

# COPD Exacerbator Phenotype is Inversely Associated with Current Smoking But Not with Haptoglobin Phenotype

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**ABSTRACT:** **Background:** Frequent chronic obstructive pulmonary disease (COPD) exacerbators are at a higher risk of adverse health outcomes when compared to infrequent exacerbators. A COPD frequent exacerbator phenotype and its definition has been reported. Haptoglobin (Hp) polymorphism has been associated with differing clinical outcomes in cardiovascular and renal disease. The Hp 2-2 phenotype has been found to have bacteriostatic properties, while the Hp 1-1 phenotype was found to be associated with infections.

**Objectives:** To determine the correlation in haptoglobin phenotypes and the frequent exacerbator status compared to COPD non-exacerbators.

**Methods:** Inclusion criteria included previous diagnosis of COPD and presence of at least two documented exacerbations of COPD in the previous 12 months (frequent exacerbator group) or absence of such exacerbations in the previous 24 months (non-exacerbator group). Descriptive data were analyzed using Fisher's exact test and the non-parametric Kruskal–Wallis test. Multivariate logistic regression analysis was performed.

**Results:** The multivariate logistic regression yielded a model in which haptoglobin phenotype did not have a statistically significant association with frequent exacerbator status. Smoking status was found to be negatively related with the frequent exacerbator status (odds ratio [OR] 0.240, 95% confidence interval (95%CI) 0.068–0.843,  $P = 0.03$ ). Number of pack-years was negatively related to being a frequent exacerbator (OR 0.979, 95%CI 0.962–0.996,  $P = 0.02$ ).

**Conclusions:** We found no relationship between haptoglobin polymorphism and frequent exacerbator status. However, frequent exacerbator status had a statistically significant association with COPD Assessment Test scores and pack-years and a negative correlation with current smoking status.

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**KEY WORDS:** chronic obstructive pulmonary disease (COPD), cigarette smoking, haptoglobin, Hp 1-1 phenotype

An acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is characterized by an increase in the frequency and intensity of chronic obstructive pulmonary disease (COPD). Symptoms include dyspnea, sputum production, and cough [1]. The occurrence of COPD has severe health implications for patients and has been associated with poor health, as well as an increase in mortality [1,2]. In particular, frequent exacerbators, defined as those who present with two or more acute exacerbations in one year [3], report decreased quality of life when compared to infrequent exacerbators [4]. Furthermore, greater pressure is placed on the larger healthcare system through extended hospital stays and higher costs [2]. Therefore, effective treatment and prevention towards frequent exacerbators has become a subject of great interest to researchers [5].

Certain people seem to be more likely than others to become frequent exacerbators. Although exacerbation frequency increases as a given patient's disease worsens [6], no clear connection has been found between exacerbation frequency and the different disease severity groups. In the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, Hurst and colleagues [3] observed that a higher proportion of moderate COPD, as opposed to severe COPD, evolved to frequent exacerbation status. In fact, 29% of those with severe COPD were deemed resistant to exacerbations altogether. Meanwhile, a history of previous exacerbations was the most significant factor associated with exacerbation frequency. Thus, researchers have been studying whether there is a COPD frequent exacerbator phenotype and determining what the definition of such a phenotype should be.

It is important to understand who is likely to become a frequent exacerbator because such patients may benefit from specific treatment plans. In a large, double-blind study [7], selective phosphodiesterase-4 inhibitors were effective in decreasing the frequency of moderate or severe exacerbations by 17% among patients with  $FEV_1 < 50\%$ . Previous exacerbations are now recommended for this indication [8]. Similarly, macrolides also reduce inflammation and may play a role in exacerbation treatment and prevention [9]. Evidence of effective measures to

reduce exacerbations makes it important to identify and treat individuals at risk for exacerbations.

#### HAPTOGLOBIN PHYSIOLOGY AND ITS IMPORTANCE IN VARIOUS DISEASE STATES

Haptoglobin (Hp) binds free hemoglobin in the blood. A major role of haptoglobin is to prevent hemoglobin and iron loss by renal excretion as well as prevent renal damage. Haptoglobin structure includes  $\alpha$  and  $\beta$  chains [10]. The  $\alpha$  chains are further separated into  $\alpha^1$ ,  $\alpha^1S$ , and  $\alpha^2$ . The alpha chains in Hp 1-1 are only those of  $\alpha^1$ . Hp 2-2 consists of only  $\alpha^2$  chains. Hp 2-1 contains both types of alpha chains. The three types of  $\alpha$  chains are encoded on the three alleles of the  $Hp\alpha$  gene found on chromosome 16q22 [11]. Haptoglobin is expressed in the liver. It binds hemoglobin in the blood and is then taken up by the CD163 scavenger receptor on Kupfer cells in the liver where it is broken down [12-14]. While this process protects the kidney from pigment nephropathy caused by hemoglobin, it also prevents the iron in hemoglobin from releasing the OH oxygen radical via the Fenton reaction [15]. The different haptoglobin phenotypes have varying utility as antioxidants according to their sizes. Because the  $\alpha^1$  chain is the smallest in size, the  $\beta$  chain is able to bind more hemoglobin [16]. Similarly, Hp 2-2 consists of the largest  $\alpha$  chains and therefore has the least antioxidant activity [14]. The Hp 2 allele, present only in humans, appears to have developed from the Hp 1 allele by a duplication of exons 3 and 4 of the Hp 1 allele approximately 100,000 years ago and has become more prevalent than the Hp 1 allele.

The protein product of the  $Hp$  gene is found in serum as a polymer of 2–10 covalently linked monomers. The haptoglobin multimerization domain is located in exon 3 of the  $Hp$  gene that is duplicated in the Hp 2 allele. It is found as a dimer in Hp 1-1 individuals, a linear polymer in Hp 2-1 individuals (2–8 monomers), and a cyclic polymer (3–10 monomers) in Hp 2-2 individuals. This size enables determination of the Hp phenotype by electrophoresis of haptoglobin in serum. In most Western civilizations, the distribution of Hp phenotypes is as follows: Hp 1-1 (16%), Hp 2-1 (48%), and Hp 2-2 (36%) [17].

Haptoglobin polymorphism plays a role in renal diseases as well as infectious diseases. The Hp 2-2 phenotype is predictive of chronic renal failure as well as end-stage renal disease in patients with diabetes [18,19]. These poorer outcomes are likely due to the decreased antioxidant activity of Hp 2-2. In relation to infectious diseases, bacterial proliferation depends on the acquisition of iron, which is prevented by haptoglobin [20]. According to this mechanism, the Hp 1-1 phenotype has more effective antibacterial properties. However, Hp 2-2 has been shown to have bacteriostatic characteristics when in the presence of *Streptococcus pyogenes*. Specifically, Hp 2-2 binds the T4 antigen, which leads to agglutination and clumping of the bacteria [14]. In addition to these two major antibacterial associations, the Hp 1-1 phenotype has been demonstrated

experimentally to allow for more robust growth of *H. influenzae* compared to Hp 2-1 and Hp 2-2 [21].

In light of these findings and the tendency for infection among carriers of Hp 1-1 and because 70 to 80% of exacerbations are associated with bacterial or viral infections [22], we hypothesized that the Hp 1-1 phenotype would be more prevalent among COPD patients who are frequent exacerbators. The aim of our study was to test the correlation between haptoglobin phenotypes and the frequent exacerbator status compared to COPD non-exacerbators. A secondary endpoint was to test other clinical variables between COPD frequent exacerbators and non-exacerbators.

## PATIENTS AND METHODS

### STUDY POPULATION

We asked COPD patients to participate in this study during their regularly scheduled visits to a referral clinic at Carmel Medical Center. After receiving permission, data were extracted from their medical charts. Inclusion criteria for the non-randomized case control study included a previous diagnosis of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [9], FEV<sub>1</sub> < 60% predicted, and presence of either at least two documented exacerbations of COPD in the previous 12 months (frequent exacerbator group) [1] or absence of such exacerbations in the previous 24 months (non-exacerbator group). Two separate intervals were chosen for the two groups to decrease the likelihood of misclassification. An exacerbation was defined as a worsening of symptoms that led to treatment with antibiotics with or without systemic glucocorticoids. To be considered separate events, exacerbations had to occur at least 21 days apart. Exacerbations, although not of frequent exacerbator status, were noted in the medical charts.

Patients with lung cancer, tuberculosis, pulmonary fibrosis, asbestosis, organ transplantation, lung volume reduction surgery, or previous lung resection were excluded. After giving informed consent, patients answered a COPD Assessment Test (CAT) questionnaire [23], and blood was drawn for haptoglobin phenotype assessment. Data regarding demographic variables, smoking status, pack-years, lung function, and medications were recorded from available patient files. A second cohort included patients with retrospective data. The analysis contained a power of 13.5% and required 1026 participants to achieve 80% power.

### DETERMINATION OF HP PHENOTYPE

Haptoglobin phenotype from patient sera was obtained through gel electrophoresis as described in detail by Levy and colleagues [17].

### CLINICAL AND SPIROMETRIC DATA

Data included smoking status, number of pack-years smoked, FEV<sub>1</sub> as percent of predicted FEV<sub>1</sub>/FVC post-bronchodilator,

concomitant medications, CAT score, and cough and sputum questions within the CAT [23]. Spirometry was performed prior to patient recruitment for the study. Categorical variables were analyzed using Fisher's exact test and continuous variables were assessed using the nonparametric Kruskal–Wallis test. A multivariate logistic regression analysis was performed with frequent exacerbator status as the dependent variable and haptoglobin phenotype as the variable of interest. Statistical analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA).

The study protocol was approved by the Carmel Helsinki committee (approval no. 0121-12-CMC) and registered with the ClinicalTrials.gov Identifier NCT01745419.

**RESULTS**

We recruited 105 COPD patients between 2 January 2013 and 11 January 2015. Four patients were excluded from the study because of a misdiagnosis of COPD, leaving 101 patients for the final analysis. The frequent exacerbator group comprised 51 patients, and the non-exacerbator group included 50 patients. Patient characteristics were analyzed according to haptoglobin phenotype [Table 1]. We found no significant differences in patient characteristics for any variable between the different haptoglobin phenotypes.

We performed a multivariate logistic regression [Table 2] in which 16 participants were not included due to incomplete data. Of the 16 participants excluded, 6 were frequent exacerbators. In this model, a high CAT score, being a past smoker (vs. current smoker), and a lower number of pack-years of cigarettes were predictive of the frequent exacerbator status. Haptoglobin phenotype was not predictive of frequent exacerbator status in this study. Interestingly, frequent exacerbator status was significantly and negatively associated with current smoking status (odds ratio [OR], 0.240, 95% confidence interval [95%CI] 0.068–0.843, *P* = 0.03) and pack-years (OR 0.979, 95%CI 0.962–0.996, *P* = 0.02).

Due to the outcome regarding smoking status and pack-years, we performed a secondary analysis to verify that the results were similar with a larger sample set. To this end, we recruited an additional 44 patients using the same criteria applied to previous participants. Haptoglobin phenotype was not assessed for these new participants. Of the total 145 patients, 94 fulfilled the criteria for frequent exacerbators and 51 were non-frequent exacerbators reflecting the seemingly low prevalence of non-frequent COPD exacerbators in the local population. Table 3 describes patient characteristics for the new sample according to exacerbator status. As with the previous sample, a significantly higher proportion of non-exacerbators vs. frequent exacerbators were current smokers. Haptoglobin phenotype, CAT scores, and pack-years data were scarce for this group and were not included in a multivariate

**Table 1.** Characteristics of the patients according to haptoglobin phenotype (primary cohort)

	Total N=101	Hp 1-1 N=9	Hp 2-1 N=38	Hp 2-2 N=54	P value
Age, mean ± SD, years	70.94 ± 9.0	73.22 ± 9.3	70.79 ± 8.2	70.67 ± 9.6	0.730
Current smoker, n (%)	27 (26.7)	1 (11.1)	11 (28.9)	15 (27.8)	0.601
Pack-years smoked, median (range)	n=92 50 (6–200)	n=8 60 (40–120)	n=38 50 (15–200)	n=46 50 (6–179)	0.675
FEV <sub>1</sub> after bronchodilator use (% of predicted value), mean ± SD	44.6 ± 11.1	42.11 ± 8.9	45.08 ± 11.3	44.7 ± 11.4	0.729
FEV <sub>1</sub> /FVC after bronchodilator use, mean ± SD	n=100 50.59% ± 9.6	n=9 49.18% ± 7.6	n=38 49.84% ± 9.5	n=53 51.26% ± 10.1	0.712
COPD assessment test	n=93 21.02 ± 9.2	n=9 22.33 ± 8.9	n=37 21.59 ± 9.9	n=47 20.32 ± 8.8	0.606
Frequent exacerbator, n (%)	51 (51.5)	6 (66.7)	19 (50.0)	26 (48.1)	0.663

FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, SD = standard deviation

**Table 2.** Factors associated with frequent exacerbator status in the multivariate logistic regression model (N=85\*)

Factor	Odds ratio estimates (95% confidence interval)	P value
Hp 1-1**	2.275 (0.296–17.477)	0.43
Hp 2-1**	0.568 (0.184–1.757)	0.33
Current smoker	0.257 (0.071–0.927)	0.04
Pack-years	0.979 (0.961–0.996)	0.02
COPD assessment test	1.155 (1.069–1.248)	< 0.001
Chronic treatment with aspirin	0.325 (0.096–1.097)	0.07
Chronic treatment with statins	2.258 (0.646–7.889)	0.20

\*Because of incomplete data, not all 101 participants could be included in the multivariate analysis

\*\*Hp 1-1 and Hp 2-1 estimates are relative to Hp 2-2

**Table 3.** Characteristics of the patients according to exacerbator status (secondary cohort)

	Total N=145	Frequent N=94	Non-exacerbator N=51	P value
Age, mean ± SD, years	70.81 ± 9.87	71.46 ± 10.62	69.61 ± 8.3	0.184
Current smoker, n (%)	36 (24.8)	17 (18.1)	19 (37.3)	0.027
Pack-years smoked, median (range)	n=112 50 (6–200)	n=71 54 (15–150)	n=41 55 (6–200)	0.388
FEV <sub>1</sub> after bronchodilator use (% of predicted value), mean ± SD	45 ± 12	45 ± 13	46 ± 9	0.359
FEV <sub>1</sub> /FVC after bronchodilator use, mean ± SD	n=135 52.20% ± 9.8	n=85 51.67% ± 9.9	n=50 53.09% ± 9.7	0.431
COPD assessment test	n=94 20.88 ± 9.2	n=48 23.85 ± 8.8	n=46 17.78 ± 8.8	0.001

FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, SD = standard deviation

**Table 4.** Factors associated with frequent exacerbator status in the multivariate logistic regression model (secondary cohort, N=132)

Factor	Odds ratio estimates (95% confidence interval)	P value
Current smoker	0.377 (0.167–0.849)	0.02
Chronic treatment with aspirin	0.592 (0.272–1.289)	0.25
Chronic treatment with statins	0.986 (0.450–2.162)	0.84

logistic regression model. The results of the model [Table 4], which included 132 patients, demonstrated a negative association between current smoking status and frequent exacerbation status (OR 0.377, 95%CI 0.167–0.849,  $P = 0.02$ ).

## DISCUSSION

We did not find a significant relationship between haptoglobin polymorphism and frequent exacerbator status. In a recent study of patients with cystic fibrosis, we found no significant correlation between haptoglobin phenotype and infectious complications [24]. Despite its importance, haptoglobin may not be an important contributor to airway uptake of hemoglobin and iron, which may explain the lack of effect of haptoglobin phenotype in these two studies.

This analysis was significantly impacted by limited power (power of 13.5% to detect a significant difference between Hp 1-1 and other Hp types) due to the small sample size of the Hp 1-1 group. Similar to previous estimates, only 9% of total participants presented with the Hp 1-1 phenotype [17]. Interestingly, 66% of the Hp 1-1 group included frequent exacerbators compared to 50% in the other haptoglobin phenotype groups. In the multivariate analysis, the Hp 1-1 phenotype group yielded an odds ratio of 2.275,  $P = 0.43$ . A sample size of 1026 participants would have been required to achieve 80% power. Furthermore, because haptoglobin phenotype varies according to different ethnicities [11], future studies may consider accounting for each participant's country of origin.

The main finding of our study was the negative association between current smoking and frequent exacerbations. The impact of smoking status and number of cigarettes smoked on frequent exacerbator status supports the hypothesis that certain people are susceptible to exacerbations due to factors irrespective of smoking history. Our analysis, paradoxically, found that those who continued to smoke at the time of the study were less likely to be frequent exacerbators. Accordingly, the amount smoked (expressed in pack-years) was negatively associated with the likelihood of being a frequent exacerbator.

These findings are in contrast with those of Hurst and colleagues [3], who found a positive relationship between COPD severity and current smoking with exacerbation frequency in the ECLIPSE study. Our inclusion criteria of  $FEV_1 < 60\%$  may have caused this discrepancy. Patients included in the ECLIPSE

study in the lower lung function group (GOLD IV) were significantly less likely to be current smokers (28% in GOLD stage IV vs. 36–38% in GOLD II–IV,  $P = 0.016$ ) while they experienced significantly more exacerbations (47% had experienced 2 or more exacerbations vs. 22–33% in GOLD II–III,  $P < 0.001$ ).

It is possible that the negative correlation between current smoking and frequent exacerbations exists only among more severe patients. Simultaneity bias may explain this phenomenon in that those patients who are more prone to exacerbations quit smoking while patients who are less inclined toward exacerbations continue to smoke. Another potential explanation of the contradiction with ECLIPSE is the retrospective nature of our analysis. The cognitive reminder that exists in a prospective study may have decreased the amount of potentially overlooked exacerbations. An underestimation of the number of exacerbations due to recall error in patients and misdiagnosis by physicians may have led to similar results as in the ECLIPSE study [25]. Moreover, we did not assess the time elapsed since smoking cessation. It is therefore possible that some of the exacerbations were due to the short-term effects of smoking cessation.

The CAT score was predictive of the frequent exacerbator status, as has been demonstrated in previous studies, reflecting the impact of exacerbations on quality of life. Although they may be impacted by simultaneity bias, self-assessment tests such as these should be considered in future studies and models that seek to identify potential frequent exacerbators.

## CONCLUSIONS

We found a positive correlation between current smoking and being a non-exacerbator. More studies exploring the mechanism of this association are needed. Haptoglobin phenotype was not found to be associated with exacerbation status. Larger studies are needed to test whether the lack of effect is true.

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## Capsule

### IgE B cells unmasked

Immunoglobulin E (IgE) antibodies play a central role in immune responses against helminth and protozoan parasites; however, they also contribute to allergies. IgE antibodies (and the B cells generating them) are rare and thus poorly characterized. **Croote** and colleagues performed single-cell RNA sequencing of peripheral blood B cells from patients with peanut allergies and delineated each cell's gene expression, splice variants, and

antibody sequences. Unlike other isotypes, circulating IgE B cells were mostly immature plasmablasts. Surprisingly, certain IgE antibodies manifested identical gene rearrangements in unrelated individuals. These IgE antibodies showed high affinity and unexpected cross-reactivity to peanut allergens.

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Eitan Israeli

## Capsule

### Alarmin S100A11 initiates a chemokine response to the human pathogen *Toxoplasma gondii*

*Toxoplasma gondii* is a common protozoan parasite that infects up to one third of the world's population. Very little is known about innate immune sensing mechanisms for this obligate intracellular parasite by human cells. By applying an unbiased biochemical screening approach, **Safronova** and collaborators showed that human monocytes recognized the presence of *T. gondii* infection by detecting the alarmin S100A11 protein, which is released from parasite-infected cells via caspase-1-dependent mechanisms. S100A11 induced

a potent chemokine response to *T. gondii* engaging its receptor RAGE, and regulated monocyte recruitment in vivo by inducing expression of the chemokine CCL2. These experiments reveal a sensing system for *T. gondii* by human cells that is based on the detection of infection-mediated release of S100A11 and RAGE-dependent induction of CCL2, a crucial chemokine required for host resistance to the parasite.

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Eitan Israeli

“Every man is guilty of all the good he didn't do”

Voltaire (1694–1778), French philosopher