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An original phylogenetic approach identified mitochondrial haplogroup T1a1 as inversely associated with breast cancer risk in *BRCA2* mutation carriers

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Abstract

Introduction

Individuals carrying pathogenic mutations in *BRCA1/2* genes have a high lifetime risk of breast cancer. BRCA1 and BRCA2 are involved in DNA double strand break repair, DNA alterations that can be caused by exposure to reactive oxygen species, a main source of which are mitochondria. Mitochondrial genome variations affect electron transport chain efficiency and reactive oxygen species production. Individuals from different mitochondrial haplogroups differ in their metabolism and sensitivity to oxidative stress. Variability in mitochondrial genetic background can alter reactive oxygen species production, leading to cancer risk. Here we test the hypothesis that mitochondrial haplogroups modify breast cancer risk in *BRCA1/2* mutation carriers.

Methods

We genotyped 22214 (11421 affected, 10793 unaffected) mutation carriers belonging to the Consortium of Investigators of Modifiers of *BRCA1/2* for 129 mitochondrial polymorphisms using the iCOGS array. Haplogroup inference and association detection were performed using a phylogenetic approach. ALTree was applied to explore the reference mitochondrial evolutionary tree and detect subclades enriched for affected or unaffected individuals.

Results

We discovered that subclade T1a1 was depleted in affected *BRCA2* mutation carriers than the rest of clade T, (Hazard Ratio (HR) = 0.55 (95% Confidence Interval (CI) 0.34-0.88, p-value = 0.01). Compared with the most frequent haplogroup in the general population *i.e.* H and T clade, the T1a1 haplogroup has an HR = 0.62 (95% CI = 0.40-0.95, p-value = 0.03). We also identified three potential susceptibility loci, including G13708A/rs28359178, which has demonstrated an inverse association with familial breast cancer risk.

Conclusions

This study illustrates how original approaches like the phylogeny-based method we used can empower classical molecular epidemiological studies aimed at identifying association or risk modification effects.

Introduction

Breast cancer is a multifactorial disease, with genetic, life-style and environmental susceptibility factors. Approximately 15-20% of the familial aggregation of breast cancer is accounted for by mutations in high-penetrance susceptibility genes [1-3] such as *BRCA1*, *BRCA2*. Pathogenic mutations in *BRCA1* and *BRCA2* confer lifetime breast cancer risk of 60%-85% [4,5] and 40%-85% [4,5], respectively. Other genomic variations (for example in genes encoding proteins interacting with BRCA1 and BRCA2) have been identified as modifiers of breast cancer risk and increase or decrease the risk initially conferred by *BRCA1* or *BRCA2* mutation [6].

BRCA1 and *BRCA2* are involved in DNA repair mechanisms, including double-strand break (DSB) repair by homologous recombination [7,8]. DSB are considered to be one of the most deleterious forms of DNA damage because the integrity of both DNA strands is compromised simultaneously. These breaks can lead to genomic instability resulting in translocations, deletions, duplications, or mutations when not correctly repaired [9]. Reactive Oxygen Species (ROS) are one of the main causes of DSBs, along with exposure to ionizing radiation, various chemical agents, and ultraviolet light [10].

ROS are naturally occurring chemical derivative of metabolism. Elevated levels of ROS and down-regulation of ROS scavengers and/or antioxidant enzymes can lead to oxidative stress, which is associated with a number of human diseases, including various cancers [11]. The electron transport chain process, which takes place in the mitochondria, generates the majority of ROS in human cells. Variations in the mitochondrial genome have been shown to be associated with metabolic phenotypes and oxidative stress markers [12]. Mitochondrial dysfunction recently was shown to promote breast cancer cell migration and invasion through the accumulation of a transcription factor HIF1α via increased production of reactive oxygen species [13].

The human mitochondrial genome (mtDNA) has undergone a large number of mutations that have segregated during evolution. Those changes are now used to define mitochondrial haplogroups. Some of these changes slightly modify metabolic performance and energy production; thus, all haplogroups do not have identical metabolic capacities [14]. It has been hypothesized that the geographic distribution of mitochondrial haplogroups results from selection of metabolic capacities mainly driven by adaptation to climate and nutrition [15,16].

Mitochondrial haplogroups have been associated with diverse multifactorial diseases, such as Alzheimer's disease [17], hypertrophic cardiomyopathy [18], retinal diseases [19] or age-related macular degeneration [20]. Variations in mtDNA have also been linked to several types of cancer, such as gastric cancer [21] or renal cell carcinoma [22]. Interestingly, variations in mtDNA have been linked to several types of female cancers: endometrial [23], ovarian [24], and breast cancer [25,26]. A recent study underlined the possibility that mitochondrial genome might be involved into the pathogenic and molecular mechanism of familial breast cancer [27].

The Collaborative Oncological Gene-environment Study [28] (COGS) is a European project designed to improve understanding of genetic susceptibility to breast, ovarian and prostate cancer. This project involves several consortia, the Breast Cancer Association Consortium (BCAC) [29], the Ovarian Cancer Association Consortium (OCAC) [30], the Prostate Cancer

Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) [31], and the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) [32]. CIMBA is a collaborative group of researchers working on genetic modifiers of cancer risk in *BRCA1* and *BRCA2* mutation carriers. As part of the COGS project, more than 200,000 single nucleotide polymorphisms (SNPs) were genotyped for *BRCA1* and *BRCA2* female mutation carriers on the iCOGS chip, including 129 mitochondrial polymorphisms. The iCOGS chip is a custom Illumina™ Infinium genotyping array, designed to test, in a cost-effective manner, genetic variants related to breast, ovarian and prostate cancers.

In this study, we explored mitochondrial haplogroups as potential modifiers of breast cancer risk in women carrying pathogenic *BRCA1* or *BRCA2* mutations. Our study includes females diagnosed with breast cancer and unaffected carriers belonging to the CIMBA. We used an original analytic phylogenetic-based approach implemented in a homemade algorithm and in the program ALTree to infer haplogroups and to detect associations between haplogroups and breast cancer risk.

Methods

Ethics statement

An informed written consent was obtained from all participants. All contributing studies involved in CIMBA received approvals from institutional review committees at their host institutions. Ethical committees that approved access to the data analyzed in this study are listed in Additional file 1.

BRCA1 and BRCA2 mutation carriers

Final analyses included 7,432 breast cancer cases and 7,104 unaffected *BRCA1* mutation carriers, and 3,989 invasive breast cancer and 3,689 unaffected *BRCA2* mutation carriers, all belonging to the CIMBA consortium. Supplementary specifications regarding inclusion profiles and studies belonging to CIMBA are available in Couch *et al.* [33] and Gaudet *et al.* [34]. All analyses were conducted separately on CIMBA *BRCA1* and *BRCA2* mutation carriers (abbreviated *pop1* and *pop2,* respectively). Eligible female carriers were aged 18 years or older and had a pathogenic mutation in *BRCA1* and/or *BRCA2*. Women mutated on both *BRCA1* and *BRCA2* were included in downstream analyses. Data were available on year of birth, age at study recruitment, age at cancer diagnosis, *BRCA1* and *BRCA2* mutation description, and self-reported ethnicity. Women with ovarian cancer history were not excluded from analyses, and represent 15% and 7% of *BRCA1* and *BRCA2* mutation carriers respectively. Information regarding mastectomy was incomplete, and was therefore not used as an inclusion/exclusion parameter.

Genotyping and quality filtering

Genotyping was conducted using the iCOGS custom Illumina Infinium array. Data from this array are available to the scientific community upon request, please see [35] for more information. Genotypes were called using Illumina's proprietary GenCall algorithm. Genotyping and quality filtering were described previously [33,34]. Initially, 129 mitochondrial SNPs were genotyped for both *BRCA1* and *BRCA2* mutation carriers. SNPs fulfilling the following criteria were excluded from downstream analyses: monoallelic SNPs

(minor allele frequency equals 0), SNPs with more than 5% data missing, annotated as triallelic, or having probes cross-matching with the nuclear genome. Heterozygous genotypes were removed from analyses, and we further filtered out SNPs having more than 5% of heterozygous calls, to limit potential for heteroplasmy affecting our results. We also did not retain SNPs representing private mutations. These mutations are rare, often restricted to a few families, and not sufficiently prevalent in the general population to be included in the reference mitochondrial evolutionary tree (see below). This last step of filtration yielded 93 and 92 SNPs for the *pop1* and *pop2* analyses, respectively (see Additional file 2). Only individuals with fully defined haplotypes, *i.e.* non-missing genotypes for the 93 and 92 SNPs selected for *pop1* and *pop2* respectively were included in downstream analyses (14,536 and 7,678 individuals respectively).

Mitochondrial genome evolution and haplogroup definition

Analyses were based on the theoretical reconstructed phylogenetic tree of the mitochondrial genome (mtTree) known as PhyloTree [36] (v.15). The mtTree is rooted by the Reconstructed Sapiens Reference Sequence (RSRS). RSRS has been identified as the most likely candidate to root the mtTree by refining human mitochondrial phylogeny by parsimony [37]. Each haplogroup in mtTree is defined by the set of mitochondrial genome SNPs that have segregated in RSRS until today in the mitochondrial genome. Each haplogroup is fully characterized by the 16569 bp sequence resulting from the application of all the substitutions that are encoded by the corresponding SNPs in RSRS sequence.

Haplogroups imputation

The phylogenetic approach used to infer haplogroups is described in Figure 1. Mitochondrial genome sequences can be reconstructed at each node of mtTree, given the substitutions that have segregated in RSRS. Each haplogroup therefore has a corresponding full-length mitochondrial sequence. However, the full-length mitochondrial sequence is not available in the data, since the iCOGs platform captured only 93 and 92 SNPs for pop1 and pop2 respectively. Thus, for each of the 7864 nodes of the phylogenetic tree, the corresponding short haplotype, i.e. the full-length sequence restricted to available loci was defined. Some of the short haplotypes are unique, and they can be matched with their corresponding haplogroup directly. However, most of the time, given the small number of SNPs analyzed, several haplogroups correspond to the same short haplotype. Consequently, a unique haplogroup cannot confidently be assigned to each short haplotype. Therefore, each short haplotype was assigned the most recent common ancestor of all the haplogroups that share the same short haplotype. Once this matching was done, short haplotypes were reconstructed in the same way for each individual in our dataset, and assigned the corresponding haplogroup. Accuracy of the method used was assessed by being applied on a set of 630 mitochondrial genome sequences of known European and Caucasian haplogroups (See Additional file 3)

Figure 1 Simplified representation of the phylogenic method used to infer haplogroups. **a.** Full-length haplotypic sequences are reconstructed at each node of the reference tree. **b.** Haplotypes are then restricted to available loci. Sequences of the same color are identical. **c.** Unique short haplotypes are matched directly with the corresponding haplogroup. **d.** Sequences matching with several haplogroups are associated to their Most Recent common Ancestor haplogroup.

Association detection

This phylogenetic approach is based on the identification of subclades in the reference phylogenetic tree of the mitochondrial genome differentially enriched for cases and unaffected controls compared with neighboring subclades. We used ALTree [38,39] to perform association testing. ALTree - Association detection and Localization of susceptibility sites using haplotype phylogenetic Trees – is an algorithm performing nested homogeneity tests comparing distributions of affected and unaffected individuals in the different clades of a given phylogenetic tree. The objective is to detect if some clades of a phylogenetic tree are more or less enriched in affected/unaffected individuals compared to the rest of tree. There are as many tests performed as levels in the phylogenetic tree. The p-value at each level of the tree is obtained by a permutation procedure in which 1000 permutations are performed: individual labels ('affected' or 'unaffected') are permutated 1000 times to see to what extent the observed distribution of affected/unaffected is different from a random distribution. A procedure to correct for multiple testing adapted to nested tests [40] is implemented in ALTree. The objective of ALTree is to detect an enrichment difference at the level of the whole tree. In order to keep computational time and resources only the most significant p-value obtained for all tests performed on one tree is corrected.

Handling genetic dependency

ALTree performs homogeneity tests to detect differences in enrichment or depletion of affected or unaffected individuals between clades in the phylogenetic tree. This kind of test can only be performed on independent data. However because in the CIMBA dataset, some individuals belong to the same family, we constructed datasets with genetically independent data by randomly selecting one individual among all those belonging to the same family and sharing the same short haplotype. To take into account the full variability of our data, we resampled one thousand times. Results of the analyses pipeline are obtained for each resampling independently, and then averaged over the one thousand re-samplings to obtain final results.

Character reconstruction at ancestral nodes

Before the ALTree localization algorithm was launched, ancestral sequences were reconstructed at each internal tree node*, i.e.* short haplotypes were inferred with maximum likelihood at all nodes that were not leaves. We used the software PAML [41] to perform the reconstruction at ancestral nodes using a maximum likelihood method. The phylogeny model used was the General Time-Reversible model (GTR or REV).

Localization of susceptibility sites

ALTree also includes an algorithm to identify which sites are the most likely ones to be involved in the association detected. For each short haplotype observed, the ALTree add-on *altree-add-S* will add to the short haplotype sequence a supplementary character called *S*, which represents the disease status associated to this short haplotype: are individuals carrying this short haplotype more often affected or unaffected? *S* is calculated based on the affected and unaffected counts, the relative proportion of affected and unaffected in the whole dataset, and sensibility parameter ε. ε was set to its default value, which is 1. After *S* character computation, haplotypes including character *S* are reconstructed at ancestral nodes.

Susceptibility site localization is achieved with ALTree by computing a correlated evolution index calculated between each change of each site and the changes of the character *S*, in the two possible directions of change. The site(s) whose evolution is the most correlated to the character *S* is the most likely susceptibility site.

Selected subclades

Analyses were carried out on the full evolutionary tree. However, the more haplogroups there are at each level, the less statistical power homogeneity tests have. Therefore analyses were also applied to subclades extracted from the tree. Subclades were defined using counts of individuals in each haplogroup of the clade in order to maximize statistical power. Chosen subclades and corresponding affected and unaffected counts are presented in .

Statistical analysis

We quantified the effect associated with enrichment discovered by applying ALTree by building a weighted Cox regression in which the outcome variable is the status (affected or non-affected) and the explicative variable is the inferred haplogroup. Analyses were stratified by country. Data were restricted to the clades of interest. The uncertainty in haplogroup inference was not taken into account in the model. The weighting method used takes into account breast cancer incidence rate as a function of age [42] and the gene containing the observed pathogenic mutation, *i.e. BRCA1* or *BRCA2*. Familial dependency was handled by using a robust sandwich estimate of variance (R package *survival*, *cluster()* function).

Results

Haplogroup imputation

In Additional file 4, absolute and relative frequencies are recapitulated for each haplogroup imputed in *BRCA1* and *BRCA2* mutation carriers. For *BRCA1* mutation carriers, we reconstructed 489 distinct short haplotypes of 93 loci from the genotypes data. Only 162 of those 489 short haplotypes matched theoretical haplotypes reconstructed in the reference mitochondrial evolutionary tree. These 162 haplotypes represented 13315 / 14536 individuals. Thus, 91.6% of *BRCA1* mutation carriers were successfully assigned a haplogroup. For *BRCA2* mutation carriers, we reconstructed 350 distinct short haplotypes of 92 loci from our genotypes data. Only 139 of those 350 short haplotypes matched theoretical haplotypes reconstructed in the reference mitochondrial evolutionary tree. These 139 haplotypes represented 6996 / 7678 individuals. Thus, 91.1% of *BRCA2* mutation carriers were successfully assigned a haplogroup. Since more *BRCA1* than *BRCA2* mutation carriers were genotyped (14,536 vs. 7,678 individuals), we logically observe more distinct haplotypes in *pop1* than in *pop2* (489 vs. 350 haplotypes).

Accuracy of the main haplogroup inference method used was estimate at 82%, and reached 100% for haplogroups I, J, K, T, U, W, X. Given the set of SNPs we dispose of, our method has difficulties to differentiate between H and V haplogroups (See Additional file 3).

Association results

For both populations of *BRCA1* or *BRCA2* mutation carriers, and for the full tree as for all selected subclades (See Table 1), we extracted the mean corrected p-value for association testing over all resamplings performed (See Table 2). The only corrected p-value that remained significant was that obtained for subclade T (abbreviated T*) in the population of individuals of *BRCA2* mutation carriers (p = 0.04).

Table 1 Counts of participants in selected subclades

Subclade	BRCA1 mutation carriers	BRCA2 mutation carriers
U8	1458	863
T	1243	651
J	1270	630
J1	1043	513
H	3706	1967
H1	582	337
U5	868	458
X1'2'3	221	103
K1a	608	364

Table 2 Mean corrected p-value for association testing with ALTree

Subclade	*pop1* corrected p-value	*pop2* corrected p-value
Full	0.830	0.681
U8	0.146	0.626
T	0.285	**0.040**
J	0.718	0.112
J1	0.621	0.150
H	0.747	0.930
H1	0.268	0.804
U5	0.829	0.747
X1'2'3	0.416	0.629
K1a	0.170	0.162

The phylogenetic tree of subclade T (see Figure 2a) contains only three levels, thus only three tests were performed within this clade. Raw p-values were examined to determine at which level of the tree ALTree detects a difference of enrichment in affected/unaffectd individuals (see Table 3). Only the p-value associated with the test performed at the first level of the tree is significant. We looked more closely at the mean frequencies of affected and unaffected individuals in the tree at this level (see Figure 2b). In the T1a1 subclade, the mean count of affected and unaffected are 32 and 47, respectively. In the T2* subclade, we observed on average 217 and 148 affected and unaffected individuals, respectively, whereas in the T subclade, we observed on average 13 and 11 affected and unaffected individuals. Ranges observed for each of these values over the 1000 resamplings are represented in Figure 2b. Based on these observations, we conclude that subclade T1a1 depleted in affected carriers compared to the neighboring subclades T and T2.

Figure 2 Phylogenetic tree of subclade T tested for association with ALTree. **a.** Phylogenetic tree of subclade T with all observed haplogroups. A homogeneity test is performed at each level of the tree. **b.** First level of phylogenetic tree of subclade T. Averaged counts, ranges, and proportion of affected and unaffected observed in resamplings are indicated below each subclade, respectively. T2* represents the entire subclade T2.

Table 3 Non-corrected p-values by level of phylogenetic tree for subclade T in *BRCA2* mutation carriers

Level	Degrees of freedom	Mean of non-corrected p-value
1	2	0.02141039
2	6	0.14355900
3	8	0.22249700

Localization results

We performed a localization analysis with ALTree. The correlated evolution index for all non-monomorphic sites observed in short haplotype sequences of subclade T are displayed in Additional file 5. The higher the correlated evolution index, the more likely it is that corresponding sites will be involved in the observed association. Three short haplotype sites - numbered 44, 57, and 72 and corresponding to SNPs T988C, G11812A/rs4154217, and G13708A/rs28359178 - are clearly distinguishing themselves, with correlation index values of 0.390, 0.324 and 0.318 respectively, whereas all other sites correlation index values ranged from −0.270 to −0.101. Table 4 shows details for these three loci.

Table 4 Description of loci identified as potential susceptibility sites by ALTree

Site	SNP Name	Position	Direction of change	Correlated evolution index	Major Allele	Minor Allele	MAF in *pop2*
44	MitoT9900C	9899	T → C	0.390	T	C	0.016
57	rs41544217	11812	G → A	0.324	A	G	0.071
72	rs28359178	13708	G → A	0.318	G	A	0.111

Effect quantification

The ALTree method is able to detect an association, but cannot to quantify the associated effect. We estimated the risk of breast cancer for individuals with the T1a1 haplogroup compared with individuals having another T subclade haplogroup in the population of *BRCA2* mutation carriers with a more classical statistical method, a weighted Cox regression. We found a breast cancer HR = 0.55 (95% CI = 0.34-0.88, p-value = 0.014). We also tested Haplogroup T1a1 compared with other T* haplogroups and the H haplogroup (the main haplogroup in the general population), and found a breast cancer HR = 0.62 (95% CI = 0.40-0.95, p-value = 0.03).

Discussion

We employed an original phylogenetic analytic method coupled with more classical molecular epidemiologic analyses in order to detect mitochondrial haplogroups differentially enriched for affected *BRCA1/2* mutation carriers. We successfully inferred haplogroups for more than 90% of individuals in our dataset. After haplogroup imputation, the ALTree method identified T1a1 in the T clade as differentially enriched in affected *BRCA2* mutation carriers, whereas no enrichment difference was found for *BRCA1* mutation carriers. The T subclade is present in 4% of African populations compared to 11% in Caucasian and east-European populations [43]. In our data, the T subclade represented 9.34% of *BRCA1* mutation carriers, and 9.30% of *BRCA2* carriers. The ALTree method also identified three potential breast cancer susceptibility loci in mitochondrial genome. The main goal of using the phylogenetic method we used was to improve statistical power by regrouping subclades according to genetic considerations, in order to limit the number of tests performed, and to precisely quantify this number. ALTree identified 3 SNPs of interest. While the association

we observed could possibly be driven by a single SNP, no difference was observed between multivariate and univariate cox models including the 3 SNPs identified by ALTree (data not shown).

In this study, we investigated to what extent mitochondrial genome variability modified breast cancer risk in individuals carrying pathogenic mutations in *BRCA1/2*. A large proportion of breast cancer heritability still remains unexplained today [44]. Different methods exist to study genomic susceptibility to a disease, such as linkage analyses (which identified the *BRCA1* and *BRCA2* susceptibility genes) or Genome-Wide Association Studies (GWAS). However, classical linkage analysis cannot be applied to the haploid mitochondrial genome. Furthermore, commercial GWAS chips available do not adequately capture the majority of mitochondrial SNPs. A non-genome-wide and mitochondrial focused approach was required to explore how mitochondrial genome variability influences breast cancer risk. Here we have shown that *BRCA2* mutation carriers representing the subclade T1a1 have between 30 and 50% less risk of breast cancer than those representing other clades which, if validated, is a clinically meaningful risk reduction and may influence choice of risk management strategies.

The association we observed among *BRCA2* but not *BRCA1* mutation carriers may reveal a functional alteration that would be specific to mechanisms involving *BRCA2*-related BC. Today it is established that *BRCA1*- and *BRCA2*-associated breast cancers are not phenotypically identical. These two types of tumors do not harbor the same gene expression profiles or copy number alterations [45]. Breast cancer risk modifiers in *BRCA1/2* mutation carriers have already been identified [46]. However, most of them are specific from one or the other type of mutation carried [47]. It is therefore not surprising that this observation is observed in *BRCA2* mutation carriers only.

Three main reasons could explain our inability to assign haplogroups to 9% of study participants. First, given the high mutation rate in the mitochondrial genome, observed combinations of mitochondrial SNPs might have appeared relatively recently in the general population, and the corresponding haplotypes might not yet be incorporated in PhyloTree. Secondly, only one genotyping error could lead to chimeric haplotypes that do not exist although, given the quality of our genotyping data, this is unlikely. Finally, the mitochondrial reference evolutionary tree PhyloTree is based on phylogeny reconstruction by parsimony, and for some subclades it might be suboptimal, especially for haplogroups relying on few mitochondrial sequences, as is the case for African haplogroups [48]. In case of uncertainty, the choice we made to assign the most recent common ancestor to the studied haplotype enables us to improve statistical power without introducing a bias in the detected association. For the association detected between T, T1* and T2* subclades, the haplogroup inference method used do not bias the counts of affected and unaffected individuals in these subclades. More details are presented in Additional file 6. Furthermore, based on the haplogroup inference with our method of 630 European and Caucasian mitochondrial genome sequences whose haplogroup is known, we successfully assigned the correct main and subhaplogroup of 100% of sequences belonging to T, T2*, and T1a1* haplogroups.

We quantified the effect corresponding to the detected association by using a more classical approach. We built a weighted Cox regression including inferred haplogroup as explicative variable. However, the uncertainty in haplogroup inference was not taken into account in this model. Nevertheless, based on haplogroup assignment and regrouping performed in clade T, affected and unaffected counts of individuals in this clade were not biased.

With only 129 loci genotyped over the 16,569 nucleotides composing the mitochondrial genome, we certainly do not explore the full variability of mitochondrial haplotypes. A characterization of individual mitochondrial genomes would require more complete data acquisition methods to be used, *e.g.*, next-generation sequencing. However, next-generation sequencing presents its own limits and challenges, because some regions of the mitochondrial genome are not easily mappable due to a high homology with the nuclear genome among other factors, and important bioinformatics treatment is necessary to overcome sequencing technology biases. Finally, even for a relatively short genome of 'only' 16569 bp, mitochondrial genome sequencing of more than 20,000 individuals would represent a major increase in cost relative to genotyping 129 SNPs.

ALTree identified T9899C, G11812A/rs41544217, and G13708A/rs28359178 as three potential susceptibility sites for the discovered association (See Additional file 7). These 3 polymorphisms are respectively located in the coding part of genes *MT-CO3*, *MT-ND4*, and *MT-ND5*. When looking at PhyloTree, T9899C seems to be involved in T1 subclade definition, whereas G13708A and A11812G are involved in T2 subclade definition. Whereas T98899C and G11821/rs41544217 are synonymous polymophisms, G10398A leads to a change of amino acid in the final protein (from Alanine to Threonine). These 2 synonymous polymophisms have never been described in a disease context in the literature. G13708A is also known for being a secondary mutation for Leber's hereditary optic neuropathy (LHON) and multiple sclerosis [49]. Although the role of secondary mutations in LHON is still controversial, G13708A could be associated with impairment of the respiratory chain in this pathology. G13708A has also been described as a somatic mutation in a breast cancer tumor, whereas it was not present in adjacent normal tissue and in blood leucocytes [50]. A high proportion of mitochondrial somatic tumor specific variants are also known mitochondrial polymorphisms, which is consistent with the hypothesis that tumor cells are prone to acquire the same mutations that segregate into mitochondrial genome by selective adaptation when humans migrated out of Africa and were confronted to new environments [51]. Interestingly, the germline variant G13708A has already been shown to be inversely associated with familial breast cancer risk (with the same direction of the association), with a breast cancer odds-ratio (OR) = 0.47 (95% CI = 0.24–0.92) [52]. None of these SNPs have been described in the context of ovarian cancer.

The corrected p-value ALTree obtained in studying clade T is 0.02, which not highly significant. A replication step should be performed to validate these results. However, it will be difficult to include enough women in this replication step, given the specific profile studied here. In fact, the estimations of BRCA2 pathogenic mutations in the general population range from 0.068% [5] to 0.69% [53]. T1a1 represents sonly a small percentage of European haplogroups (from 1% to 2%). The number of women concerned by this association is therefore low. However, women carrying such mutations are confronted with drastic choices regarding the prevention of breast cancer, notably prophylactic mastectomy or complete hysterectomy. If breast cancer risk is really reduced by 2 for T1a1 women, this could be an important fact to take into account for breast cancer prevention.

Conclusions

This and our results suggest that mitochondrial haplogroups T1a1 may modify the individual breast cancer risk in *BRCA2* mutation carriers. For now, this observation cannot be extended to the general population. Further investigation of the biological mechanism behind the associations we observed may further reinforce the hypothesis that the mitochondrial genome

is influential in breast cancer. risk, particularly among carriers of *BRCA2* mutations and, if validated, is of a level to influence cancer risk management choices.

Abbreviations

aHR, alternative homologous recombination; CI, confidence interval; CIMBA, consortium of investigators of BRCA1/2 mutation carriers; COGS, collaborative oncological gene-environment study; GWAS, genome-wide association study; HR, hazard ratio; mtDNA, mitochondrial genome; OCAC, ovarian cancer association consortium; PRACTICAL, prostate cancer association group to investigate cancer associated alterations; ROS, reactive oxygen species; RSRS, reconstructed sapiens reference sequence; SNP, single nucleotide polymorphism; SSA, single-strand annealing; SSB, single-strand break

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception and design: DGC GT. Development of methodology: SB CBa VD. Acquisition of data: LM, SHe, DB, ALe, JD, KBK, PS, MBT, WKC, DEG, SSB, RJ, LT, NT, CMD, EJvR, SLN, YCD, AMG, BE, FCN, TvOH, AO, JBe, RA, ES, JNW, MThe, PP, PR, VP, RDo, BB, BP, DZ, GSc, SMan, LV, GLC, LP, LO, DY, IK, JGa, UH, AD, ABr, CBr, CF, DGE, DF, DE, FDo, JCo, JA, JBa, LW, LI, LES, MJK, MTi, MTR, MEP, PJM, RP, RE, RDa, SHo, TCo, AKG, CI, KC, KDL, AM, AG, BW, CS, CE, DN, DS, HP, KK, KR, ND, NA, RV, RKS, SP, NB, SW, AdP, CLe, CLas, DL, ER, FDa, GSC, HD, LB, LG, NU, VB, VS, YB, JCa, LVL, MP, PAD, MdlH, TCa, HN, KA, AJag, AMvdO, CMK, CMA, FEvL, FBH, HEM, JCO, KvR, MAR, PD, RBvdL, EO, OD, AT, CLaz, IB, JDV, AJak, GSu, JGr, JLu, KD, KJ, BAA, CM, AA, MM, MRT, ABS, WF, CO, NLi, VSP, CIS, ALinc, LJ, MC, MR, JV, ABe, AF, CFS, CR, DGK, GP, MTe, MHG, PLM, GR, EI, AMM, GG, ILA, ST, AET, ISP, MTho, TAK, UBJ, MAC, EF, JZ, YL, ALind, BM, BA, NLo, RR, OIO, RLN, SR, KLN, SMD, TRR, BKA, GM, BYK, JLe, SO, DSL, GT, JS, FJC, KO, DFE, GC, ACA, SMaz, CMP, OMS. Analysis and interpretation of data: SB DGC ACA. Writing the manuscript: SB DGC ACA SH ABS GC SLN AET ILA JCO KO MTho GM. All authors have read and approved the final version of this manuscript.

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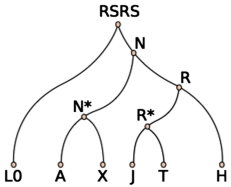
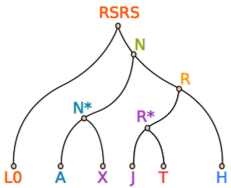
a - Complete Haplotypes : 16569 nt long sequences



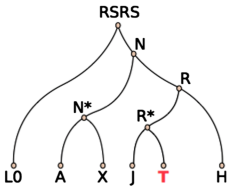

```
RSRS  ACTGGGTAACGATCGTGATC.....AATTGGCTTCGACATCCGGTAACTGGGA
L0    ACTGAGTAACGATCGTGATC.....AATTGGCTTCGACATCCGGTAACTGGGA
N     AGTTGGTAACGATCGTGATC.....AATTGGCTTCGACATCCGGTAACTGGGA
N*    AGTTGGTAACGATCGTGCTC.....AATTGGCTTCGACATCCGGTAACTGGGA
A     AGTTGGTAACGATCGTGCTC.....AATTGGCTTCGACATCCGGTAACTGGGA
X     AGTTGGTAACGATCGTGCAC.....AATTGGCTTCGACATCCGGTAACTGGGA
R     AGTTGGTAACGATCGTGATT.....AATTGGCTTCGACATCCGGTAACTGGGA
R*    AGTTGGTAACGATCGTGATT.....AATGGGCTTCGACATCCGGTAACTGGGA
J     AGTTGGTAACGATCGTGATT.....AATGGGCTTCGACATCCGGTAACTGGGA
T     AGTTGGTAACGATCGTGATT.....TATGGGCTTCGACATCCGGTAACTGGGA
H     AGTTGGTAACGATCGTGATT.....AATTGACTTCGACAGCCGGTAACTGGGA
```

b - Short Haplotypes : 92 nt long sequences




```
RSRS  ACAACGACGTAC.....AATTGGCTTCG
L0    ACAACGACGTAC.....AATTGGCTTCG
N     AGAACGACGTAC.....AATTGGCTTCG
N*    AGAACGACGTCC.....AATTGGCTTCG
A     AGAACGACGTCC.....AATTGGCTTCG
X     AGAACGACGTAT.....AATGGGCTTCG
R*    AGAACGACGTAT.....AATGGGCTTCG
J     AGAACGACGTAT.....AATGGGCTTCG
R     AGAACGACGTAT.....AATTGGCTTCG
T     AGAACGTCGTAT.....TATGGGCTTCG
H     AGAACGATGTAT.....AATTGACTTCG
```

c - When a short haplotype corresponds to only one haplogroup

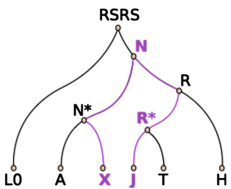


AGAACGTCGTAT.....TATGGGCTTCG

↓

Haplogroup T

d - When a short haplotype corresponds to several haplogroups



AGAACGACGTAT.....AATGGGCTTCG

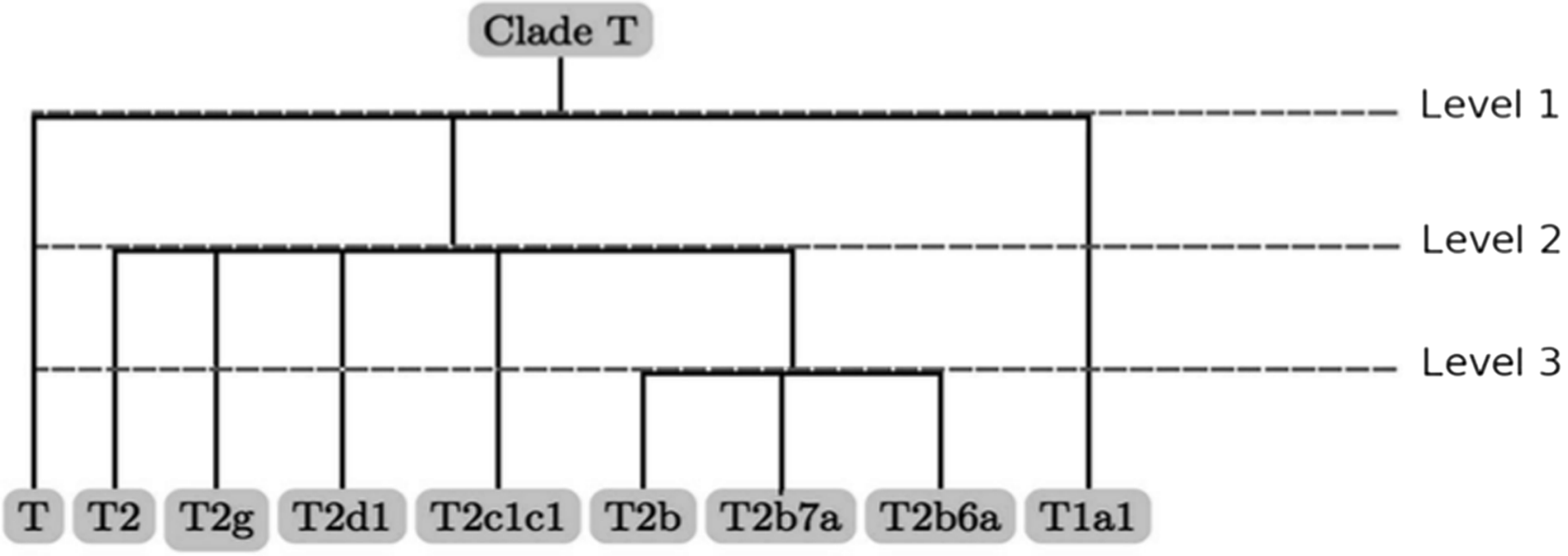
↓

Most Recent common Ancestor of { J, R*, X }

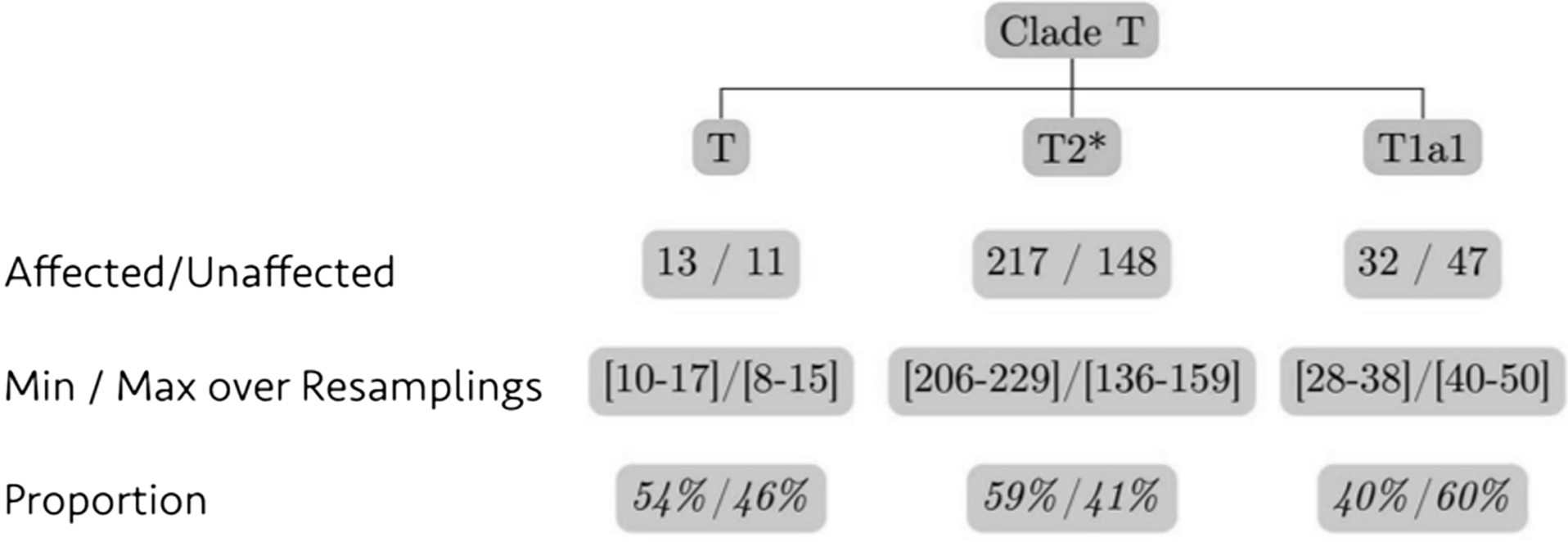
↓

Haplogroup N

a


Clade T
Level 1
Level 2
Level 3
T
T2
T2g
T2d1
T2c1c1
T2b
T2b7a
T2b6a
T1a1

b


Clade T
T
T2*
T1a1
Affected/Unaffected
13 / 11
217 / 148
32 / 47
Min / Max over Resamplings
[10-17]/[8-15]
[206-229]/[136-159]
[28-38]/[40-50]
Proportion
54%/46%
59%/41%
40%/60%

Additional files provided with this submission:

Additional file 1. List of ethical committees that approved the access to the data analyzed in this study. List of ethical committees that approved the access to the data analyzed in this study (157kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s1.docx

Additional file 2. SNPs selected for downstream analyses. Table containing SNPs selected for downstream analyses (54kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s2.xlsx

Additional file 3. Description and results of the procedure used to estimate the accuracy of our haplogroup inference methodology. Description and results of the procedure used to estimate the accuracy of our haplogroup inference methodology (148kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s3.docx

Additional file 4. Absolute and relative frequencies of imputed haplogroups by population. Table containing absolute and relative frequencies of imputed haplogroups for BRCA1 and BRCA2 mutation carriers (38kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s4.xlsx

Additional file 5. Correlated evolution index for all non-monomorphic sites observed in short haplotype sequences of subclade T. Table containing correlated evolution index for all non-monomorphic sites observed in short haplotypes sequences of subclade T (10kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s5.xlsx

Additional file 6. Details of haplogroups inference results for subclade T. Details of haplogroups inference results for subclade T (95kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s6.docx

Additional file 7. Coevolution Index computation. Methods used to compute coevolution index (98kb)
http://breast-cancer-research.com/content/supplementary/s13058-015-0567-2-s7.docx