Introduction

Despite recent advances in the treatment modality, management of breast cancer is still challenging and it remains to be one of the leading causes of death due to cancer all over the world. Genetics not only plays a significant role in the elucidation of breast cancer causation and progression, but also majorly contributes to the disparities in pharmacotherapy. Germline or somatic genetic variants in genes encoding proteins involved in the absorption, distribution, metabolism and excretion (ADME) of anti-cancer agents are the major factors responsible for the variability in the treatment outcomes. These genetic abnormalities are now being applied to predict clinical response and drug related toxicity in cancer therapeutics.

Aromatase inhibitors (AIs)-anastrozole, letrozole and exemestane are the preferred anti-estrogen agents for treating postmenopausal women with breast cancer. These drugs cease the synthesis of endogenous estrogens by inhibiting the aromatization of the target protein and thus it exhibits antitumor effect on endocrine tumors. AIs offer superiority in the treatment of breast cancer both in adjuvant and metastatic settings over tamoxifen in terms of disease free survival and adverse events. Nevertheless, treatment with AIs result in lessening of bone mass accompanied by musculoskeletal symptoms (joint pain, muscle pain, bone pain and arthritis), a manifestation known to be linked with estrogen depletion. Generally,
healthy women experience musculoskeletal pain after menopause and this pain may further aggravate in women on AIs. Nearly half of the patients develop joint-related symptoms during treatment with AIs. In addition, musculoskeletal toxicity appears to be the principal cause for early discontinuation of AIs treatment. Till now no specific informative genetic marker has been available with regard to AIs induced toxicity.

Research on the pharmacogenetics of AIs has shown the influence of CYP19A1 genetic variants on AI associated side effects. The first comprehensive genome-wide (GWAS) approach on musculoskeletal adverse events was carried out by Ingle et al in 878 AIs treated white patients with early stage endocrine sensitive breast cancer. They scanned 551,395 single nucleotide polymorphisms (SNPs) and identified four variants close to T-cell leukemia 1A (TCL1A) gene, which were found to be associated with musculoskeletal toxicity risk. Interestingly, the subsequent in vitro analysis revealed altered estrogen response for the above TCL1A variants compared to the wild alleles and the imputed SNP rs11849538 created a new estrogen response element. The gene encoding TCL1A protein, belonging to the TCL1 family is expressed in activated T lymphocytes and B lymphocytes. This 14 kDa protein encoded by TCL1A gene located at 14q32.1 is implicated in various hematopoietic malignancies.

A number of studies have described the profound differences in the incidence of polymorphic variants of ADME genes in various racial groups. Very recently, we described significant inter-ethnic variations in the distribution of CYP19A1 pharmacogenetic variants in South Indians. Since remarkable inter and intra-ethnic differences in the distribution of these variants have been highlighted in the previous South Indian reports, it is pertinent to evaluate the functional variant alleles of TCL1A in this population. In this study, we have chosen four polymorphisms (rs7158782, rs7159713, rs2369049 and rs11849538) of TCL1A gene associated with AIs induced musculoskeletal toxicity to determine the genetic variability and haplotype profile in South Indians and compare our observations with 8 HapMap populations viz CEU (Utah residents with Northern and Western European ancestry), GIH (Gujarat Indians in Houston, Texas), HCB (Hans Chinese in Beijing, China), JPT (Japanese in Tokyo, Japan), LWK (Luhya in Webuye, Kenya), MEX (Mexican ancestry in Los Angeles), TSI (Toscans in Italy) and YRI (Yoruba Ibadan, Nigeria).

**Materials and methods**

**Study volunteers**

Two hundred and forty seven unrelated healthy South Indians were enrolled. Participants comprised of 127 male and 120 female adults between ages 18 and 76 years, mean age 34.34 ± 13.28 (SD). After explaining the procedures, written informed consent was obtained from each participant and 5 ml of venous blood was drawn in sterile EDTA tubes. The research protocol was approved by the Ethics and Research Committee of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India.

**DNA extraction and genotyping**

Extraction of lymphocyte DNA was done by standard phenol-chloroform method and quantified by multianalyzer (TECAN Infinite M200, Switzerland). After ensuring quality and quantity of DNA, genotyping was carried out for rs7158782 (C_29078024_10), rs7159713 (C_19276662_10), rs2369049 (C_1927663_20) and rs11849538 (C_1927667_10) using TaqMan prevalidated genotyping assays. The 5 μl total PCR reaction mixture consisted of 1.25 μl of 50 ng of template DNA, 2.5 μl of 2 x universal PCR master mix, 0.125 μl of 20 X genotyping assays and 1.125 μl of autoclaved Milli Q water. Amplification was performed according to the conditions described previously on ABI 7300 real time PCR system and the alleles were discriminated by means of sequence detection software version 1.4. The reproducibility of the above genotyping method was confirmed by repetition in over 30% of the total samples and it was found to be 100 percent accurate.

**Data analysis**

Statistical significance (p<0.05) of Hardy-Weinberg equilibrium (HWE) and comparison between the study group and HapMap populations were assessed by χ² test. All the statistical analysis of the data was performed by Graph Pad Instat 3 (Graph Pad Software Inc., San Diego, CA, USA) statistical software. A 95% confidence interval (CI) was calculated by CI analysis software version 1.0. For the four loci, haplotype estimation and pairwise linkage disequilibrium (LD) analysis were executed by Haploview software version 4.2, and D’ and r² pairwise values were calculated.

**Results**

The allele and genotype frequencies of TCL1A gene polymorphisms are presented in Table 1. The genotype distribution of the study polymorphisms were in HWE, with the exception of rs2369049 in which the heterozygous conditions were more in number than the expected. The polymorphic variant allele (G) frequencies of rs7158782, rs7159713, rs2369049 and rs11849538 were 22.1%, 23.5%, 18.2% and 22.9%, respectively. Compared to the frequencies of those in Europeans (CEU and TSI) and American Indian populations (GIH), our estimation in South Indians revealed significantly high frequency of the variant alleles. However no statistical significance was noted for the frequency of rs7158782 in TSI (22.1% vs. 15.9%) and rs2369049 in CEU (18.2% vs. 13.3%). Conversely, the mutant allele frequencies are similar to those values reported in the two Asian populations (JPT and HCB), apart from rs2369049 G which showed lower frequency of 9.3% and 3.5% in HCB and JPT, respectively (p< 0.05). The differences in the mutation frequencies of rs7158782, rs7159713 and rs2369049 in South Indians and Hispanics (MEX) were not statistically different. On the other hand, exceedingly greater frequency of the mutants was found in Africans...
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(YRI and LWK) compared to South Indians and other populations of HapMap (p < 0.001). This indicates that the African breast cancer patients are likely to exhibit more risk to musculoskeletal toxicity than any other ethnics when treated with AIs. Interestingly, the homozygous variant genotypes of all the studied markers were not observed in JPT and likewise for rs2369049 in HCB and rs11849538 in CEU.

Overall LD across the TCL1A loci is depicted in Table 2. As observed in the recent genome-wide association studies GWAS study, the four polymorphisms showed strong LD with each other. The complete LD (D’ > 1) was observed between rs7158782 and rs7159713. Strong linkage was found among rs7158782, rs2369049 and rs11849538 (D’ = 0.92), between rs7159713 and rs2369049 (D’ = 0.96) and between rs7159713 and rs11849538 (D’ = 0.91). Owing to the non availability of rs11849538 genotype information for some populations from HapMap database, comparison of the LD pattern and haplotype structure was made only with CEU, HCB, JPT and YRI. Though no difference in the LD pattern, lower D’ values were displayed in South Indians than the HapMap populations excluding MEX (Table 2). Four different haplotypes, each of which having a frequency of above 1% were estimated in South Indian using an expectation-maximization algorithm (Table 3). Similarly, 4 haplotypes were assigned in JPT, 2 in CEU, 3 in YRI and Chinese, respectively. Of the inferred haplotypes, the most common haplotype observed in all the ethnic groups (but not in YRI) was H1 A-A-A-C (74.9%) which included the normal alleles of all four polymorphisms. This reference haplotype was present at highest and lowest frequency in CEU (90.6%) and YRI (17.0%), respectively. Followed by H2 G-G-G-G (16.6%) carrying all the variant alleles was the second most common haplotype in South Indians, which occurred at a very low frequency (3.8%) in JPT than the other populations analyzed. Noteworthy findings of our study were three haplotypes that were found to be population specific viz H4 A-A-A-G (1.2%) for South India, H5 G-G-A-C (1.3%) for JPT and H6 G-G-G-C (40.4%) for YRI. Further, H3 G-G-A-G (2.3-16.3%)

| Alleles and genotypes | SI (247) | CEU (111) | GIH* (87) | HCB (43) | JPT (82) | LWK* (90) | MEX* (50) | TSI* (88) | YRI (111) |
|-----------------------|---------|----------|----------|----------|----------|----------|----------|----------|-----------|
| A                     | 77.9    | 86.3     | 86.9     | 74.4     | 82.6     | 22.8     | 79.0     | 84.1     | 15.8      |
| G                     | 22.1    | 13.7†    | 13.1†    | 25.6     | 17.4     | 77.2**   | 21.0     | 15.9     | 84.2***   |
| rs7158782             |         |          |          |          |          |          |          |          |           |
| AA                    | 37.7    | 26.6     | 23.9     | 44.2     | 34.9     | 93.3     | 40.0     | 29.6     | 97.3      |
| AG                    | 31.2    | 25.7     | 21.6     | 37.2     | 34.9     | 32.2     | 38.0     | 27.3     | 26.1      |
| GG                    | 6.5     | 0.9      | 2.3      | 7.0      | 0        | 61.1     | 2.0      | 2.3      | 71.2      |
| rs7159713             |         |          |          |          |          |          |          |          |           |
| A                     | 76.5    | 86.3     | 86.4     | 74.4     | 82.6     | 22.8     | 79.0     | 84.1     | 15.6      |
| G                     | 23.5    | 13.7†    | 13.6†    | 25.6     | 17.4     | 77.2**   | 21.0     | 15.9     | 84.1***   |
| rs7158782             |         |          |          |          |          |          |          |          |           |
| AA                    | 39.7    | 26.6     | 25.0     | 44.2     | 34.9     | 93.3     | 40.0     | 29.6     | 97.3      |
| AG                    | 32.4    | 25.7     | 22.7     | 37.2     | 34.9     | 32.2     | 38.0     | 27.3     | 26.5      |
| GG                    | 7.3     | 0.9      | 2.3      | 7.0      | 0        | 61.1     | 2.0      | 2.3      | 70.8      |
| rs2369049             |         |          |          |          |          |          |          |          |           |
| A                     | 81.8    | 86.7     | 89.2     | 90.7     | 96.5     | 23.9     | 87.0     | 84.7     | 15.9      |
| G                     | 18.2    | 13.3     | 10.8†    | 9.3‘‘    | 3.5‘‘    | 76.1‘‘   | 13.0     | 15.3‘‘   | 84.1‘‘    |
| rs2369049             |         |          |          |          |          |          |          |          |           |
| AA                    | 31.2    | 25.7     | 19.3     | 18.6     | 7.0      | 93.3     | 24.0     | 29.5     | 97.3      |
| AG                    | 25.9    | 24.8     | 17.0     | 18.6     | 7.0      | 34.4     | 22.0     | 28.4     | 26.5      |
| GG                    | 5.3     | 0.9      | 2.3      | 0        | 0        | 58.9     | 2.0      | 1.1      | 70.8      |
| rs11849538            |         |          |          |          |          |          |          |          |           |
| C                     | 77.1    | 91.2     | -        | 74.4     | 84.5     | -        | -        | -        | 55.9      |
| G                     | 22.9    | 8.8‘‘    | -        | 25.6     | 15.5     | -        | -        | -        | 44.1‘‘    |
| rs11849538            |         |          |          |          |          |          |          |          |           |
| Carriers              | 38.9    | 17.5     | -        | 44.2     | 31.0     | -        | -        | -        | 62.7      |
| CC                    | 61.1    | 82.5     | -        | 55.8     | 69.0     | -        | -        | -        | 37.3      |
| CG                    | 32.0    | 17.5     | -        | 37.2     | 31.0     | -        | -        | -        | 37.2      |
| GG                    | 6.9     | 0        | -        | 7.0      | 0        | -        | -        | -        | 25.5      |

Values in parentheses indicate total number of subjects; *rs11849538 genotype information is not available for these populations in HapMap. SI South Indians, CEU Utah residents with Northern and Western European ancestry, GIH Gujarati Indians in Houston, Texas, HCB Hans Chinese in Beijing, China, JPT Japanese in Tokyo, Japan, LWK Luhya in Webuye, Kenya, MEX Mexican ancestry in Los Angeles, TSI Toscans in Italy and YRI Yoruba Ibadan, Nigeria. *** p<0.0001, ** p<0.01, * p<0.05.

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haplotype occurred primarily in Asians and virtually was absent in Africans.

**Discussion**

Indian population comprises of numerous sub-groups and it is the most populated nation in the world after China. The contemporary Indian sub-populations are evolved from two paternal races namely the ‘Ancestral North Indians’ (ANI) and ‘Ancestral South Indians’ (ASI). These two populations are different from each other in terms of their genetic constitution, caste, language, geography and ancestry. The South Indians are Dravidian speakers, those who do not share their genetic signatures with the rest of the world. The region conquering 19.31% of the Indian mainland is populated by 252 million humans living in the southern states of Tamilnadu, Pondicherry, Andhra Pradesh, Kerala and Karnataka. Of the total Indian population, 21.7% is contributed by South Indians (http://www.censusindia.govt.in/2011census, accessed on May, 2013).

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**Table 2.** Pairwise LD analysis for a set of 4 TCL1A genetic polymorphisms in 247 SI subjects and differences with HapMap populations

| Populations | SNP1-SNP2 r² D' | SNP1-SNP3 r² D' | SNP1-SNP4 r² D' | SNP2-SNP3 r² D' | SNP2-SNP4 r² D' | SNP3-SNP4 r² D' |
|-------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| SI (N=247)  | 1.0             | 0.89            | 1.0             | 0.89            | 1.0             | 0.89            |
| CEU (N=111) | 1.0             | 0.80            | 1.0             | 0.76            | 1.0             | 0.68            |
| GIH (N=87)  | 0.95            | 0.29            | 1.0             | 0.29            | 1.0             | 0.29            |
| HCB (N=43)  | 1.0             | 0.18            | >1.0            | 0.91            | 1.0             | 0.91            |
| JPT (N=82)  | 0.94            | 0.94            | 1.0             | 1.0             | 0.94            | 1.0             |
| LWK (N=90)  | 1.0             | 0.44            | 0.89            | 0.44            | 0.89            | 1.0             |
| MEX (N=50)  | 1.0             | 0.95            | 1.0             | 0.95            | 1.0             | 1.0             |
| TSI (N=88)  | 1.0             | 1.0             | 1.0             | 1.0             | 1.0             | 1.0             |
| YRI (N=111) | 1.0             | 1.0             | 1.0             | 1.0             | 1.0             | 1.0             |

*SNP single-nucleotide polymorphism, SNP1 rs7158782, SNP2 rs7159713, SNP3 rs2369049, SNP4 rs11849538, SI South Indian, CEU Utah residents with Northern and Western European ancestry, GIH Gujarat Indians in Houston, Texas, HCB Hans Chinese in Beijing, China, JPT Japanese in Tokyo, Japan, LWK Luhya in Webuye, Kenya, MEX Mexican ancestry in Los Angeles, TSI Toscans in Italy and YRI Yoruba Ibadan, Nigeria.*

**Table 3.** Structures of TCL1A haplotypes in South Indians and their comparisons with HapMap populations

| Haplotype Structures | rs7158782 A>G | rs7159713 A>G | rs2369049 A>G | rs11849538 C>G | Frequency % |
|----------------------|--------------|--------------|--------------|---------------|-------------|
|                      | SI CEU GIH* HCB JPT LWK* MEX* TSI* YRI |               |              |               |             |
| H1                   | 74.9 90.6 86.4 74.5 82.5 22.8 77.9 84.1 17.0 |               |              |               |             |
| H2                   | 16.6 8.5 10.8 9.3 3.8 76.1 11.9 15.3 42.6 |               |              |               |             |
| H3                   | 4.3 - 2.3 16.3 12.5 - 9.1 - - |               |              |               |             |
| H4                   | 1.2 - - - - - - - - |               |              |               |             |
| H5                   | - - - - 1.3 - - - - |               |              |               |             |
| H6                   | - - - - - - - - 40.4 |               |              |               |             |
| H7                   | - - - - - - - - 1.1 - - |               |              |               |             |
| H8                   | - - - - - - - - 11.0 |               |              |               |             |

*The white color indicates wild allele and gray denotes mutant allele; *rs11849538 genotype information is not available for these populations in HapMap; H, haplotypes; CEU (Utah residents with Northern and Western European ancestry), GIH (Gujarat Indians in Houston, Texas), HCB (Hans Chinese in Beijing, China), JPT (Japanese in Tokyo, Japan), LWK (Luhya in Webuye, Kenya), MEX (Mexican ancestry in Los Angeles), TSI (Toscans in Italy) and YRI (Yoruba Ibadan, Nigeria).*
In the present study, we tested four genetic polymorphisms of \textit{TCL1A} gene associated with AIs induced musculoskeletal toxicity in 247 South Indian individuals. The outcome of our findings showed that there were significant racial differences in the distribution of \textit{TCL1A} alleles between South Indians and HapMap populations. AIs-induced musculoskeletal toxicity is a manifestation known to be caused by estrogen deprivation. The four studied polymorphisms were found to be associated with higher odds of musculoskeletal toxicity in patients treated with AIs with a \textit{p} value < 1E-06. Among them, the imputed SNP rs11849538 had the least \textit{p} value (6.67E - 07) with an odds ratio of about 2.21, variant allele frequency 17.2\% in cases and 9.1\% in controls.\textsuperscript{11} The functional studies following GWAS\textsuperscript{11} demonstrated the polymorphism dependent expression of \textit{TCL1A} gene in estradiol exposed lymphoblastoid cell lines and further the transcription of a series of genes involved in the musculoskeletal pathophysiology were also regulated. This includes genes encoding cytokines and cytokine receptors such as \textit{IL-17RA}, \textit{IL-17}, \textit{IL-12RB2}, \textit{IL-12} and \textit{IL-1R2}.\textsuperscript{19} In spite of these studies, very little is known about \textit{TCL1A} gene. Henceforth, further understanding and validation of these mechanisms will open a new paradigm in estrogen driven musculoskeletal pain during endocrine therapy. Unpredictable efficacy and drug-induced adverse reactions of anti-cancer agents are often the hallmarks of cancer therapeutics. Over the decade, significant progress made in genetics and genomics brought revolution in genomic medicine. As with most anti-cancer drugs, research is focused on identifying genetic markers to predict the safety and effectiveness of a drug. The prominent examples of FDA recommending pharmacogenetic biomarkers on oncology drug labels includes \textit{TPMT} on mercaptopurine and thioguanine, Estrogen receptor on Tamoxifen, \textit{KRAS} on Cetuximab, \textit{UGT1A1} on irinotecan and nilotinib, \textit{ERBB2} on trastuzumab and pertuzumab etc. (Pharmacogenomic Biomarkers in Drug Labels, home page [http://www.fda.gov, accessed on October, 2013]. Likewise, \textit{TCL1A} gene polymorphic variants could be used to personalize AIs treatment as it has been linked with AIs-induced musculoskeletal adverse events.

Our investigation is the first independent population-based analysis to describe the distribution of four musculoskeletal toxicity risk related \textit{TCL1A} gene pharmacogenetic variants, genotypes and haplotypes in Indian population. Wide inter-ethnic variability observed in this study indicates the distinct genetic composition of the South Indian population. It corresponds to the Indian genome variation consortium assessment on Dravidian populations, a finding that explained the variation between South Indians and HapMap populations.\textsuperscript{20}

\textbf{Conclusion}

The outcome of this study contributes for calculating the sample size which will aid in designing further pharmacogenetic association studies of \textit{TCL1A} gene polymorphisms with AIs-induced musculoskeletal toxicity. Additionally, the therapeutic utility of these variants should be validated in large cohorts of South Indian breast cancer patients before considering the translational approach.

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\textbf{Ethical issues}

The current study was approved and carried out in accordance with the Institute Ethics and Research Committee guidelines of JIPMER, Pondicherry, India.

\textbf{Competing interests}

The authors declare no competing interests.

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