, 228 T allele 346	[28]
	g.G1790A	Exon 12	PCR-RFLP	346	55˚C, 1.5 mM	*Aci*I	G allele 145, 201 A allele 346	[28]
MDM2	SNP309T > G	Promoter	PCR-RFLP	351	59˚C, 1.5 mM	*Msp*AII	T allele-232, 88, 31 G allele-186, 88, 46, 31	[29]
*VEGFR*1	−710C/T	Promoter	PCR-RFLP	665	65˚C, 1.5 mM	*Nla* III	C allele-665 T allele-520, 145	[30]

ARMS-PCR: Amplification refractory mutation system—Polymerase chain reaction; PCR-RFLP: Polymerase chain reaction—Restriction fragment length polymorphism.

had been previously reported to be related to cancer risk due to their effect on protein expressions or functions.

2. Methods

Case Presentation

The proband was healthy son aged 35 years (IV:2) of a 60 year old male breast cancer (MBC) patient (III:1) (**Figure 1(I)**). The proband sought information about his own susceptibility to cancer as he also had a positive family history; his grandfather (II:4) and paternal grand uncle (II:3) had died of throat and blood cancer respectively. His father, the MBC patient (III.1, **Figure 1(I)**) had presented with a growth (2 × 1 cm) in outer upper quadrant of left breast with a history of inflammation on left breast for past two years at the time of diagnosis. The clinical examination and histopathology confirmed infiltrating ductal carcinoma of breast, stage II (ER+, PR+, Her-2neu –ve). After written informed consent, blood samples of both subjects were collected in EDTA and heparin vacutainers. Heparinised blood was used to set up standard 72 hour peripheral blood culture [31]. Cultured cells were G-banded, karyotypes were made and described as per ISCN, 2016 [32]. Genomic DNA was extracted from EDTA anticoagulated blood using standard phenol-chloroform method [33]. Twenty five variants of six genes (*TP*53, *MDM*2, *HIF*1*A*, *VEGF*, *VEGFR*1 and *BRCA*1) were screened by PCR-RFLP or direct PCR method using previously published primer sequences (**Table 1**). The samples were also analyzed using Illumina Human Cyto SNP array and data was analyzed using KaryoStudio (v 1.2). This study was approved by the Ethics Committee of Guru Nanak Dev University, Amritsar, Punjab, India.

3. Results

Karyotypic analysis by G-banding showed increased frequency of chromosomal aberrations in MBC patient (79.9%) especially numerical aberrations than proband, his healthy son (73.9%). The proband had low level mosaicism and increased chromosomal instability; he had a monosomy of chromosome 11, numerical and structural anomalies in chromosome 6 along with structural aberrations in chromosome 13, 14, 21, 22, marker chromosomes and ring chromosomes (**Table 2**). The proband also had copy neutral LOH (CN-LOH) in adrenal hyperplasia associated region on 6p22.3 - 6p21.2, duplication in Yp11.2 and Yp11.3 and deletion in 7q11-21 pericentromeric region (**Figures 1(II)-(A)-(D)**). In MBC patient, monosomy of chromosome 12, 17, 19, loss of Y and trisomy of 21 was observed. Chromosome 21 was also involved in translocations with chromosomes 1, 14 and 15 (**Table 2**). The SNP-A of MBC patient showed a loss of Yq11.22.2 and gain in Yq11.22.1 in the azoospermia (AZF) region (**Figure 1(III)-(a)** and **Figure 1(III)-(b)**).

Among polymorphic variants analyzed, the MBC patient was homozygous for variant allele of 5 polymorphisms; *MDM*2 SNP 309T > G and four polymorphisms of *VEGF* (−2578C/A, −417C/T, −152G/A, −116G/A). The proband was

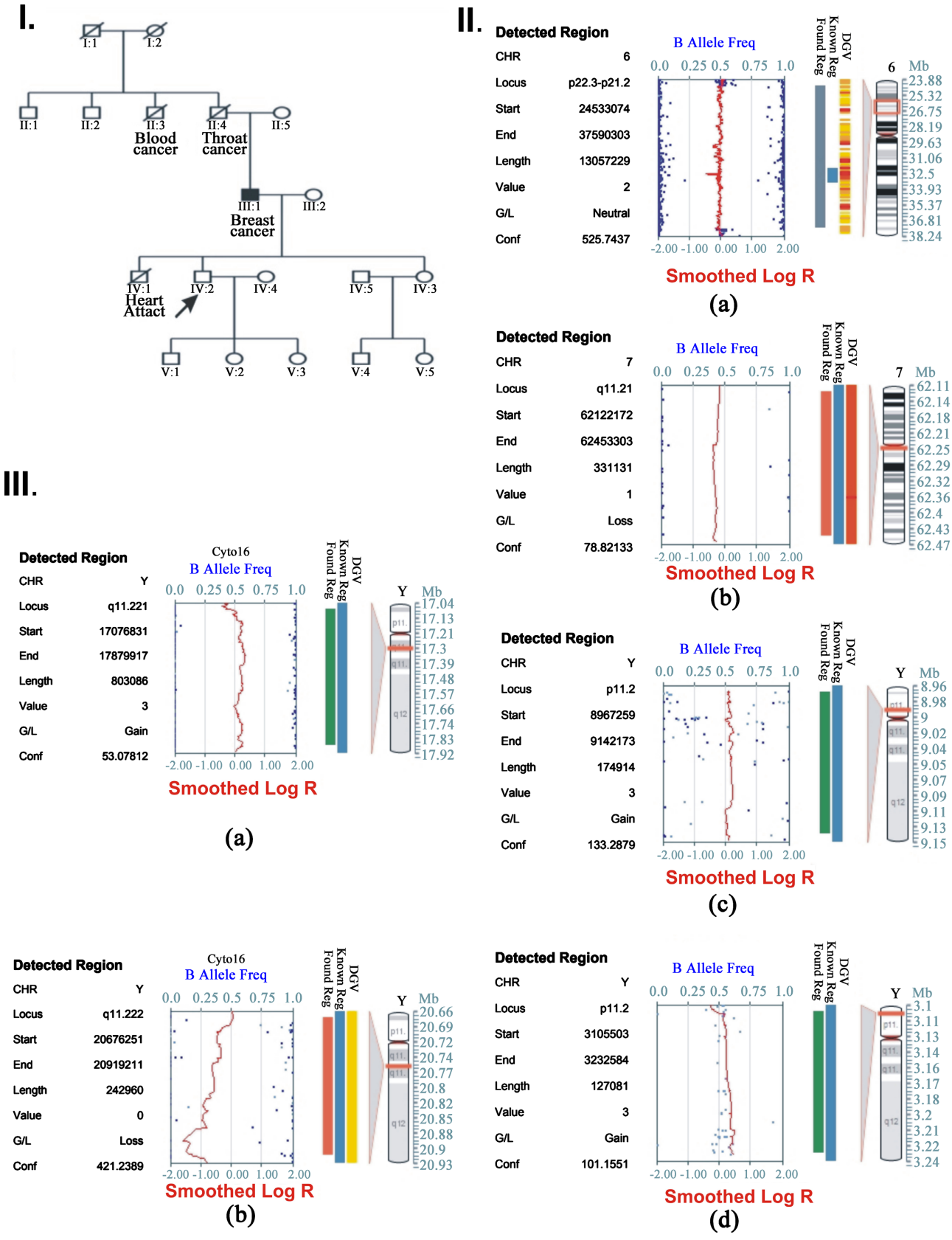

Figure 1. (I) Family Pedigree; (II) SNP-A analysis showing CN-LOH (a), loss (b) and gains (c) and (d) in proband; (III) SNP-A analysis showing gain (a) and loss (b) in male breast cancer patient.

Table 2. Cytogenetics profile of MBC patient and his healthy son.

	Proband (Son)	MBC Patient (Father)
Classical Cytogenetics with GTG banding		
Representative Karyotypes	43,Y,-X,-11,-12,-13,-16,+2mar/44,XY,-11,t(13;?)(q;?),+13,-14/45,XY,dic(2;6)(qter→p24::p23→qter),+6,chtb(9)(q2?),-11/45,XY,dic(21;22)(qter→p13?::p13?→qter)/45,XY,rob(13;14)(q10;q10)/45,XY,-4,+5,-6,+19,-20,-21,+mar/46,XY,del(1)(pter→q10:)[4]/Ring, Triradials, Polyploidy/46,XY[11]	45,X,-Y[2]/45,XY,-19/46,XY,-17,+21/45,XY,tas(1;21)(q44;q11.2),chtb(5)(q13),-12,+21/46,XY,tas(7;20)(q36;p13)/46,XY,add(4)(q?),add(7)(q?),+9,-12,+16,-22/84,XXYY,+X,+1,-4,-5,-7,-9,-10,-11,-11,-12,-14,-17,+19,-20,+21,-22/Polyploidy[10], dmin[2]/46,XY[11]
SNP-A Profile		
Gain	Yp11.2, Yp11.3	Yq11.22.1
Loss	7q11-21	Yq11.22.2
CN-LOH	6p22.3-6p21.2	-

homozygous for variant allele of *VEGF* -417C/T and *MDM2* 309T > G polymorphisms. The proband was heterozygous for 8 polymorphisms, three in *TP*53 (p.R72P, PIN3 Ins 16bp and r.13494g > a) and four in *VEGF* (−2549I/D, −2578C/A, −152G/A, −116G/A) and one in *BRCA*1 (p.Pro871Leu). For *VEGF* +936C/T and *HIF*1*A* g.C1772T polymorphism, the MBC patient was heterozygous while his son (proband) had wild type genotype (**Table 3**).

4. Discussion

Polymorphisms have an important role in promoting susceptibility to diseases as well as the response of the individuals to various drugs [34]. As individual polymorphism may confer a minor increase of disease risk, collectively the common cancer associated SNPs can cause a substantial elevated risk. In current study both MBC patient and his healthy son had RP-GG genotype for *TP*53 p.R72P and *MDM2* 309T > G polymorphism. The *MDM2* GG genotype has been associated with deficiency in p53 response, being a negative regulator of p53. It is also associated with a significantly reduced age of onset for p53 dependent cancer. The R72 allele has 15-fold greater capacity for inducing apoptosis than P72 allele. Though both PP genotype of *TP*53 p.R72P and GG genotype of *MDM2* 309T > G polymorphisms have not been independently associated with overall breast cancer risk [35], they are believed to act as effect modifier instead of being causal [36].

The MBC patient was heterozygous for *BRCA*1 p.Pro87leu, *TP*53 p.R72P, *VEGF* + 936C/T and *HIF*1*A* g.C1772T polymorphisms. *BRCA*1 acts as a transcriptional co-activator and increases p53 dependent transcription from *p*21 and *BAX* promoters [37]. *BRCA*1 has been reported to block *VEGF* promoter activity by oestrogen receptor alpha [38]. An upregulated local concentration of estrogen selectively supports survival and proliferation of breast cancer cells with *BRCA*1 mutations [39]. The MBC patient was ER + ve, PR + ve and HER-2-neu negative. MBC patients usually have high ER (90%) and PR (81%) positivity and lower Her-2-neu positivity (2% - 15%) [40]. Hormonal, environmental factors

Table 3. Molecular genetic profile of male breast cancer patient and his healthy son.

Gene	Variant	RefSNP	Proband	MBC Patient	Functional Relevance
*BRCA*1	p.Pro871Leu (c.2612C > T)	-	CT	CT	Associated with increased BRCA1 expression
	p.Cys64Arg (c.190T > C)	-	TT	TT	Prevents BRCA1-BARD1 binding
	130delT	-	WT	WT	Premature stop codon at AA residue 409
	p.G1738R (g.5331G > A)	-	GG	GG	Destabilizes protein folding
*TP*53	p.R72P	rs1042522	RP	RP	Plays role in apoptosis
	*PIN*3 *Ins* 16*bp*	rs17878362	A1A2	A1A1	Affects function and expression of p53
	p.P47S	rs1800371	PP	PP	Plays role in apoptosis
	p.R213R	rs1800372	AA	AA	Role in activity of protein
	r.13494g > a	rs1625895	GA	GG	Affects function and expression of p53
VEGF	−2549I/D	rs35569394	ID	II	D allele associated with increased transcriptional activity
	−2578C/A	rs699947	CA	AA	Alters the binding of GATA-2 transcription factor
	+936C/T	rs3025039	CC	CT	Alters binding of transcription factor activating enhancer binding protein
	−417C/T	rs833062	TT	TT	-
	−172C/A	rs59260042	CC	CC	Associated with ↑ VEGF m-RNA level
	−165C/T	rs79469752	CC	CC	-
	−160C/T	-	CC	CC	-
	−152G/A	rs13207351	GA	AA	-
	−141A/C	rs28357093	AA	AA	-
	−116G/A	rs1570360	GA	AA	A allele associated with reduced plasma VEGF level
	−7C/T	rs25648	CC	CC	-
*HIF*1*A*	g.C1772T	rs11549465	CC	CT	Associated with higher transcriptional activities and enhanced angiogenesis
	g.G1790A	rs11549467	GG	GG	
	g.C111A	-	CC	CC	
*MDM*2	SNP309T > G	rs2279744	GG	GG	Associated with enhanced MDM2 expression and attenuates function of TP53 protein
*VEGFR*1 (*FLT*1)	−710C/T	-	CC	CC	-

can be a cause of breast cancer as Polycyclic Aromatic Hydrocarbons (PAHs), benzol (*a*), pyrene have been found to reduce *BRCA*1 mRNA levels in MCF-7 human breast cells [41]. The MBC patient and his son were agriculturists. Former had a self reported long term exposure to agricultural chemicals especially chemical fertilizers and pesticides like organochlorines which are known carcinogens and tumor promoters.

Chromosomal translocations are considered non-random and may lead to cancer by formation of oncogenic fusion proteins or activation of oncogenes by a promoter or enhancer [42]. The MBC patient had translocations involving chromosome 21 as well as copy number changes in 21. Chromosome 21 harbors

genes *RUNX*1 and *DYRK*1*A* which have been implicated in tumorigenesis [43] [44]. Translocations have been reported to be influenced by spatial position of broken loci, recombinations or DNA repair elements [42] [45] [46]. In proband, chromosome 13 was involved in translocations and copy number changes. Chromosome 13 harbors two well known genes *BRCA*2 and *RB* involved in tumorigenesis. Chromosome 6 showed copy number changes, was involved in translocations, formed a dicentric and also had copy neutral loss of heterozygosity (CN-LOH). The LOH region harbours various genes like *ALDH*5*A*1, *HFE*, *CDSN*, *NEU*1, *C*2, *SKIV*2*L*, *CYP*21*A*2, *TNXB*, *TAP*2, *TAP*1, *TAPBP*, *PSMB*8, *COL*11*A*2, *TULP*1 and *PNPLA*1, some of which have role in proliferation.

Many chromosomal regions showing uniparental disomy (UPD) are consistent and specific for tumor types and appear more frequently in solid tumors than leukemia [47]. UPD has been previously reported in breast cancer [48] [49] and other tumors. Mutated genes in UPD have been considered indicative of patient outcome with implications in response to chemotherapy. Constitutional UPD is associated with meiotic errors, resulting in developmental diseases, however, it can also be observed in healthy controls, probably because of early mitotic errors and autozygosity [50]. The CN-LOH at 6p22.3-p21.2 observed by SNP-A analysis in proband has been previously reported in patients of developmental delay as well as in healthy controls [14]. Loss of 6p22.3 has been associated with developmental delays and autism spectrum disorders with a possible haploinsufficiency of *ATXN*1 [51] [52]. Acquired UPD are common in both hematologic and solid tumors constituting 20% - 80% of LOH seen in human cancers [53] [54]. In myeloid malignancies CN-LOH has been associated with loss of normal allele of *JAK*2, *MPL*, *cCKIT* and *FLT*3 along with duplications of oncogenic mutations [14]. CN-LOH 6p22.1 and loss of chromosome 9, 15, 18 have been observed in tumor tissue of tubulocystic renal cell carcinoma [55]. The adrenal hyperplasia region on 6p21.3 also has gene for 21-hydroxylase enzyme which controls cortisol synthesis. The cortisol synthesis pathway shares steps with aldosterone, androgens and estradiol synthesis pathways. The 6p22.3-6p21.2 region harbours many genes like *HFE*, *EHMT*2, *CLIC*1, *DAXX*, *DDR*1, *E2F*3, *ID*4, *BAK*1, *HLA-G*, *IER*3, *LTA*, *MAPK*14 with role as channel proteins or in apoptotic pathways [56]. Genetic variants in the region 6p21.1 - p22.3 along with *VEGFA* and *CDKAL*1 have also been associated with type 2 diabetes [57]. Hypoandrogenism, liver disease causing hyperestrogenism, gynaecomastia, obesity and alcohol intake are among possible risk factors for breast cancer apart from family history [58]. The MBC patient did have a past history of alcohol consumption but the proband had no past history of alcohol intake or smoking.

The copy number variations, deletions and duplications in Y chromosome observed were different in both father and son. In MBC patient, the azoospermia factor region on Yq showed both gain and loss. The AZF region has genes involved in germ cell differentiation and spermatogenesis. Though they are not directly linked to breast cancer yet, mosaic deletions in these genes have been pro-

posed as risk marker for non-Hodgkins lymphoma and testicular cancers. Post zygotic AZF deletions occur during early embryogenesis and may precede appearance of a testicular tumor by many years [59]. In the MBC patient, a complete loss of Y chromosome was also observed in karyotypic analysis of some metaphases. A study on colorectal and prostate cancer patients had found a strong association between the mosaic loss of Y chromosome in peripheral blood and carcinogenesis in males [60].

The son did not inherit the Yq deletions observed in his father but had a *de novo* duplication of Yp11.2-11.3. This duplication, a rare event, has been reported as a constitutional duplication of a portion of Yp in two brothers of Italian descent, one with B cell lymphoma and his healthy sibling, presumed to be inherited from their father [61]. Phylogenetic sequence comparisons show that duplications of the human Yp11.2/Yp11.1 region were already present in the macaque-human ancestor as multiple paralogs located predominantly in subtelomeric regions [62]. The short arm of the human Y chromosome harbor various genes viz. *TSPY*1, *TSPY*2, *TSPY*3, *TSPY*4, *TSPY*8, *TBL*1*Y*, *TGIF*2*LY*, *AMELY*, *SRY*, *ZFY*, etc. Among them variant expression of *TSPY*, a protooncogene, has been observed in gonadoblastoma [63], germ cell neoplasia, liver cancer, melanoma and prostate cancer along with another male specific gene *TGIF*2*LY*, found to be upregulated in liver cancer [64]. Thus, in the proband the duplication of the Yp region may lead to ectopic expression of genes influencing the development and progression of cancer.

Y chromosome loss and rearrangements have been associated with different types of cancer, such as bladder cancer [65], male sex cord stroma tumors [66], lung cancer [67] and esophageal carcinoma [68]. In a previous report, in an infertile man with severe oligoasthenoteratozoospermia, an approximate 2.4 Mb inherited duplication region in Yp11.2 and a *de novo* partial AZFb deletion (which spanned 5.25 Mb including eight protein coding genes and four non-coding transcripts) was observed which did not remove the *RBMY* gene family [69]. The proband in our study with Yp duplication was fertile and had three offsprings (**Figure 1(I)**).

The proband also had deletion in 7q11-21 region. The pericentromeric region of chromosome 7q contains intrachromosomal segmental duplications that give rise to recurrent constitutional genomic rearrangements. A majority of patients with Williams-Beuren syndrome (WBS) have a micro-deletion of about 1.5 Mb from chromosome 7q11. Also, deletions flanking the typical breakpoints of the WBS microdeletion in two genes, *NCF*1 and *GTF*2*IRD*2 have shown reduced expression levels, presumably because their transcription control elements are affected by the deletion [70].

Monosomy of chromosome 11 observed in proband is among the chromosome anomalies frequently observed in bladder cancer. The numerical aberrations of chromosome 11 in which *Cyclin-D* is located, deletion of 11p and also mutations of the *H-RAS* located on 11p might reflect alterations implicated in the genesis and pro-

gression of bladder cancer. Translocations of genetic material between chromosome 11 and other chromosomes have been associated with leukemias and lymphomas [71]. The cytogenetic analysis of malignant primitive neuroectodermal SK-PN-DW tumor cell line have revealed several chromosomal rearrangements like translocations involving chromosomes 1, 7, 11,17, 22 and loss of chromosomes Y, 11,13 and 18 [72]. Aneusomy of chromosome 1, 11, or 17 has been correlated significantly with some clinicopathologic features of breast tumors, such as lymph node status, histologic grade, or ER and PR status, indicating that chromosomal aneusomy can be a new biologic marker of breast carcinoma [73] [74].

5. Conclusion

In the proband, the risk genotype GG-TT of *MDM2* 309T > G and *VEGF*-417C/T polymorphisms along with chromosomal instability shown by cytogenetic analysis and SNP-A, rare *de novo* duplication Yp, deletion in 7q pericentromeric region indicate an increased risk in the proband (the son of MBC patient). Some of the additional anomalies observed in SNP-A analysis have not been reported in male breast cancer earlier. The results add to the database of anomalies associated with MBC and can have utility in counselling the relatives of MBC patients.

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Ethical Approval

All the study subjects gave their written consent to participate in the study. This study was approved by the Institutional Ethics Committee of Guru Nanak Dev University, Amritsar, Punjab, India.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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