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# NAD (P) H: QUINONE OXIDOREDUCTASE 1 GENE C609T POLYMORPHISM AND ALZHEIMER'S DISEASE RISK

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**Abstract:** NAD (P) H: Quinone Oxidoreductase 1 (NQO1) is an enzyme that reduces cellular oxidative stress by scavenging free radicals. Variant NQO1 enzyme role in Alzheimer's disease (AD) susceptibility is controversial. The aim of the present study was to assess NQO1 C609T polymorphism as a risk factor for Alzheimer's disease (AD). The authors performed a meta-analysis from published case-control studies that examined the association between C609T polymorphism and AD (735 cases and 828 controls). The pooled Odd Ratios (OR) was estimated by both fixed effects and random effects models. The meta-analysis with random effects model showed that there was 38% heterogeneity between five included studies. The random effect pooled OR is 1.38 (95% CI; 1-14 to 1.66) and Cochran Q was 6.45 (df = 4). The results of present meta-analysis showed that NQO1 gene C609T polymorphism is a risk factor for AD pathogenesis.

**Keywords:** Alzheimer's disease, C609T polymorphism, NQO1 gene, Oxidative stress, Risk.

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## INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease (Verma, 2017). AD is characterized by changes in the brain that lead to deposits of amyloid-beta plaques (senile plaques) between the neurons and neurofibrillary tangles within neurons. Approximately 44 million people are living with AD worldwide, making it a global crisis and it is increasing at an alarming rate. According to the World Health Organization, AD is the seventh leading cause of death worldwide and is the most common form of dementia and may contribute to 60-70% of cases. AD is a multifactorial pathology resulting from interaction of both the environmental and genetical factors. Several gene polymorphisms are reported risk factors for AD pathogenesis (ABP, presnilin 1, presnilin 2, Tau, ApoE4, and MTHFR etc.). NQO1 is also considered as a potent gene for AD susceptibility because the NQO1 enzyme reduces oxidative stress in neurons.

The NQO1 enzyme belongs to the quinine oxidoreductase family and in humans it is found in different tissues, including the heart, liver, lung, kidney, cornea, and peripheral and central

nervous systems (CNS). The NQO1 enzyme is a flavoprotein, composed of a NAD (P) H-binding domain and a quinone-binding domain. NQO1 tightly binds flavin adenine dinucleotide (FAD; as a cofactor), which is important for the stability and activity of NQO1 enzyme. NQO1 is a cytosolic enzyme, but a smaller quantity is also present in the nucleus.

The NQO1 gene is located on chromosome 16q22.16; it is approximately 17 kb long and contains six exons. Several single nucleotide polymorphisms (SNPs) is reported in NQO1 gene, but the most studied SNP is C609T (rs1800566), in which a cytosine (C) to thymine (T) change at nucleotide position 609 in exon six which results in a proline-to-serine (Pro187Ser) amino acid change at codon 187 of the amino acid sequence of the protein (Fig. 1). The NQO1 C609T polymorphism was shown to have an established and strong impact on enzymatic activity of the NQO1 protein by extremely decreasing stability, as the variant enzyme is rapidly ubiquitinated and degraded by the proteasome (Siegel *et al.*, 2001). Heterozygous carriers (C/T) show about 50% NQO1 activity compared to individuals with C/C genotype and homozygote carriers (T/T) only harbour very low to undetectable residual NQQO1 activity (Chhetri *et al.*, 2018). NQO1 has a crucial role in the protection against oxidative stress and was shown to be a multifunctional antioxidant and an exceptionally versatile cytoprotector (Dinkova-Kostova and Talalay, 2010).

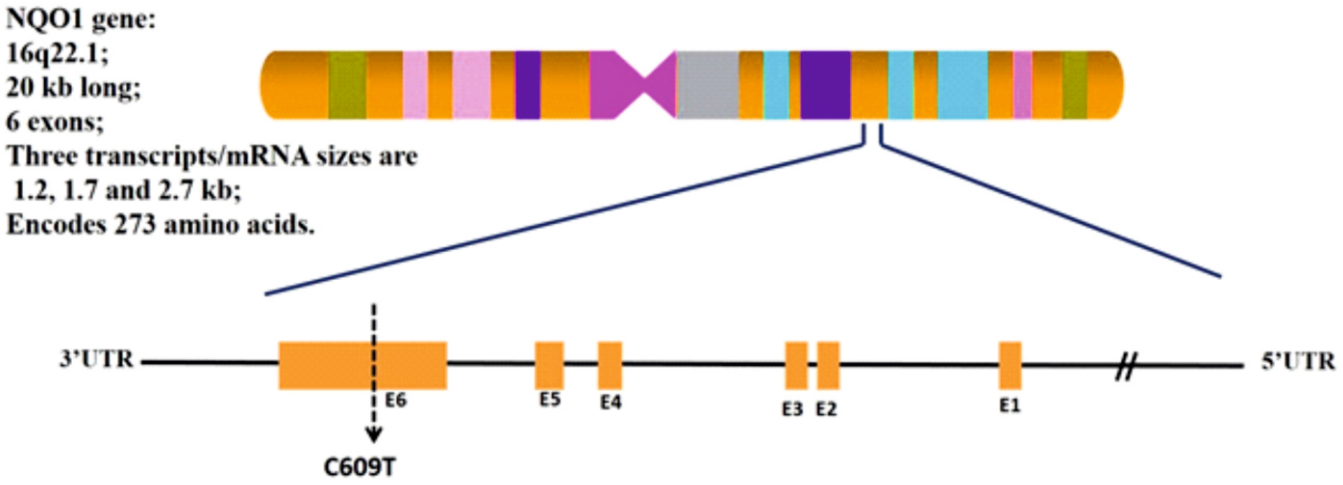


**Fig. 1. NQO1 C609T polymorphism**

In past, several studies have been investigated the relationship between NQO1 gene C609T polymorphism with different diseases in different races and reported 609T allele as risk factor- Coronary Artery Disease (Boroumand *et al.*, 2017), metabolic syndrome (Martínez-Hernández *et al.*, 2015), Macular Degeneration Disease (Yousefnia, 2019), Parkinson's disease (Dai *et al.*, 2014), Alzheimer's disease (Luo *et al.*, 2016), acute lymphoblastic leukemia (Li *et al.*, 2014), digestive tract cancer (Yadav *et al.*, 2018), hepatocellular carcinoma (Fan *et al.*, 2014), breast cancer (Yadav *et al.*, 2016), lung cancer (Yin *et al.*, 2001), esophageal cancer (Yanling *et al.*, 2013), bladder cancer (Gong *et al.*, 2013) etc. The present meta-analysis is carried out to find the association between NQO1 gene C609T polymorphism and AD risk.

## MATERIALS AND METHODS

Meta-analysis was carried out according to meta-analysis of observational studies in epidemiology (MOOSE) guidelines. Eligible studies were identified by searching the following databases- Pubmed, Springer link, ScienceDirect and Google Scholar up to July 11, 2024. The following search terms were used: 'NQO1', 'NAD (P) H: Quinone Oxidoreductase 1', and 'C609T' in combination with 'Alzheimer's disease', or 'AD'. The authors also reviewed the bibliography of included articles to identify additional articles not retrieved by database search.

The following inclusion criteria were used: (i) published studies, (ii) case control approach, and (iii) reported complete information of NQO1 genotype/allele numbers. Studies were excluded if: (i) not providing complete information for number of genotype and/or allele calculation, (ii) studies based on pedigree data and (iii) review, editorials etc.

Relevant information was extracted from all selected studies like family name of author, year of publication and number of cases and controls for each C609T genotype (CC, CT and TT genotypes). Allelic frequencies for the cases and controls were calculated from corresponding genotypes. Authors tested heterogeneity between studies using Cochran's Chi-square-based Q-statistic and estimated the degree of heterogeneity with $I^2$ ($I^2$ = {(Q-(k-1))/Q} ×100%), where k indicates number of studies). $I^2$ ranges from 0% to 100%. It indicates the proportion of between-study variability in point estimates that was due to heterogeneity rather than sampling error (Higgins, and Thompson, 2002). An overall OR and 95% confidence interval (CI) was estimated under the Mantel-Haenszel's fixed-effects model (Mantel and Haenszel, 1959), if there was no evidence for heterogeneity (I2 < 50%), otherwise ($I^2$ = 50%) under the DerSimonian-Laird random-effects model (DerSimonian and Laird, 1986). A random effects modelling assumes a genuine diversity in the results of various studies, and it incorporates between-study variance into the calculations. The statistical analyses were performed using the program Meta-analysis with Meta-disc (version 1.4).

## RESULTS AND DISCUSSION

After applying the inclusion and exclusion criteria, only 5 studies were found suitable for the inclusion in the present meta-analysis (Ma *et al.*, 2003; Wan *et al.*, 2005; Ouyang *et al.*, 2006; Wang *et al.*, 2006; Bian *et al.*, 2008) (Table 1). All five studies were carried out in China.

In all five included studies, the total number of AD cases was 735 with CC (146), CT (419) and TT (170), and the number of controls was 828 with CC (258), CT (415), and TT (158). In cases, the number of C and T alleles were 711 and 759 respectively, and in control the number of T allele was 728 (Table 1; Fig. 2).

**Table 1: Details of included studies.**

| Study | Ethnicity/Country | Case | Control | Case Genotype | | | Control Genotype | | | Case allele | | Control allele | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | CC | CT | TT | CC | CT | TT | C | T | C | T |
| Ma *et al.*, 2003 | Asia/China | 120 | 122 | 15 | 78 | 27 | 36 | 66 | 20 | 108 | 132 | 240 | 138 |
| Wan *et al.*, 2005 | Asia/China | 65 | 110 | 11 | 39 | 15 | 44 | 48 | 18 | 61 | 69 | 130 | 136 |
| Ouyang *et al.*, 2006 | Asia/China | 135 | 138 | 17 | 87 | 31 | 40 | 74 | 24 | 121 | 149 | 270 | 154 |
| Wang *et al.*, 2006 | Asia/China | 104 | 128 | 27 | 53 | 24 | 31 | 70 | 27 | 107 | 101 | 208 | 132 |
| Bian *et al.*, 2008 | Asia/China | 311 | 330 | 76 | 162 | 73 | 107 | 154 | 69 | 314 | 308 | 622 | 368 |

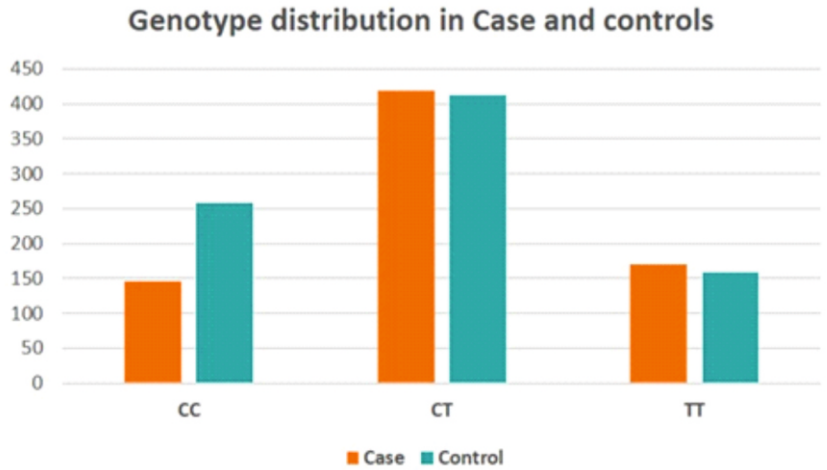


**Fig. 2: Distribution of genotypes in case and control samples of included studies.**

An ethnic variation in the prevalence of NQO1 C609T polymorphism has been extensively studied. In China, nearly 50% of the population are heterozygous (CT) and up to 22% are homozygous (TT), whereas among Caucasians only up to 33% of the population are heterozygous (CT) and up to 5% are homozygous (TT) (Fig. 3) (Chhetri *et al.*, 2018). Highest T allele frequency is reported from China, so the majority of the studies are published from China and have shown significant association between C609T polymorphism and AD risk (Chhetri *et al.*, 2018). The pooled Odd Ratios were estimated by both fixed effects (Mantel and Haenszel, 1959) and

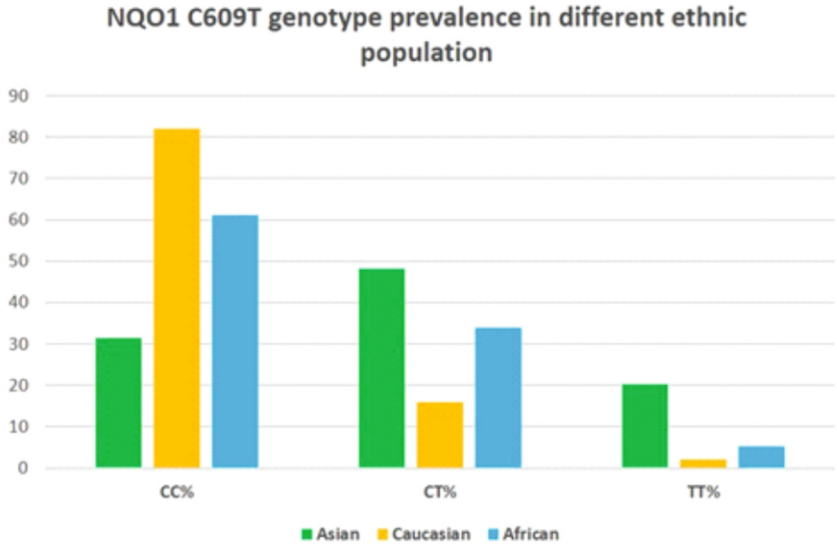


**Fig. 3: Distribution of CC, CT and TT genotypes in different ethnic population (Chhetri *et al.*, 2018).**

random effects (DerSimonian and Laird, 1986) models. The meta-analysis with fixed effects showed that there was 38% heterogeneity between the five studies. The fixed effect pooled OR was 1.35 (95% CI; 1.19 to 1.54) and Cochran Q was 24.13 (df = 7; p=0.0011). The study was significant and showed strong association. The random effect pooled OR was 1.38 (95% CI;1.14 to 1.66) and Cochran Q was 6.45 (df = 4; p=0.16). The random effect pooled OR showed strong association between NQO1 607T allele and Alzheimer's disease.

The NQO1 enzyme is involved in cellular detoxification and protection against oxidative stress. In CNS, free radicals exert neurotoxic effects, resulting in neurodegenration in different parts of the brain. NQO1 enzyme protects neurons against oxidative damage and maintains cellular homeostasis through the reduction of free radicals and detoxifying deleterious quinones as well as the modulation of antioxidant genes. In addition NQO1 modulates several signalling pathways directly or indirectly, which affects cell proliferation (Xiao *et al.*, 2020; Oh *et al.*, 2023), apoptosis (Zhou *et al.*, 2019), and neuroinflammation (Park *et al.*, 2021).

The abnormalities of NQO1 enzyme activity have been linked to the pathophysiological mechanisms of multiple neurological disorders, including multiple sclerosis, epilepsy, cerebrovascular disease, Parkinson's disease, and Alzheimer's disease (Alexoudi *et al.*, 2015; Son *et al.*, 2015; Luo *et al.*, 2016; Volmering *et al.*, 2016).

Meta-analyses are continuously published to evaluate disease risk of small effect genes like cleft lip and Palate (Rai, 2015), NTD (Yadav *et al.*, 2015), Down syndrome (Rai, 2011; Rai *et al.*, 2014), OCD (Kumar and Rai, 2020a), schizophrenia (Rai *et al.*, 2017b), bipolar disorder (Rai *et al.*, 2022), autism (Rai, 2016a; Rai and Kumar, 2018a), alcohol dependence (Rai and Kumar, 2021; Chaudhary *et al.*, 2021; Kumar *et al.*, 2023), migraine (Rai and Kumar, 2021), epilepsy (Rai and Kumar, 2018b), Alzheimer's disease (Rai, 2016b), male infertility (Rai and Kumar, 2017), osteoporosis (Yadav *et al.*,

2020), polycystic ovarian disorder (Rai and Kumar, 2024), Uterine Leiomyoma (Kumar and Rai, 2018a), lung cancer (Rai, 2014a, 2020), breast cancer risk (Rai, 2014b; Rai *et al*., 2017a), esophageal cancer (Kumar and Rai, 2018b), Prostate cancer (Yadav *et al*., 2016, 2021; Kumar and Rai, 2020b), endometrial cancer (Kumar *et al*., 2020) and MTHFR polymorphism (Yadav *et al*., 2017).

Limitations of current meta-analysis should also be considered like (i) less number of case-control studies are included, (ii) results are based on unadjusted estimates, (iii) significance between-study heterogeneity was detected, and (iv) the chance of publication bias still exists, due to the inclusion of published studies and lack of availability of any possible unpublished data.

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