Ethnic Variations in the CHRNA5 rs16969968 Polymorphism and Nicotine Dependence: A Meta-Analysis

Walimuni Arachchilage C.S.M*, Donghwa Yoon*, Uddin Jalal*, Jungwoon Kang*, Mincheol Kim*
*Dept. of Management Information Systems, Faculty of Data science for Sustainable Growth, Jeju National University
e-mail: chathurimuthu7@gmail.com, kathy1548@jejunu.ac.kr, uddinjalal@stu.jejunu.ac.kr, kangjw0310@nate.com, mck1292@jejunu.ac.kr

Abstract

The research examines the connection between the CHRNA5 (rs16969968) polymorphism and nicotine dependence among different ethnic populations through a combined data analysis method. A thorough research of PubMed, GWAS Catalog and Scopus databases led to the identification of 11 studies suitable for the review. The use of a random-effects model was justified because studies exhibited significant variance (I^2 = 94%). The CHRNA5 (rs16969968) polymorphism showed a statistically significant correlation involving Asian populations (OR = 2.07, 95% CI: 1.41-3.02) and Latin American populations (OR = 1.75, 95% CI: 1.30-2.37) but no significant relation in European populations (OR = 1.17, 95% CI: 0.72-1.92). The analyses of publication bias showed slight asymmetry through a Funnel plot visualization and Egger's regression asymmetry test. Sensitivity tests that excluded the Chen_2020 study showed that the analysis results continued to support the main conclusions. The genetic effect of rs16969968 on nicotine dependence shows different intensities across population groups because ethnicity matters when building smoking cessation tactics.

1. Introduction

Smoking is a major cause of early death worldwide, with 67% of smokers dying from smoking-related illnesses [1]. By 2030, it is projected to cause 6.8 million deaths [2]. Nicotine dependence (ND) is the most prevalent substance use disorder, with 85% of smokers meeting ND criteria [3]. ND leads to significant impairment or distress, and is associated with other health issues like lung cancer and cardiovascular disease [4]. Currently, preventative and treatment options for ND have low success rates [5]. Many smokers fail to quit due to ND, despite various treatments [2]. Genetic factors contribute to relapse, with a 50% risk of failed attempts [6]. Genome-wide association studies(GWAS) have identified new genetic variants, such as the CHRNA5-A3-B4 gene cluster, associated with nicotine dependence, which could predict treatment success [7]. However, the effect of these variants may vary across ethnic groups, yet few studies have comprehensively examined these associations in an ancestry-stratified meta-analysis. This study aims to quantify the association between CHRNA5 polymorphisms and nicotine dependence, and to explore how these effects differ across diverse ethnic groups.

2. Methodology

2.1 Data Collection

In this study, we analyzed the association between CHRNA5 (rs16969968) gene polymorphism and nicotine dependence and compared how genetic effects differ according to various ethnic groups. For data collection, papers were selected by searching "rs16969968" and "nicotine dependence" from PubMed, GWAS Catalog, and Scopus, and the search results for each database were 104 PubMed, 1 GWAS Catalog, and 110 Scopus. First, excluding papers published before 2015, 45 PubMed, 1 GWAS Catalog, and 50 Scopus remain. After that, as a result of removing duplicate papers and selecting papers suitable for meta-analysis through Abstract review, a total of 19 cases were first selected, and among them, only 11 studies were included in this meta-analysis by finally selecting the papers mentioning the figures necessary for meta-analysis.

2.2 Data Analysis

In this study, the integrated effect size was calculated by applying a random effect model in consideration of

the possibility of clinical and methodological differences between individual studies during meta-analysis. In other words, it was judged that the actual effect size may not be constant due to differences in the study target group, measurement method, and research design, and a random effect model was used to reflect this heterogeneity [8]. The logOr and standard error (SE) extracted from each study are shown in Table 1, and the analysis was performed using Review Manager (RevMan) 5.4.

[Table 1] Characteristics of included studies and meta-analysis results

Study (Year)		log [Odds Ratio]	SE	Weight	Odds Ratio IV,Random, 95% CI
Asia	Pandey (2017) [9]	1.502	0.746	2.90%	4.49 [1.04, 19.38]
	Ganbold (2021) [10]	0.738	0.247	9.60%	2.09 [1.29, 3.39]
	Chaity (2022) [1]	0.182	0.511	5.00%	1.20 [0.44, 3.27]
Europe	Selya (2018) [11]	1.502	0.746	2.90%	4.49 [1.04, 19.38]
	Hubacek (2017) [12]	0.278	0.103	12.50%	1.32 [1.08, 1.62]
	Chen (2020) [13]	−0.21	0.02	13.30%	0.81 [0.78, 0.84]
Latin America	Zuo (2024) [14]	0.693	0.25	9.60%	2.00 [1.23, 3.26]
	Tomaz (2018) [15]	0.489	0.229	10.00%	1.63 [1.04, 2.55]
	Saccone (2017)[16]	0.278	0.052	13.10%	1.32 [1.19, 1.46]
	Morales (2018) [17]	1.138	0.3	8.50%	3.12 [1.73, 5.62]
	Rubio [18] (2019)	0.542	0.289	8.70%	1.72 [0.98, 3.03]
Total				100.00%	1.64 [1.23, 2.18]
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 159.33$, df = 10 ($P < 0.00001$); $I^2 = 94\%$					
Test for overall effect: Z = 3.42 (P = 0.0006)					
Test for subgroup differences: $Chi^2 = 3.21$, df = 2 (P = 0.20), $I^2 = 37.7\%$					

3. Results

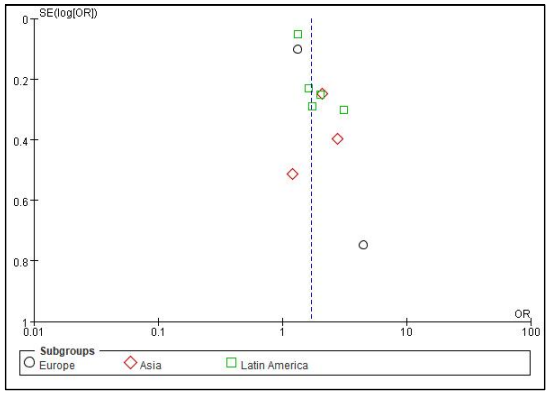
3.1 Heterogeneity and Publication Bias Assessment

Cochran's Q statistic and I^2 index were calculated to evaluate the consistency of the results between studies, and heterogeneity in this study was calculated using equation (1) and found to be very high heterogeneity at 94%, but excluding the Chen_2020 study, it showed heterogeneity lowered to 55% [19].

$$I^2 = \frac{Q - df}{Q} \times 100\% \quad \cdots (1)$$

Publication bias was evaluated to evaluate the consistency of the results between studies, and the possibility of publication bias was visually evaluated as shown in Figure 1 through Funnel Plot. In addition, Egger's regression test was performed, and equation (2) was used to test whether the asymmetry of the Funnel plot was statistically significant [20]. In equation (2), SND is the reciprocal of the standard error of the study, a is the intercept, and b is the slope.

$$SND_i = a + b \times precision_i \quad \cdots (2)$$



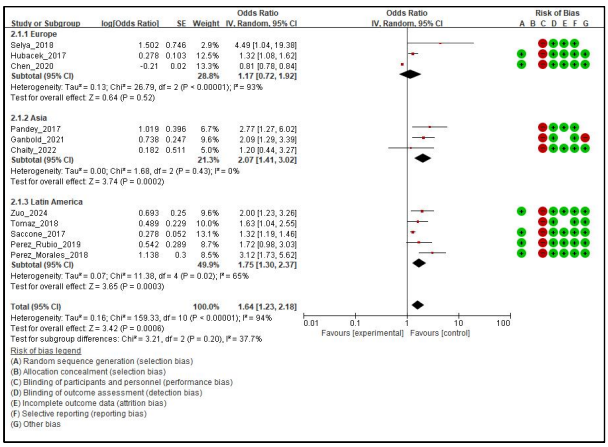
[Fig. 1] Funnel plot evaluating publication bias by continent

The funnel plot showed a symmetrical shape, but some asymmetry was observed, and the distribution tended to be unbalanced in studies with small effect size. As a result of calculating Egger's test, the intercept of the regression equation was statistically significantly different from 0 (intercept = 13.56, $p < 0.0001$). The heterogeneity between the included studies was very high ($I^2 = 94\%$, $p < 0.00001$).

3.2 Subgroup Analysis by Continent

The consistency and heterogeneity of the study results were evaluated through the analysis of small groups by continent. European studies showed an integrated effect size (OR) of 1.17 (95% CI: 0.72-1.92) and heterogeneity was very high, $I^2 = 93\%$. Asian studies showed significant results with an integrated OR of 2.07 (95% CI: 1.41-3.02) and heterogeneity was not observed as $I^2 = 0\%$. Latin American studies showed an integrated OR of 1.75 (95% CI: 1.30-2.37), and heterogeneity was moderate $I^2 = 65\%$. As a result of evaluating the difference in effect size

between small groups, no statistically significant difference was observed between continental studies (Chi^2 = 3.21, p = 0.20).



[Fig. 2] Forest plot of genetic variant (rs16969968) and nicotine dependence by continent

3.3 Sensitivity Analysis

A sensitivity analysis was conducted to evaluate the robustness of the meta-analysis results. In particular, in consideration of the high heterogeneity (I^2 = 93%) observed in European studies, re-analysis was performed after excluding the Chen_2020 study. As a result of excluding the Chen_2020 study, the overall heterogeneity decreased from 94% to 55%, and the integrated effect size (OR) increased from 1.64 (95% CI: 1.23-2.18) to 1.69 (95% CI: 1.40-2.06). This means that the Chen_2020 study had a great influence on the heterogeneity, but the direction and significance of the integrated effect size were maintained. Therefore, the results of this meta-analysis were not excessively influenced by some studies and are generally considered to be robust.

4. Discussion and Conclusion

The meta-analysis reviews research data from different studies that investigate the relationship between the rs16969968 polymorphism in CHRNA5 gene and nicotine dependence. The research supports that polymorphic genetic determinants, specifically rs16969968 function as main elements in nicotine dependence throughout various groups of participants, similar to Saccone et al. (2009) who found evidence that the CHRNA5-A3-B4 cluster increases risk for nicotine dependence [21].

The CHRNA5 gene, together with other genes, exists within a cluster that controls brain nicotine receptor functionality. Human susceptibility to nicotine addiction results from a combination of hereditary elements together with external influences. Numerous studies show genetic variations in this gene cluster increase susceptibility to nicotine dependence, which matches the conclusions of the research.

The association between CHRNA5 risk alleles and nicotine dependence can be evaluated through functional analyses conducted by Chen et al. (2016) and Falvella et al. (2010) [22][23]. Rs16969968 affects CHRNA5 expression, according to Chen et al. (2016) which modifies the brain receptor's interaction with nicotine, and Falvella et al. (2010) established a link between genetic variation and lung cancer in smoking patients [22][23].

The research examines rs16969968 solely while excluding analysis of other significant SNPs. The majority of studies conducted in these samples follow cross-sectional designs that minimize the potential to determine cause-and-effect relationships. Future research should expand to additional SNPs and study the interactions between genes and environments while following participants through time to uncover nicotine dependence mechanisms fully.

Research by this meta-analysis demonstrates that rs16969968 polymorphism from CHRNA5 plays a vital role in nicotine dependence according to the expanding scientific knowledge about hereditable smoking behavior factors and related medical outcomes.

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