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Protocol: A Systematic Review of Graves' Disease and its Interconnection with MHC Class II

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ABSTRACT

Graves' disease continues to be a problematic autoimmune thyroid condition debilitating patients with hyperthyroidism. HLAs play a central role in Graves' disease pathology, with a multitude of publications on specific HLAs linked to the condition. MHC class II, such as HLA-DQ and HLA-DRB1, are being more often mentioned, yet determining exact HLA that predispose an individual to Graves' disease can be conflicting. Through meta-analysis, data from research can be extracted and evaluated to find specific HLA-DRB1 and HLA-DQ with increased or decreased odds of Graves' disease; this has potential use in evaluating patient risk of later Graves'. Additionally, through finding a new value through meta-analysis, HLA with increased odds of Graves' may be studied further in future research to find how they play a role in pathology development.

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Introduction

4 Rationale

Through meta-analysis, data from research can be extracted and evaluated to find specific HLA-DRB1 and HLA-DQ molecules associated with increased or decreased odds of contracting Graves' disease; this has potential use in evaluating a patient's future risk of

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Graves'. Additionally, through finding a new value through meta-analysis, HLA genes with increased odds of Graves' may be studied further in future research to find how they play a role in pathology development.

Objectives

1. To determine the HLA-DRB1 genes which have higher or lower odds for Graves' disease development.

2. To investigate HLA-DQ (including HLA-DQA1 and HLA-DQB1) to determine which ones increase or decrease odds of Graves' disease development.

Methods

5 **Eligibility Criteria**

Only studies published after 1990 will be included in analysis. Studies which cannot be accessed, those which do not have all information needed to conduct a proper review of how data was gathered, or those with confusing, unintelligible, or difficult-to-interpret data are not used.

Information Sources

Databases used for this study include PubMed and Google Scholar. No attempt will be made to contact authors for access to articles, but institutional access will be used when available for journals which may not be open access. Data will be gathered for approximately a few weeks to a month.

Search Strategy

Searching will be conducted using the following terms: "HLA and Graves' disease", "Graves' disease and HLA-DRB1", "Graves' disease and HLA-DQA1" and "Graves' disease and HLA-DQB1". When available, searches required both the HLA and Grave's disease to both appear in the article as a limitation of the search. One researcher, Dylan Thibaut, was assigned the role of searching and collecting data.

6 **Study Records**

Data Management:

All data collected during the search will be compiled in Excel sheets for analysis with statistical software. This will be shared with other researchers on the project.

Selection Process:

Studies are selected based on their ability to contain all relevant data items or enough data to calculate the data items, on the explained methods as to how the data was collected somewhere in the publication, and that the study was accessible. A minimum of three articles are necessary to include an HLA for meta-analysis.

Studies are excluded if they do not contain the data necessary for forest plot meta-analysis, if the data does not compare Graves' disease to controls in some way with an HLA, and if the study is outside of the set minimum year requirement. Studies with exorbitantly large confidence intervals for their odds ratios are additionally excluded.

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Data Collection Process:

Data is individually collected by one researcher on one Excel sheet. If there is a question regarding the legitimacy of the data or the numbers themselves, it is presented to the other researchers on the study. If the other researchers still have trouble making a determination, the PI is consulted for final say.

Data Items:

Data items collected include number of cases of Graves' disease with the associated HLA, total number of cases with Graves' disease, number of healthy controls with the HLA, and total number of healthy controls. Odds ratios and confidence intervals were found from this data as part of the analysis.

7 Outcomes and Prioritization

Data will be gathered to meet the objectives of the study. HLA are included based on having at least three eligible studies for analysis. HLA outside of HLA-DRB1, HLA-DQA1, and HLA-DQB1 are not included. Additional overall analysis of all HLA-DRB1, all HLA-DQA1, and all HLA-DQB1 will also be performed as a secondary analysis to see if there is an overall trend across the HLA groups.

Risk of Bias in Individual Studies

Risk of bias is assessed through the NIH Quality Assessment Tool of Case Control Studies (cited below).

National Heart, Lung, and Blood Institute. Study Quality Assessment Tools. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Updated 2021 July.

8 Data Synthesis

A: Revman 5.4 software (cited below) will be used for statistical analysis. Case number with each HLA, case total, control number with each HLA, and control total will be inputs for forest plot creation and analysis.

B: Odds ratios and their confidence intervals will be assessed to form a single, combined odds ratio and confidence interval. Data will be assessed with I^2 as a measure for heterogeneity, though other measures may additionally be included.

C: In the case of multiple of the same HLA type (HLA-DQA1*0301 and HLA-DQA1*0501 as an example combined to see if HLA-DQA1 overall has an effect), a subgroup analysis can be performed to assess the overall HLA in its totality. Sensitivity analysis may be performed via Revman or other software such as MetaXL.

D: See above.

Review Manager (RevMan) [Computer Program]. Version 5.4, The Cochrane Collaboration, 2020.

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9 Meta-bias and Confidence in Cumulative Evidence

GRADE criteria will be used (cited below).

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004 Jun 19;328(7454):1490. doi: 10.1136/bmj.328.7454.1490. PMID: 15205295; PMCID: PMC428525.

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