HLA and Ménière's disease Susceptibility: A Meta-analysis of Worldwide Studies

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Background

Ménière's disease (MD) is an inner ear disorder characterized by dysfunctional endolymph resorption that results in endolymph accumulation and a classical triad of peripheral vertigo, unilateral sensorineural hearing loss and unilateral tinnitus. Multiple etiologies have been proposed including an acquired endolymph resorption defect, vascular predisposition, allergies, viral infections, and an autoimmune component.

Human Leukocyte Antigen (HLA) are variable genes that encode numerous Major Histocompatibility Complex (MHC). MHC's function as antigen presenting proteins which have roles in nearly all human cell lines in regard to immunity and detection of malignancies. Autoimmune pathologies have been associated with quantifiable levels of specific HLA alleles

Purpose

- The goal of this systematic review is to further elucidate the association between MD and HLA alleles in characterizing the autoimmune component by analyzing literature on the linkage of the HLA-A, HLA-B, HLA-C, and HLA-DR serotypes to MD.
- Calculate odds ratio and forest plot of these allele's association with MD.

Data Analysis

- Systematic literature review with exclusion of articles that included small sample sizes, and subjects considered deceased, animal, or cell subjects/samples.
- PRISMA guidelines for a was utilized.

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Methods

Study Design

In this systematic review, multiple HLA-A, HLA-B, HLA-C, and HLA-DR serotypes and the odds of developing MD were explored.

- PubMed, Google Scholar, ScienceDirect, and Cochrane Library were consulted, and articles were included if living subjects were used, odds ratio was available or could be ascertained from the study, and if it was not a meta-analysis of other researcher's works.
- MetaXL software was used to generate data for analysis and a forest plot was generated for each.
- Eleven studies conducted between 1998 and 2018 met study selection criteria for the combined MD meta-analysis (790 patient alleles and 3,229 control alleles). [1-11]

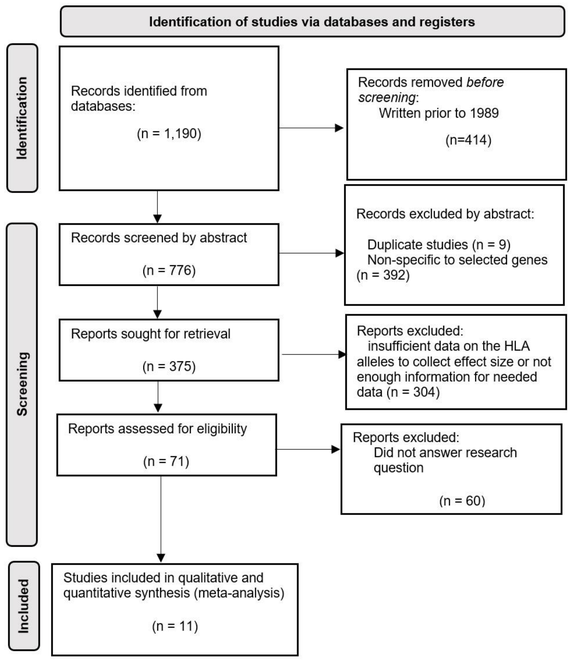

Figure 1. PRISMA flow guideline/checklist for meta-analysis. Figure represents included articles from 1989 – 2018 that met study criteria.

Results

- Thirty-six investigated serotypes with a minimum of three studies were eligible for analysis. 3 HLA-A serotypes, 14 HLA-B serotypes, 7 HLA-C serotypes, and 12 HLA-DR serotypes met the meta-analysis requirements. These alleles are showed in table 1.
- Combined odds ratio was calculated using an Inverse Variance Heterogeneity Model and plotted using a Forest Plot. Analysis with I^2 value for heterogeneity > 25% did not meet significance criteria and were not eligible to be considered significant.
- The presence of the HLA-DR11 conferred 1.81 times increased odds of developing MD as compared to healthy controls. This result is shown in figure 2.
- The presence of the HLA-DR11 conferred 0.62 times decreased odds of developing MD as compared to healthy controls. This result is shown in figure 2.

HLA	Serotype
HLA-A	A1, A2, A11
HLA-B	B7, B8, B13, B27, B35, B37, B38, B39, B44, B51, B52, B55, B57, B58
HLA-C	C1, C2, C3, C4, C5, C6, C7, C8
HLA-DR	DR1, DR3, DR4, DR7, DR8, DR9, DR10, DR11, DR12, DR13, DR15, DR16

Table 1. HLA serotypes that were analyzed for significance in Ménière's disease

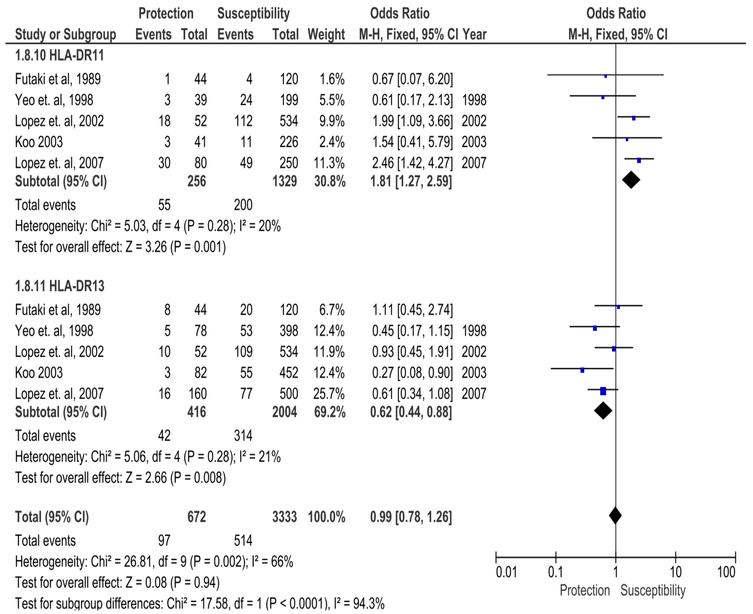

Figure 2. Forest Plots for HLA-DR11 and HLA-DR13 in Ménière's disease

Discussion

- The query returned a total of 1,190 studies, and 11 of those trials met the inclusion criteria. 790 MD patient alleles 3,229 control alleles in 11 trials were assessed.
- Demographic groups included in these studies consisted of ethnically Japanese, South Korean, Iranian, Spanish, and British populations.
- Despite the extensive investigation of autoimmunity within MD, the findings of this comprehensive meta-analysis identified only two HLA serotypes that had significance among the combined patient population.
- Odds of MD was increased in patients with HLA-DR11 (OR=1.81, 95% CI [1.27, 2.59], I2=20%, p<0.05) as compared to normal controls.
- Odds of MD was decreased in patients with HLA-DR13 (OR=0.62, 95% CI [0.44, 0.88], I2=21%, p<0.05) as compared to normal controls.
- A majority of the studies focused on the effect of a single haplotype on prevalence MD, with few also comparing effects of linkage disequilibrium, or combined HLA allele frequencies on disease prevalence.
- Future research should focus on combined haplotypes such as the HLA A1-B8-DR3 which has shown significance in individual studies in sensorineural hearing loss and MD.[12,13]
- Another potential for investigation is the HLA class III genes "HSPA1" that represent the heat shock protein genes that are often tested in clinical practice when diagnosing MD.[14]

Conclusion

- The evidence on HLA-DR11 as a risk factor for MD and HLA-DR13 as a protective factor across several ethnic backgrounds is significant. These results warrant further investigation into a more global subset of patients with MD, with an emphasis in frequencies of combined haplotypes such as HLA A1-B8-DR3 common ancestry gene and the HSPA1 heat shock protein gene.

Literature Cited

1. Gazquez, I., Moreno, A., Aran, I., Soto-Varela, A., Santos, S., Perez-Garrigues, H., ... & Lopez-Escamez, J. A. (2012). MICA-STR A. 4 is associated with slower hearing loss progression in patients with Meniere's disease. Otology & Neurotology, 33(2), 223-229.
2. López-Escámez, J. A., López-Nevot, A., Cortes, R., Ramal, L., & López-Nevot, M. A. (2002). Expression of A, B, C and DR antigens in definite Meniere's disease in a Spanish population. European archives of oto-rhino-laryngology, 259, 347-350.
3. Lopez-Escamez, J. A., Vilchez, J. R., Soto-Varela, A., Santos-Perez, S., Perez-Garrigues, H., Aran, I., & Lopez-Nevot, M. A. (2007). HLA-DRB1* 1101 allele may be associated with bilateral Meniere's disease in southern European population. Otology & Neurotology, 28(7), 891-895.
4. Dabiri, S., Ghadimi, F., Firouzifar, M., Yazdani, N., Mohammad-Amoli, M., Vakili, V., & Mahvi, Z. (2016). HLA-Cw Allele Frequency in Definite Meniere's Disease Compared to Probable Meniere's Disease and Healthy Controls in an Iranian Sample. Iranian Journal of Otorhinolaryngology, 28(87), 262.
5. Khorsandi, Mohammad-Taghi, et al. "Associations between HLA-C alleles and definite Meniere's disease." Iranian Journal of Allergy, Asthma and Immunology (2011): 119-122.
6. Yeo, Sang W., et al. "Influence of Human Leukocyte Antigen in the Pathogenesis of Me´ niere's Disease in the South Korean Population." Acta oto-laryngologica 122.8 (2002): 851-856.
7. Koyama, Sumiko, et al. "HLA associations with Meniere's disease." Acta oto-laryngologica 113.5 (1993): 575-578.
8. Koo, J-W., et al. "Association of HLA-DR and type II collagen autoimmunity with Meniere's disease." Tissue Antigens 61.1 (2003): 99-103.
9. Melchiorri, Loredana, et al. "Human leukocyte antigen-A,-B,-C and-DR alleles and soluble human leukocyte antigen class I serum level in Ménière's disease." Acta oto-laryngologica 122.5 (2002): 26-29.
10. Khorsandi, Mohammad-Taghi, et al. "Associations between HLA-C alleles and definite Meniere's disease." Iranian Journal of Allergy, Asthma and Immunology (2011): 119-122.
11. Chan, Kai-Chieh, et al. "Association of Meniere disease with human leukocyte antigen in Taiwanese population." Ear, Nose & Throat Journal 97.12 (2018): 396-402.
12. Psillas, G., et al. "Sudden bilateral sensorineural hearing loss associated with HLA A1-B8-DR3 haplotype." Case Reports in Otolaryngology 2013 (2013).
13. Xenellis, J., Morrison, A. W., McClowskey, D., & Festenstein, H. (1986). HLA antigens in the pathogenesis of Meniere's disease. The Journal of Laryngology & Otology, 100(1), 21-24.
14. Rauch, Steven D., et al. "Serum antibodies against heat shock protein 70 in Meniere's disease." The American journal of otology 16.5 (1995): 648-652.