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Haplotype analyses of the c.1027C>T and c.2167_2168delAT recurrent truncating mutations in the breast cancer predisposing gene PALB2

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Abstract

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Compliance with ethical standards

Conflict of interest. The authors declare that they have no conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Purpose—Breast cancer predisposing mutations *PALB2* c.1027C>T (p.Gln343*) and *PALB2* c.2167_2168delAT have each been observed multiple times in breast cancer families of Italian ancestry. More recently, the c2167_2168delAT mutation was identified in unrelated breast cancer cases of various ancestries. For each mutation, we investigated whether the origin was multiple mutational events (a “hot-spot”) or a single event (a founder allele).

Methods—We genotyped and reconstructed haplotypes for 36 participants of Italian, Italian-American, Hispanic, and Nigerian ancestries, using seven short tandem repeat (STR) markers that covered 3 Megabases within and flanking *PALB2* on chromosome 16.

Results—For *PALB2 c.1027C>T*, a shared haplotype of minimum size 150 kb was shared by all 19 carriers investigated, all of Italian ancestry. This result suggests that this allele arose as a single event in a shared ancestor. For *PALB2 c.2167_2168delAT*, all 12 carriers from American/Italian and Italian families shared a 1 MB haplotype, the 3 Hispanic carriers shared a different haplotype of size 2MB, and the Nigerian carrier had different alleles at all 7 STR markers. These results suggest that *PALB2* c.2167_2168delAT arose multiple times, but that within each population, *PALB2* c.2167_2168delAT likely represents a single mutational event.

Conclusion—We identified two *PALB2* mutations that are founder alleles in Italian families, one of which is, independently, also a founder mutation in American-Hispanic breast cancers.

Keywords

breast cancer; PALB2; founder mutations; haplotype

Introduction

In 2006, *PALB2* (partner and localizer of BRCA2), also known as *FANCN*, was identified as a key player in homologous recombination [1]. It was first described as a breast cancer-predisposing gene with identification of pathogenic mutations in familial cases [2]. Subsequent studies found carriers of truncating mutations in familial cases of almost all populations investigated with confirmation that pathogenic mutations were associated with breast cancer risk [3]. So far, more than 300 different mutations of *PALB2* have been reported (http://databases.lovd.nl/shared/genes/PALB2). and it is ncluded on clinical multigene breast cancer panels. We had previously identified a recurrent mutation – the c.1027C>T (p.Gln343*) in Northern Italy; it was detected in 6 of 113 familial cases and 2 of 477 controls all from the Bergamo province [4]. A second *PALB2* mutation, c.2167_2168delAT (p.Met723Valfs*21), has been identified multiple times in individuals from geographically diverse areas by independent research groups. This mutation was found in an Italian and an Italian-American families, three Hispanic probands from Southern California, and a Nigerian proband ([4–6]; S. Neuhausen/J. Weitzel, personal communications; F. Olopade, personal communication). Because *PALB2* c.1027C>T and c.2167_2168delAT mutations have been encountered in a number of breast cancer cases from either the same or from different ancestries, we investigated haplotypes to assess whether these recurrent mutations originated from independent or single mutational events.

Participants and methods

Subjects

Women with breast cancer and female controls were enrolled into research studies to identify breast cancer susceptibility genes. For the specific individuals in this study, they either carried or were a family member of a carrier with either a *PALB2* c.1027C>T mutation (16 individuals from 4 independently ascertained families, 6 singleton carriers) or a *PALB2* c.2167_2168delAT mutation (16 individuals from 2 independently ascertained families and 4 singleton probands). The 44 individuals were ascertained at the following centers: The Unit of Medical Oncology of the Azienda Ospedaliera Papa Giovanni XXIII in Bergamo, Italy; the Medical Genetic Units of the Fondazione IRCCS Istututo Nazionale dei Tumori in Milan, Italy; the Associazione Volontari Italiani Sangue (AVIS), Bergamo, Italy; the Departments of Medical Genetics and Genome Sciences, University of Washington, Seattle, WA, US, the Clinical Cancer Genomics Community Research network at City of Hope, and the University of Chicago (Table 1). All individuals participating in this study signed an informed consent to the use of their biological samples for research projects. The study was approved by the Ethics Committee of each participating centers.

PALB2 mutations were previously identified through Sanger sequencing or targeted next generation sequencing ([4, 7]; Weitzel/Neuhausen personal communication). When available, relatives of *PALB2* mutation carriers were genotyped for their family-specific mutations by Sanger sequencing using primers previously described [4, 8].

Short tandem repeat (STR) marker genotyping

In total, 22 individuals were studied for haplotypes associated with *PALB2* c.1027C>T mutation, and 20 individuals for the *PALB2* c.2167_2168delAT mutation. Seven STR markers were selected which span a region of approximately 3 Mb on chromosome 16p flanking and intersecting *PALB2* (at chr16:23,614,483–23,652,678; hg19) (Figure 1 and Table S1). Four of the seven STR markers were custom developed for genotyping of *PALB2* mutation carriers [8] and three were STR markers previously deposited in the Marshfield comprehensive human genetic map [9, 10]. These markers were assayed by fluorescent PCR and capillary electrophoresis on an ABI PRISM 3130 or 3730xL Sequencer using standard methods. Primers and PCR conditions used to genotype the STR markers are reported in Supplementary Table 1. Genotyping was carried out at IFOM, The FIRC Institute of Molecular Oncology (Milan, Italy), Beckman Research Institute of City of Hope (Duarte, CA, USA) and University of Washington (Seattle, WA, USA). Allele sizes were called using the software Gene Mapper (Applied Biosystems/Life Technologies, Foster City, CA, USA). For consistent calling of allele sizes across centers, common controls were used by all centers.

Haplotype analysis

In families, haplotypes were reconstructed manually according to the known mutation status and the genotypes observed at each marker in the family members. In the families where it was not possible to reconstruct haplotypes with certainty, or in single individuals, haplotypes

were reconstructed according to the hypothesis of the maximum conservation of a common mutation haplotype.

Results

PALB2 c.1027C>T haplotype analysis

DNA samples extracted from blood from 16 individuals from 4 families, and 6 single individuals, all of Italian/Bergamo ancestry were genotyped (Table 1; Figure 2A). Enlarged pedigrees with family cancer history were previously published for these individuals except for BG149 and BG363 [4]. Four haplotypes across the seven STR markers were reconstructed. A core haplotype is shared by all 19 mutation carriers (Table 2, Figure 2A). This core haplotype, with a size of ~0.15Mb, is defined by recombination events 3′ of *PALB2* between markers D16S412 and 23622TCTA14 and 5′ of *PALB2* between markers D16S417 and D16S401 (Figure 1A, Table 2). This shared haplotype indicates that the *PALB2* c.1027C>T mutation occurred as a unique event in a single ancestor related to all 10 families in this study with this mutation.

PALB2 c.2167_2168delAT haplotype analysis

Germline DNA samples from 16 members of 2 families of Italian and American/Italian ancestry, 3 female breast cancer cases of Hispanic ancestry and one female breast cancer case of Nigerian ancestry were genotyped (Table 1, Figure 2B). Haplotype construction suggests that there were three unique events (Table 2). All 12 mutation carriers in the Italian and American/Italian families share a conserved haplotype, of approximate size of 1 Mb, defined by a recombination event 3′ of *PALB2* between markers D16S412 and 23622TCTA14 (Figure 1A, Table 2). The three Hispanic individuals share a conserved haplotype of 2 Mb defined by a recombination event 5′ of *PALB2* between markers D16S417 and D16S401 (Figure 1A, Table 2). The Nigerian breast cancer case carries alleles which are not part of any of the previously described haplotypes. These unique events, at least in the Italian and Hispanic ancestry cases, resulted in independent founder mutations in these two populations.

Discussion

Overall, *PALB2* loss of function mutations have been found in 0.6 to 3.9% of high-risk breast cancer families, with an average cumulative risk of breast cancer of 35% by age 70 years [5]. In this manuscript, we describe the haplotype analysis of two recurrent *PALB2* mutations. Five other truncating mutations have been identified to be recurrent in specific populations. The *PALB2* c.509_510delGA (p.Arg170Ilefs*14) was found in Poland in 4/648 (0.6%) familial breast cancer cases and in 1/1310 controls (0.08%) [11], with no evidence of shared alleles. This mutation was later detected in approximately 0.25% of unselected breast cancer cases from Central and Eastern Europe [12]. With such a narrow distribution of the mutation, yet an apparent lack of a shared haplotype, it is not clear whether this is a single founder mutation or whether there were multiple mutation events at this site. The *PALB2* c.2323C>T (p.Gln775*) was found in approximately 0.5% of tested French-Canadian early onset breast cancer cases and in 0 of 6,000 controls. Genotyping of four STR markers

showed that mutation carriers shared common alleles suggesting that the *PALB2* c.2323C>T is a founder mutation [13]. In Finland, a recurrent founder mutation *PALB2* c.1592delT (p.Leu531Cysfs*30) was identified [14]. They were able to estimate that this mutation was associated with a 40% cumulative risk for developing breast cancer by age 70 years. In Australia, a founder *PALB2* c.3113G>A (p.Trp1038* or complete or partial deletion of exon 10) was identified, and they estimated a 91% cumulative risk of developing breast cancer by age 70 years [15]. Analyses of founder mutations allow for determination of mutation-specific risks, which still vary by population and the extent of family history.

The common haplotype shared by all four Italian families and six Italian single individuals with the *PALB2* c.1027C>T mutation suggests that this mutation occurred as a single event in an ancestor common to all the families and single individuals studied. This mutation, to our knowledge, has been found only in individuals from Bergamo and represents one of the few examples of population-specific mutation in Italians. Its limited range to this specific area in Northern Italy may reflect limited migration of the local population, possibly due to territory geographical conformation characterized by several secluded valleys that may have caused genetic isolation [4]. Consistent with this hypothesis, the *BRCA1* c.190T>C (p.Cys64Arg) founder mutation is only found in breast cancer families from Bergamo, and was estimated to be more than 3,000 years old [16]. There are too few families and family members with the *PALB2* c.1027C>T to estimate the age of the mutation. However, the shorter length of the *PALB2* c.1027C>T haplotype with respect to the *BRCA1* c.190C>T haplotype may indicate that the c.1027C>T is an older mutation.

PALB2 c.2167_2168delAT has been observed in an African, Italians, North Americans, and Hispanics. Based on haplotype and allele sharing, these mutations appear to represent different mutational events in each of the three populations. No haplotype sharing was observed among the Nigerian, Hispanic, and Italian carriers. However, a conserved haplotype was found between the North American family who is of Italian ancestry and the Italian family ascertained in Milan, representing evidence of a common ancestor. We investigated whether the Italian-American family (CF1908) and the Milan family (MI03) originated from the same geographic region in Italy. Surnames are often informative with respect to Italian region of origin [17]. The two ancestors in the Italian-American family, who migrated to America at the beginning of the 1900 century, were from Sasso Ferrato (AN) and Genga (AN), two small towns from the province of Ancona in the Italian Appennini Mountains, located at a distance of about 10 kilometers from each other. In the Italian family from Milan, the paternal aunt of the proband was originally from Mondavio, a small town in the province of Pesaro-Urbino, 45 kilometers from the above mentioned locations (Figure 3). A genealogy search also found that, based on actual frequency and distribution, the family names originated from the region Marche in Central Italy, confirming the geographic origin of their families. The three Hispanic breast cancer cases share the same associated-mutation alleles indicating a putative Amerindian mutational event (data not shown). This *PALB2* mutation was identified in 3 of 188 unrelated Hispanic breast cancer cases (1.6%), and we have since identified additional Hispanic breast cancer cases with this mutation (personal communication). Interestingly, the *PALB2* c.2167_2168delAT appears to have arisen through multiple independent mutation events, yet within populations, it appears likely to be a founder mutation.

In conclusion, we've identified two founder mutations of Italian ancestry, of which one is an independent founder in those of Amerindian ancestry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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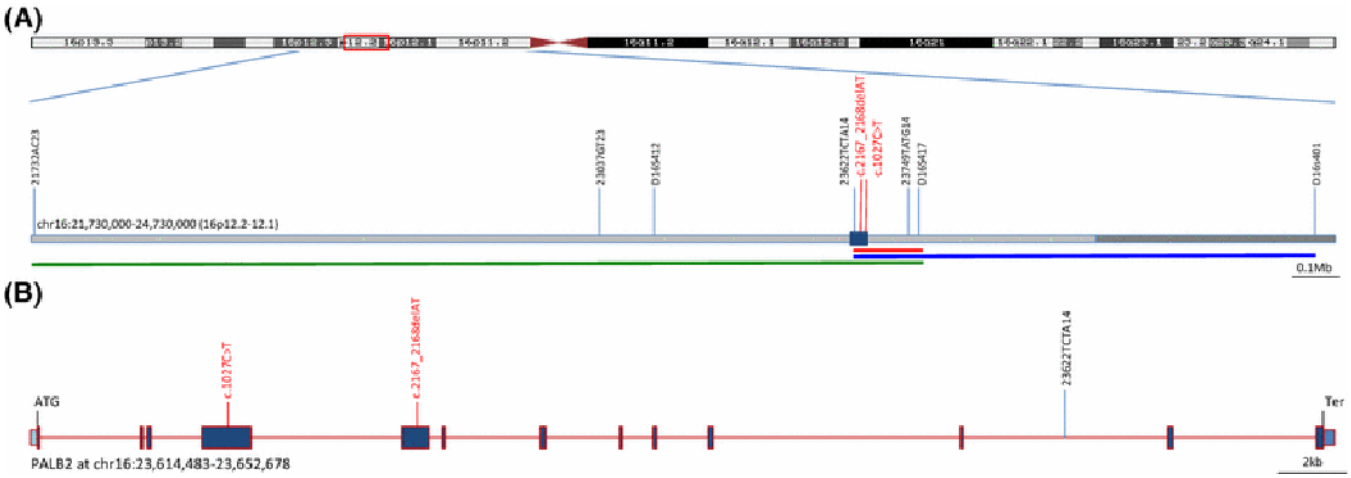

Figure 1.

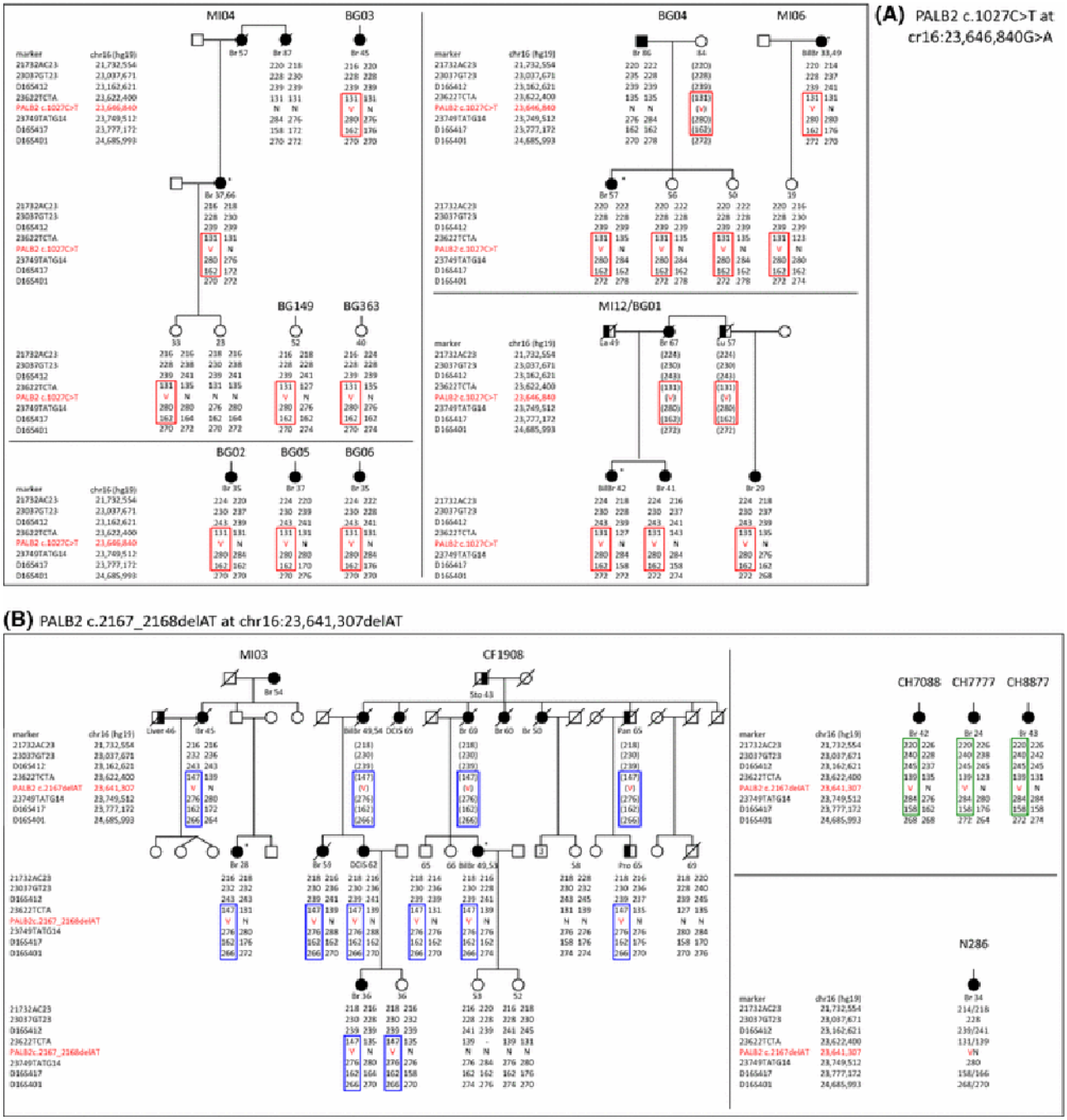

Figure 2.

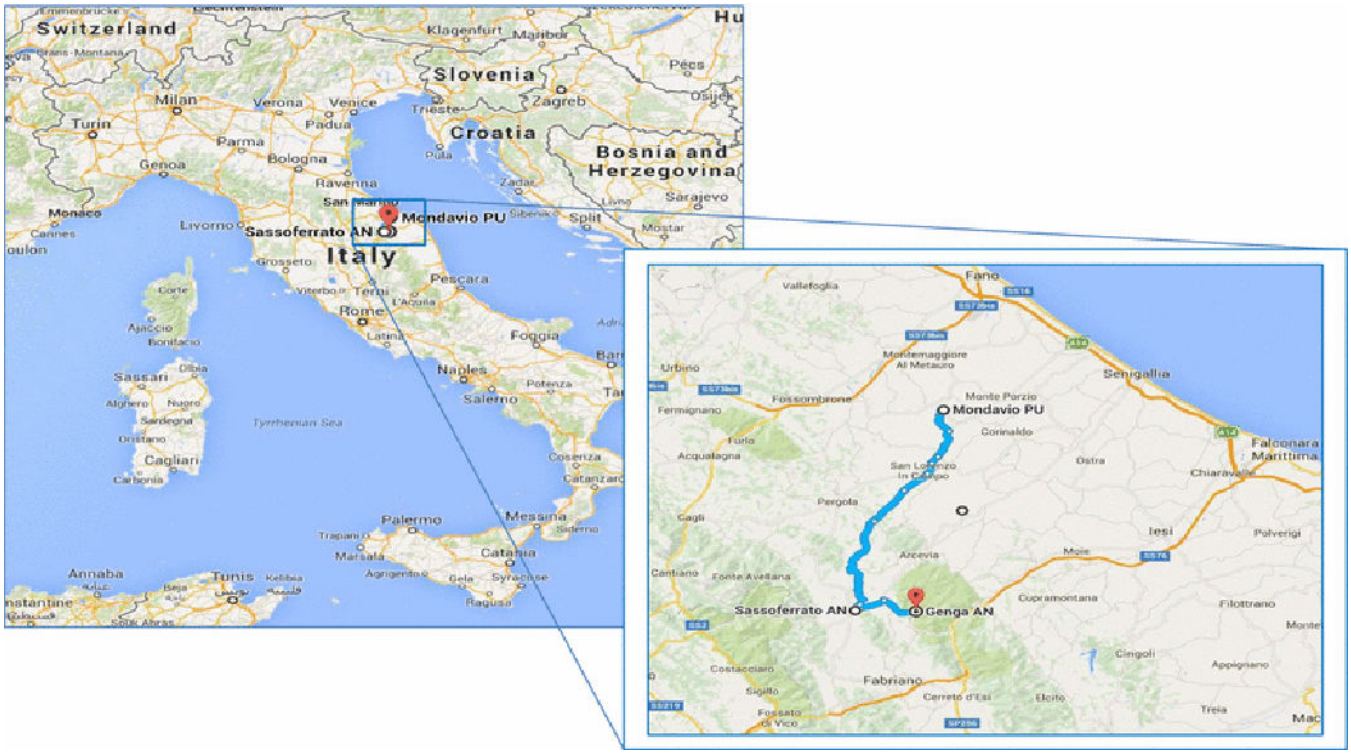

Figure 3.

Table 1

PALB2 mutation carrier phenotypes, ancestry, and demographics.

			Phenotypes in carriers[a]				
Mutation	**Family**	**# carriers**	**# female breast (age)**	**# other cancers (age)**	**# unaffected**	**Ancestry**	**Ascertainment center**
c.1027C>T	BG149	1			1	Italian, Bergamo	AVIS, Bergamo
c.1027C>T	BG363	1			1	Italian, Bergamo	AVIS, Bergamo
c.1027C>T	BG02	1	1 (35)			Italian, Bergamo	Ospedale Papa Giovanni XXIII, Bergamo
c.1027C>T	BG03	1	1 (45)			Italian, Bergamo	Ospedale Papa Giovanni XXIII, Bergamo
c.1027C>T	BG04	4[a]	1 (57)		3	Italian, Bergamo	Ospedale Papa Giovanni XXIII, Bergamo
c.1027C>T	BG05	1	1 (37)			Italian, Bergamo	Ospedale Papa Giovanni XXIII, Bergamo
c.1027C>T	BG06	1	1 (35)			Italian, Bergamo	Ospedale Papa Giovanni XXIII, Bergamo
c.1027C>T	MI04	2	1 (37)		1	Italian, Bergamo	Istututo Nazionale dei Tumori, Milan
c.1027C>T	MI06	2	1 (33)		1	Italian, Bergamo	Istututo Nazionale dei Tumori, Milan
c.1027C>T	MI12/BG01	5[a]	4 (29, 41, 42,67)	Lung (57)	1	Italian, Bergamo	Istututo Nazionale dei Tumori, Milan
c.2167delAT	MI03	2	2 (28, 45)		1	Italian, Marche	Istututo Nazionale dei Tumori, Milan
c.2167delAT	CF1908	10[a]	6 (36, 49, 49, 59, 62, 69)	Pancreatic (65) Prostate (65)	2	Italian-American	University of Washington, Seattle
c.2167delAT	CH7088	1	1 (42)			Hispanic	City of Hope, Los Angeles, CA
c.2167delAT	CH7777	1	1 (24)			Hispanic	City of Hope, Los Angeles, CA
c.2167delAT	CH8877	1	1 (43)			Hispanic	City of Hope, Los Angeles, CA
c.2167delAT	N286	1	1 (34)			Nigerian	Nigeria/University of Chicago, Chicago

[a]Includes obligate mutation carriers.

Table 2

Genotypes and haplotypes identified in carriers of *PALB2* c.1027C>T and PALB2 c.2167_2168delAT

				Markers and genotypes and haplotypes[a]						
Mutation	**Ancestry**	**Family**	**# carriers**	**21732AC23**	**23037GT23**	**D16S412**	**23622TCTA14**	**23749TATG14**	**D16S417**	**D16S401**
c.1027C>T	Italian	BG03	1	216/220	228	239	131	280	162	270
c.1027C>T	Italian	BG149	1	216/218	228	239/241	131	280	162	270/274
c.1027C>T	Italian	BG363	1	216/224	228	239	131	280	162	270/274
c.1027C>T	Italian	MI04	2	216	228	239	131	280	162	270
c.1027C>T	Italian	BG04	4	220	228	239	131	280	162	272
c.1027C>T	Italian	MI06	2	220	228	239	131	280	162	272
c.1027C>T	Italian	BG02	1	224/220	230/238	243/241	131	280	162	270/276
c.1027C>T	Italian	BG05	1	224/220	230/236	243/239	131	280	162	270
c.1027C>T	Italian	BG06	1	224/220	230/228	243/241	131	280	162	270
c.1027C>T	Italian	MI12/BG01	5	224	230	243	131	280	162	272
c.2167delAT	Italian	MI03	2	216	232	243	147	276	162	266
c.2167delAT	Italian	CF1908	10	218	230	239	147	276	162	266
c.2167delAT	Hispanic	CH7088	1	220/226	240/228	245/237	139/135	284/276	158/162	268
c.2167delAT	Hispanic	CH7777	1	220/226	240/238	245	139/123	284/280	158/176	272/264
c.2167delAT	Hispanic	CH8877	1	220/226	240/242	245	139/131	284	158	272/274
c.2167delAT	Nigerian	N286	1	214/218	228	239/241	139	280	158/166	268/270

[a]Core haplotypes shared among unrelated families are underlined