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Abstract

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Introduction: Pigeon Breeder's Pneumonitis (PBP) results due to a complex pathophysiology that includes exposure to avian antigens. Susceptibility has been linked to human leukocyte antigen (HLA) class II, though consensus has not been reached. The goal of this systematic review is to further elucidate the association between PBP and HLA-DR subtypes.

Methods: Databases utilized included PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Inclusion required a minimum of three studies in English presenting HLA-DR alleles of PBP and control subgroups. Exclusion was due to insufficient data or non-feasible control groups. Forest plots were created for HLA-DR subtypes' association with PBP. The NIH Bias assessment tool and LFK index assessed bias.

Results: 4 studies were included in the meta-analysis. HLA-DR3 was associated with the pooled PBP subgroups (OR=1.86 [1.13, 3.05], p

Discussion: Limitations included limited sources, with multiple study methodology unacceptable to this review. These findings expand on previous research on HLA variants and PBP frequency, and offer further clarity supporting novel approaches in treatment of PBP.

Keywords

human leukocyte antigen, Hypersensitivity Pneumonitis, Pigeon Breeder's Pneumonitis, HLA-DR1, HLA-DR3, meta-analysis

Conflict of Interest Statement

Conflict of Interest/Financial Disclosure The authors have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest to disclose.

META-ANALYSIS/SYSTEMATIC REVIEW

Extrinsic Allergic Alveolitis: A Systematic Review of HLA-DR in Pigeon Breeder's Disease

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Abstract

Introduction: **Pigeon Breeder's Pneumonitis (PBP) results due to a complex pathophysiology that includes exposure to avian antigens. Susceptibility has been linked to human leukocyte antigen (HLA) class II, though consensus has not been reached. The goal of this systematic review is to further elucidate the association between PBP and HLA-DR subtypes.**

Methods: **Databases utilized included PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Inclusion required a minimum of three studies in English presenting HLA-DR alleles of PBP and control subgroups. Exclusion was due to insufficient data or non-feasible control groups. Forest plots were created for HLA-DR subtypes' association with PBP. The NIH Bias assessment tool and LFK index assessed bias.**

Results: **4 studies were included in the meta-analysis. HLA-DR3 was associated with the pooled PBP subgroups (OR=1.86 [1.13, 3.05], p<0.05), while HLA-DR1 was inversely associated with the PBP subgroups (OR=0.48 [0.27, 0.83], p<0.05). Both had low heterogeneity. No other HLA-DR alleles were found to have significance.**

Discussion: **Limitations included limited sources, with multiple study methodology unacceptable to this review. These findings expand on previous research on HLA variants and PBP frequency, and offer further clarity supporting novel approaches in treatment of PBP.**

Keywords: Human leukocyte antigen, Hypersensitivity pneumonitis, Pigeon breeder's pneumonitis, HLA-DR1, HLA-DR3, Meta-analysis

1. Introduction

Hypersensitivity Pneumonitis (HP) encompasses an array of disorders that are primarily interstitial lung pathologies typically triggered by the inhalation of antigenic organic compounds. These disorders involve a genetic and immunological predisposition to a substance, as well as the environmental exposure to specific substances. This exposure leads to a pathological insult to the alveolar walls, thus this disorder is also known as "extrinsic alveolar alveolitis".[1,2]

HP is subdivided based on the organic particle (<5 microns in size) that triggers the immunologic pathology. Farmer's Lung HP (moldy hay actinomycete spore), Pigeon Breeder's Lung HP (avian proteins), and Humidifier Lung HP (multiple actinomycete spores) are the most described of the pneumonitis types, with Pigeon Breeder's Pneumonitis (PBP) being the most prevalent of the HP.[3,4] The specific protein antigens in PBP has been described in previous work to include immunoglobulin lambda-like polypeptide 1, pigeon γ-globulin, pigeon serum albumin, and pigeon β-globulin.[5] These antigens in PBP have been shown to affect upper lung field alveolar walls in the form of "diffuse centrilobular nodules, ground glassing - diffuse or patchy predominant in upper lobes, fibrosis with or without traction bronchiectasis, honeycombing, and mediastinal lymphadenopathy".[6,7]

PBP, and all HP as a class, involve two types of hypersensitive responses. The immune complexes

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developed by the bird antigens activate complement and a neutrophilic response as a type III hypersensitivity. At the same time, continued exposure elicits a cell-mediated response that exaggerates a TH2 response that is thought to be a potential cause of the fibrotic effect on lungs that is shared among chronic HP subtypes.[8]

Human Leukocyte Antigens (HLAs) are integral components of immune responses, as they code the major histocompatibility complexes (MHCs) that center the antigen presenting proteins in every nucleated cell in the human body. The polygenicity and polymorphisms encoding the HLA-MHC axis is a core component of the immune system's ability to adapt and equip a diverse immune response to potential threats.[9]

However, this HLA-MHC axis has been attributed to cause autoimmune consequences in previous literature, such HLA-DR4 alleles association with Rheumatoid arthritis (R.A.), polymyalgia rheumatica (P.M.R.), and Type 1 Diabetes Mellitus (T1DM).[10-12]

PBP affects a more exclusive population than R.A., PMR, or T1DM and likely requires both the environmental exposure and genetic components. Selman and colleagues determined HLA-DR7 to be associated with a relative risk of developing PBP to be 4.79.[13] Another example would be Rittner et. al who found a significant association of HLA-DR3 and PBP.[14] This systematic review and meta-analysis is a retrospective analysis of the association between the subtypes of HLA-DR alleles and the development of PBP.[13]

This HLA meta-analysis with pigeon breeder's pneumonitis will offer a comprehensive analysis of HLA-DR alleles to aid in the earlier identification of disease. The earlier identification of genetic predispositions, especially in families with multiple instances of disease, can offer an opportunity for earlier medical, social, and environmental interventions.

2. Methodology

Inclusion and exclusion criteria for the analysis were set prior to starting the research via an agreed upon protocol.[15] Inclusion criteria required that a minimum of three studies meet criteria to provide data for the HLA-DR serotype to be analyzed. Each study was required to have data including PBP cases with the HLA-DR, total PBP cases, controls with the HLA-DR, and total controls. Additionally, only studies available in English were included. To be included, the serotype needed to have data available: the serotype was used rather than individual alleles alone, as inclusion of single alleles would not adequately cover the serotype. This was chosen to avoid double counting, as adding up multiple alleles together could lead to one person being counted twice (as there are inherited genes from both parents). Studies which lacked adequate data for analysis of individual serotypes rather than single alleles were excluded. Additionally, studies published prior to 1975 were excluded.

Databases used for analysis included PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Two reviewers participated in data collection and sorting of articles. Values found through searching were compiled in a single document. If a disagreement occurred, the data was shared to a third researcher for a decision. If an agreement could not be reached, the article was sent to the PI of the project for final decision as to whether it should be included. Once compiled onto the shared document and articles were fully searched, the data was put into statistical software separately by two researchers. Once separately completed, the results were compared to make sure the analysis was correctly performed from the data and that both researchers got equivalent results.

Bias assessment was performed via the NIH bias assessment tool.[16] Studies were assigned bias as poor, fair, or good depending on the results of the bias analysis. Effect measurements to evaluate meta-analysis results were determined by odds ratio and 95% confidence interval. If the odds ratio was not listed in the study, it was calculated from the data available in the study. Studies which met inclusion and exclusion criteria requirements with adequate data for odds ratio and confidence interval were compiled in Revman software for analysis.[17] Results were displayed using a forest plot generated by the statistical software. Heterogeneity was assessed using I^2 with $I^2 \leq 25\%$ as indicative of low heterogeneity. MetaXL was used to calculate LFK index as an additional measure of bias as well as sensitivity analysis.[18]

3. Results

PRISMA guidelines were utilized in selecting the studies used in this meta-analysis; this is shown in Fig. 1. A total of 1060 records were identified from searching PubMed, Google Scholar, ScienceDirect, and Cochrane Library. Before screening by the abstract, 146 articles were removed as they were not published in English. 914 articles were screened by

abstract, 713 of those abstracts were not specific to PBP, and 6 were duplicate studies, these were removed. 120 of the remaining 195 articles were removed due to insufficient data on the HLA-DR alleles, or data that was not usable for the present meta-analysis. 68 articles were then removed as they did not contain the answer to the research question. After the screening process, 4 articles were used for this meta-analysis.

The NHLBI quality assessment tool was utilized to assess the four included studies for internal validity and is summarized in Table 1. 3 of the 4 studies were considered "good".[13,14,19] These studies' data have high probability to produce risk factors and outcomes that represent true associations not invalidated by internal flaws in study design. These studies typically outlined the gender, ethnicity, location, but may have lacked the population age distribution. All the studies assessed did not provide any sample size justification which would have ensured the study had an adequate power for association determination. One study was considered to be "fair".[20] In addition to similar flaws among the "good" group, this study did not adequately distinguish their "symptomatic pigeon breeders" vs "asymptomatic pigeon breeders". The possibility that genetically related individuals were part of both case and control group creates the possibility of bias within population selection.

Four studies were included for analysis across seven serotypes (DR1, DR2, DR3, DR4, DR5, DR6, and DR7). A total of 155 PBP and 447 controls were compared for analysis.[13,14,19,20] Analysis findings are summarized in Table 2. Only two of the seven serotypes were found to have significance and low heterogeneity ($I^2 \leq 25\%$) on analysis: HLA-DR1 and HLA-DR3. Odds of PBP was decreased in patients with DR1 compared to controls (OR = 0.48 [0.27, 0.83], $I^2 = 0\%$, $p = 0.009$) while it was increased in patients with DR3 compared to controls (OR = 1.86, [1.13, 3.05], $I^2 = 14\%$, $p = 0.01$). Forrest plots for analyses are found in Fig. 2.

4. Discussion

It is estimated that the prevalence of PBP amongst those with high avian exposure is 20 to 20,000 people per 100,000 people at risk.[21] The disparities in prevalence can be attributed to varying diagnosis criteria, different climates, aviation breeds, smoking exposure, and exposure intensity.[22] The majority of individuals with high avian exposure do not develop symptoms of PBP, indicating a high possibility of a genetic susceptibility in those affected.[23] The findings of this meta-analysis show an increased frequency of the HLA-DR3 allele ($p < 0.01$) and a decreased frequency of the HLA-DR1 allele ($p < 0.009$) in populations with PBP. This suggests the presence of HLA-DR3 as a risk factor for PBP, and the presence of HLA-DR1 as a protective factor for PBP.

Previous research has also shown the HLA-DR3 allele has a higher frequency in a variety of autoimmune conditions, such as T1DM, myasthenia gravis, and celiac's disease.[14,24-26] Additionally, research on the HLA A1-B8-DR3 allele as contributing to polymorphisms within the TNF-alpha gene as a significant risk factor towards autoimmunity is a complementary observation to the current meta-analysis conclusions. This allele has been associated with other autoimmune diseases such as insulin-dependent diabetes mellitus, systemic lupus erythematosus, Graves' disease, autoimmune chronic hepatitis, celiac disease and others.[27-29] Although not the goal of the current meta-analysis on HLA-DR alleles, future research should include investigation of the HLA A1-B8-DR3 alleles with the array of HP subtypes.

Previous research has begun to show connections between cases of coexistence of PBP and other autoimmune conditions. In one instance, leukocytoclastic vasculitis with PBP was discovered and subsequently treated with corticosteroids in an individual with avian exposure; the conclusion that there may exist a link between vasculitis and PBP.[30,31] Another study on hypersensitivity pneumonitis as a whole found a significant association with the haplotype allele DRB1*03:01-DQB1*02:01, which has been previously described as a major genetic determinant of autoimmune pathologies.[32-35] Further research on the instance of DRB1*03:01-DQB1*02:01 allele in multiple subtypes of hypersensitivity pneumonitis including PBP would be of importance.

Further complicating the standard gene-exposure-disease sequence theory is the possibility that antibodies coded by genetic predisposition may require another precipitating trigger. Muers et al. hypothesized a viral activation of antibodies may be required to prime the pre-existing antibodies to react to the bird antigens in PBP, a potential limitation among existing literature. A potential confounding factor described by Muers et al., is the previously described association with HLA-DR3 allele with celiacs disease patients, whose pathology can include pulmonary fibrosis. Celiac disease patients may produce beta globulin antibodies to consumed egg yolk, that are identical to beta

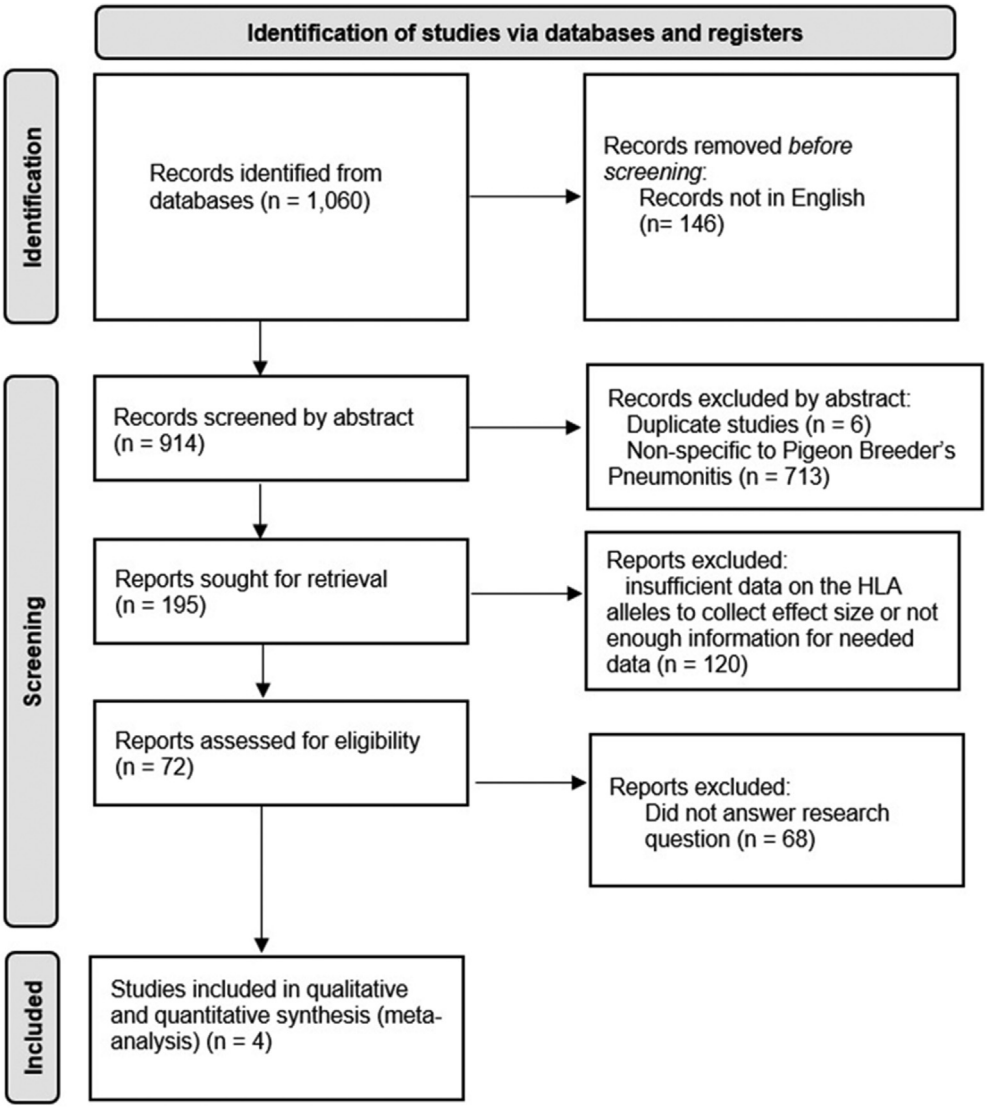

Fig. 1. Search flow diagram.

Table 1. Bias assessment.

Study	Case Total	Control Total	Sample	Bias	1	2	3	4	5	6	7	8	9	10	11	12
Selman et al., 1987	48	200	Mexican	G	Y	Y	N	Y	Y	Y	–	Y	Y	Y	Y	Y
Rittner et al., 1983	52	64	Caucasian	G	Y	Y	N	N	Y	Y	–	Y	Y	Y	Y	Y
Muers et al., 1982	23	154	Caucasian	G	Y	Y	N	Y	Y	Y	–	Y	Y	Y	Y	Y
Rodey et al., 1978	32	29	Caucasian	F	Y	N	N	Y	Y	N	–	Y	N	Y	Y	Y

Table 2. Meta-analysis results.

HLA	Case	Total	Control	Total	OR [95% CI]	Association	I^2	LFK
DR1	19	155	97	447	0.48 [0.27, 0.83]	↓	0%	−2.04
DR2	47	155	91	447	1.51 [0.96, 2.36]	↔	0%	−1.89
DR3	51	155	87	447	1.86 [1.13, 3.05]	↑	14%	−1.17
DR4	47	155	177	447	0.98 [0.45, 2.11]	↔	67%	0.91
DR5	22	155	72	447	0.76 [0.42, 1.39]	↔	15%	2.01
DR6	14	103	63	383	0.67 [0.32, 1.42]	↔	0%	−0.36
DR7	42	155	94	447	1.36 [0.44, 4.21]	↔	81%	−1.19

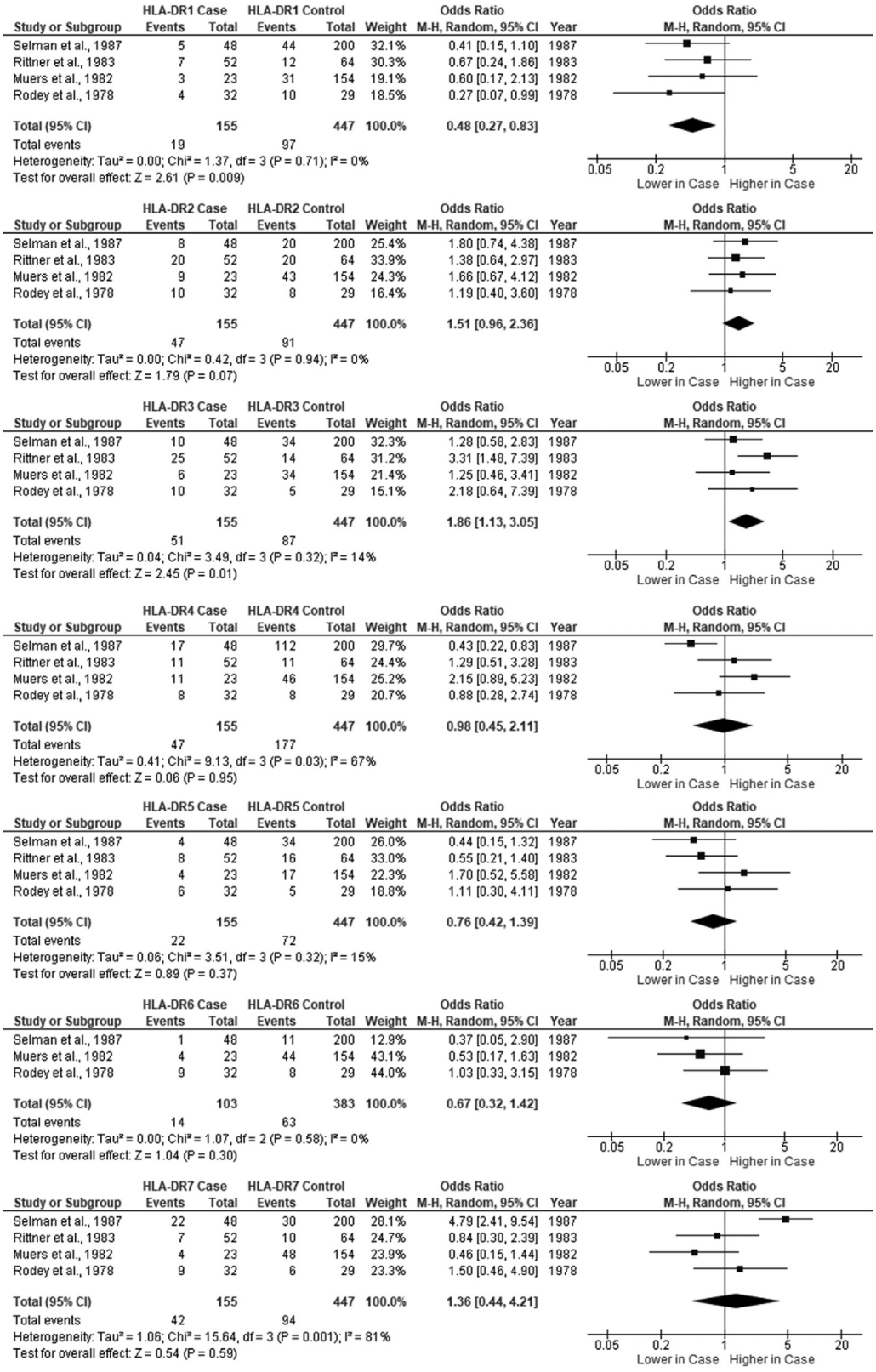

Fig. 2. Forrest plot results.

globulins against avian sera in PBP. Therefore, the HLA-DR3 allele association in PBP may be over-represented due to the possibility of comorbid celiacs disease.[19]

By continuing to analyze genetic predispositions including HLA alleles towards the array of HP's, prognostic and therapeutic opportunities for earlier intervention will be a possibility as genomic healthcare becomes more accessible to the public. Naturally, the base advantage of patient's understanding their genetic predisposition in PBP is the opportunity for earlier antigen avoidance, and reducing other pulmonary misdiagnoses that often prelude an eventual HP diagnosis.[35] In families with strong predispositions towards hypersensitivity pneumonitis, it is reasonable to avoid prolonged exposure to antigens if the patient is found to possess the HLA-DR3 allele. Earlier diagnosis using the HLA-DR3 allele and thus permissively earlier treatment with glucocorticoids can allow for reduction in morbidity associated with HP interstitial pathophysiology.

Limitations of this study include lack of consistency and reproduction of data on the PBP. Although every serotype of HLA allele found during search was recorded, only the HLA-DR alleles had sufficient data for an appropriate analysis. Further, unacceptable variations in the methodology of otherwise appropriate studies included studies that only provided genotypic frequencies or studies whose control group consisted of relatives of PBP affected individuals.

5. Conclusion

This meta-analysis examined 4 previous studies of PBP and the frequencies of HLA-DR1-7 alleles variants. Based on the findings, PBP has a significant positive association with the HLA-DR3 allele and a significant negative association with the HLA-DR1 allele.

Conflict of Interest/Financial Disclosure

The authors have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest to disclose.

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