The p.Pro47Ser Polymorphism of TP53: A Systematic Review

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ABSTRACT

The tumor suppressor gene TP53 rs1800371 polymorphism (g.11370 C>T, c.139C>T, p.Pro47Ser) has been extensively investigated as a potential risk factor for different types of cancers and many diseases, but the results have been inconclusive. After searching multiple electronic databases to investigate the association between the p.Pro47Ser polymorphism and disease susceptibility, the present study has identified eleven eligible case-control studies, after investigating 2,502 cases and 3,740 controls. Also, four case-studies were included, investigating 225 cases. The genotypic frequency of Pro/Pro genotype in all the case-control studies was 100% (approximately). That led to conclude that there is no association between TP53 rs1800371 polymorphism and disease susceptibility. Published results seem to be driven by technical artifacts rather than justified biological effects. In order to determine the potential clinical implications of this polymorphism, future genetic association studies should use more rigorous genotyping methods and avoid the use of tumor tissue as a source of DNA to prevent genotype misclassification due to loss of heterozygosity.

Key words: Polymerase chain reaction, restriction fragment length polymorphism, single strand conformation polymorphism, proline, serine

INTRODUCTION

TP53, a tumor suppressor gene (OMIM, 191170) localized on 17p13. It consists of 11 exons spanning 20 kbp resulting in a transcript of 2629 bp which encodes for p53, a nuclear phosphoprotein of 393 amino acids and 53 kD (McBride et al., 1986; Levine, 1997). The p53 protein is comprised of multiple functional domains with an acidic N-terminus containing activation domain which serves as a transcriptional activator, a hydrophobic central DNA Binding Domain (DBD) which binds to specific DNA sequences (repeats of the consensus RRRCA/TA/TGGYY) within regulatory regions of target genes and a basic C-terminus which contains tetramerization domain and multiple nuclear localization sequences as well as multiple lysine residues which are key to regulating p53 activity (Hainaut and Hollstein, 2000). TP53 is mutated in 50-70% of human sporadic cancers (Hollstein et al., 1991; Levine, 1997). Approximately, 85 polymorphisms and 27880 somatic mutations are known in the TP53 (Petitjean et al., 2007). Predisposition to several human cancers and other diseases has been associated with genetic polymorphisms, which may represent an important contribution to disease susceptibility.

Many genetic alterations like mutations and polymorphisms results in dysfunctioning and inactivation of p53 leading to cancer development and many other diseases. Several polymorphisms
have been identified within the TP53, both in non-coding and coding regions (Murphy, 2008; Bojesen and Nordestgaard, 2008; Costa et al., 2008; Whibley et al., 2009). Most of these polymorphisms are single-nucleotide polymorphisms (SNPs) affecting a single base. The extensively studied polymorphisms of TP53 in exon 4 are codon 72 (rs1042522) and codon 47 (rs1800371) as these polymorphisms lead to an amino acid change. On codon 72, there is a change from Arginine (A) to Proline (P) whereas, on codon 47, there is a change from Proline (P) to Serine (S).

p.Pro47Ser (rs1800371) is a rare polymorphism in the N-terminal transactivation domain of p53. The N-terminal domain of p53 undergoes phosphorylation which regulates its transactivation properties (Dumaz and Meck, 1999; Chao et al., 2003; Kruse and Gu, 2008). Serine 46 phosphorylation plays an important role in p53-dependent apoptosis which has been demonstrated by several groups (Bulavin et al., 1999; Oda et al., 2000; Sanchez-Prieto et al., 2000; Takekawa et al., 2000; Okamura et al., 2001). Li et al. (2005) reported that Ser46 is phosphorylated by p38 and homeodomain-interacting protein kinase 2 (HIPK2), which enhances the transcription of apoptosis-related genes and hence promotes p53-mediated apoptosis. These kinases are directed to phosphorylation sites by a proline residue adjacent to Ser46 and thus, replacement of proline at 47, as occurs with the p.Pro47Ser polymorphism, leads to decreased phosphorylation at Ser46. This reduced phosphorylation at Ser46 results in decreased induction of the pro-apoptotic genes p53AIP1 (p53-regulated apoptosis-inducing protein 1) and BBC3 and decreased apoptosis in human cell lines transfected with the Ser47 variant (Li et al., 2005). Therefore, the Ser47 polymorphism would be predicted to impair phosphorylation on serine 46 as occurs with the p.Pro47Ser polymorphism, decrease transactivation of pro-apoptotic target genes and thus potentially increase cancer risk (Feng et al., 2006; Kurihara et al., 2007). Several epidemiologic studies have addressed the influence of this polymorphism on cancer risk and many other diseases; however, small sample sizes and deficiencies in study design have contributed to conflicting results. To propose a comprehensive evaluation of the potential association of this polymorphism with disease susceptibility, we conducted a systematic study and meta-analysis of candidate genetic association studies that still remains unexplored.

**TP53 GENE POLYMORPHISM**

Many scientists have explored various aspects of science, health, diseases and obtained productive results (Abdi et al., 2010; Abd El-Hady, 2011; Abd El-Hady et al., 2011; Raja and Thilagavathi, 2011; Issaoui et al., 2011; Das et al., 2011; Rocco, 2011; Aan et al., 2011; Adedayo, 2012; Chauhan and Kaith, 2012) yet a lot remains unexplored in the field of biosciences including genetics. To identify genetic association studies published before July 4, 2012, investigating the association between the rs1800371 polymorphism located within the TP53 gene, using computer-based searches (last search: July 3, 2012) of MEDLINE (PubMed), the Human Genome Epidemiology Network (HuGE Net) Literature Finder and the NIH Genetic Association Database, using keywords related to the TP53 gene and polymorphisms (the full search strategy is available from the authors on request). Additionally, we searched two TP53-specific databases that collect information related to TP53 polymorphisms: the IARC TP53 database and the p53 website (Fig. 1). We also hand-searched the reference lists for all retrieved studies and relevant review articles, as well as journals known to publish studies relevant to the topic. Studies using an analytic design (case-control, nested case-control, or cohort) and employing validated genotyping methods to examine the frequency of rs1800371 among patients and controls were eligible for inclusion. Family-based studies were not considered eligible owing to different design
Fig. 1: Organization of TP53 and p53 protein. The amino-terminus of p53 contains AD1 (activation domain 1), AD2 (activation domain 2), PRD (proline rich domain), NES (nuclear exclusion domain) and HCD I (highly conserved domain 1). The carboxy-terminus of p53 contains tetra (4D) (oligomerization domain), NEG (negative regulation domain), NES (nuclear exclusion domain) and NLS (nuclear localization domain). The grayish part of exon 1, 2 and 11 are UTR (un-translated regions) regions.

Considerations. We considered studies published in all languages. The following information was abstracted from each study: First author, journal, year of publication, study design, matching, ethnicity of participants, definition and numbers of cases and controls, DNA extraction and genotyping methods, source of genetic material for genotyping cases, frequency of genotypes and the number of cases and controls for each TP53 genotype (Table 1).

Other studies which investigated this polymorphism are as follows. Fifty four thin prep-processed fine needle breast aspirates and 31 surgical specimens were used for detection of TP53 alterations. The investigators detected codon 47 polymorphism in one aspirant and concluded that DNA suitable for analysis of TP53 sequence changes can be extracted from thin prep-processed breast fine-needle aspirates (Pollett et al., 2000). Eighty five Canadian children diagnosed with a sporadic malignant central nervous system tumor were investigated for the presence of TP53 sequence alterations in exon 4 (p.P47S and p.R72P) and exon 6 (p.R213R) using PCR-SSCP analysis and direct sequencing. No association was found between p.Pro47Ser polymorphism and central nervous system tumor (Portwine et al., 2001). Two hundred African American cancer patients were studied for the p.Pro47Ser polymorphism of TP53 using genotyping analysis was performed, GST Fusion proteins and p38 MAPK, HIPK2 Kinase assays and Apoptosis Assay (TUNEL analysis and multi caspase assay). The authors observed that Ser47 polymorphism might play an important role in cancer risk, progression and the efficacy of therapy (Li et al., 2005). Seventy eight Brazilian renal transplant recipients and 151 controls were studied for p.Pro47Ser polymorphism of TP53 and the susceptibility to herpes virus type 6 (HHV6) and herpes virus type 1 (HHV1) infection in renal transplant recipients. The authors suggested that genotyping of p.Pro47Ser polymorphism of TP53 might not be useful in screening for patients at higher risk for post-transplant infections (Leite et al., 2006). Ninety four Brazilian bladder cancer patients (76 males and 18 females) and 159 healthy controls (104 males and 55 females) were investigated.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Population</th>
<th>Genotyping method</th>
<th>Source of DNA in cases</th>
<th>Patients</th>
<th></th>
<th></th>
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</tr>
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<td>American and African Caucasians</td>
<td>PCR-RFLP</td>
<td>Blood</td>
<td>98</td>
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<td>3</td>
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<td>Breast cancer tissues</td>
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</table>
for p.Pro47Ser polymorphism of TP53 using univariate logistic regression analysis and multivariate regression analysis. The investigators concluded that the effect of TP53 p.Pro47Ser is not associated with susceptibility to bladder cancer (Santos et al., 2011).

META-ANALYSIS OF GENETIC ASSOCIATION STUDIES

Our initial search identified many studies, of which few were considered potentially eligible for inclusion in this review and were retrieved in full text and some as abstracts. Of those, 20 were considered eligible for the meta-analysis (references to excluded studies are available on request). The first was published in 1993 and the last in 2012. Detailed study characteristics are presented in Table 1. These twenty studies include fifteen studies on different types of cancer and five studies on other diseases. The investigated cancer cases in four case studies were 225, respectively and in seven case-control studies, the number of cases and controls were 6,514 and 9,334, respectively. In another four case-control studies which were on different diseases (schizophrenia, neural tube defect, juvenile chronic and rheumatoid arthritis and primary open angle glaucoma), the number of cases and controls investigated were 1,472 and 2,746, respectively. Age and gender matched unrelated healthy individuals were taken in all the eleven case-control studies. Of these twenty studies, eighteen studies showed no association of p.Pro47Ser polymorphism with disease susceptibility whereas studies by Li et al. (2005) on cancer and Almada et al. (2009) on extra-axial brain tumors showed that this polymorphism is associated with cancer risk, progression and the efficacy of therapy.

CONCLUSION

This systematic review and meta-analysis of genetic association studies shows that TP53 p.Pro47Ser is unlikely to be a major risk factor for different types of cancers and many diseases. Several sources of bias, including the use of inappropriate genotyping material and the lack of quality control, need to be addressed in the design of future studies to determine the potential clinical implications of this polymorphism in pathogenesis of cancer and other disease. Also, future genetic association studies should use more rigorous genotyping methods and avoid the use of tumor tissue as a source of DNA to prevent genotype misclassification due to loss of heterozygosity.

REFERENCES


