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GLCCI1 rs37973 does not influence treatment response to inhaled corticosteroids in white asthma subjects

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To The Editor:

Inhaled corticosteroids (ICS) are the primary anti-inflammatory therapy for the control and management of asthma, but their effects are characterised by some inter-individual variability that may have a genetic basis[1–4]. Identification of genetic markers that predict ICS treatment response will facilitate individualised treatment for asthma patients in the future, particularly in those with more severe disease. An association between genetic variation in *GLCCI1* and response to ICS therapy in non-Hispanic white asthma subjects was observed by Tantisira *et al.*[5] Genome wide association analysis of 118 trios (one asthmatic child and two parents) from the NHLBI Childhood Asthma Management Program (CAMP) identified 13 single nucleotide polymorphisms (SNPs) with evidence for association with the level of ICS treatment response. These 13 SNPs which included the *GLCCI1* promoter polymorphism rs37972, were genotyped and evaluated in four additional independent collections: adult studies SOCS (Salmeterol Or CorticosteroidS) and SLIC (SalmeteroL ± Inhaled CorticosteroidS) (n=264); a second adult study (n=385); LOCCS

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(Leukotriene modifier Or Corticosteroid or Corticosteroid-Salmeterol) (n=185) and CARE (Childhood Asthma Research and Education) (n=101). In three of the four replicate populations *GLCCI1* rs37973, a functional promoter polymorphism[5] in complete linkage disequilibrium with rs37972 in white populations, was associated (P<0.05) with change in FEV^1 (forced expiratory volume in one second) after 4–8 weeks of ICS treatment. The combined P value measuring association between rs37973 and ICS response over the four collections (n=935) was 0.0007. Tantisira *et al*. concluded that this functional *GLCCI1* polymorphism, rs37973, was associated with response to ICS in asthma patients.

Using data from a recently completed genome wide association study of response to steroid therapy, we sought to confirm this observation in a homogeneous, well-characterised population of n=1,924 non-Hispanic white subjects by testing for association between rs37973 and measures of corticosteroid response in subjects treated with either fluticasone furoate (FF) or fluticasone propionate (FP) in seven GSK-sponsored clinical trials (NCT01165138; NCT01134042; NCT01086384; NCT01159912; NCT00603382; NCT00603278; NCT00603746). All seven studies were randomised, double blind, placebo controlled, parallel group multicentre studies in adolescent and adult subjects and employed change from baseline in FEV^1 as their primary end-point, apart from HZA106837 which also investigated asthma exacerbations. HZA106837 (N=616) required each subject to have an asthma exacerbation within the 12 months prior to enrolment, whereas the other studies excluded subjects with previous asthma exacerbations. FEV^1 was assessed at week 8 for all studies except HZA106837, which used week 12 data. Overall, except for FF and FP dose, baseline demographics and study characteristics were similar across all seven studies (Table 1).

Germline DNA was extracted from peripheral blood collected from all 1,924 subjects all of whom provided consent for genetic analysis. Genotyping used either the KBiosciences Competitive Allele Specific PCR SNP genotype System (KASPar) (Hoddesdon, Herts, UK) or the Illumina Omni1-Quad panel (Expression Analysis, Durham, NC, USA). Analysis was undertaken in 1,916 subjects, including four with imputed data from rs37972. Eight subjects had missing covariate data.

Genetic association between rs37973 and ICS response was evaluated, with ICS treatment response defined as change from baseline in trough FEV^1 using the last observation carried forward (in any subject who did not complete the specific trial), to week 8 or week 12 of FF or FP treatment. Change in trough FEV^1 was regressed against covariates identified in this asthma population: age, percent of predicted baseline FEV^1, study, height, asthma duration and drug (FF versus FP). We also evaluated the influence of rs37973 on subject placement within the highest and lowest response quartiles. Subjects who fell into the lowest (n=479) and highest (n=479) response quartiles were identified. Logistic regression was used to fit a model with quartile of response as the dependent variable, and genotype and relevant covariates as the independent variables. The P value measuring heterogeneity among the seven studies was 0.98, allowing pooling of data at the subject level.

The minor allele frequency of rs37973 was 0.44 and its genotype frequencies were consistent with Hardy-Weinberg equilibrium (P=0.48). Covariate-adjusted FEV^1 change was regressed on rs37973 genotype (Figure 1). Rs37973 did not influence change from baseline in FEV^1 in this sample of 1,916 non-Hispanic white subjects treated with either FF or FP (P=0.15). However, this regression analysis suggested a trend toward a slightly lower ICS response for each additional copy of the rs37973 G allele. This direction of effect was consistent with that observed by Tantisira *et al*. In addition, the percentage change from baseline FEV^1 (unadjusted for covariates, results not shown) was 10.4±0.8% in AA

homozygotes and 8.8±1.0% in GG homozygotes, while the overall mean response was 9.8±0.4%.

This genetic marker did not influence subject membership within response quartiles (P=0.08, Odds Ratio (OR) =1.39, 95% CI 0.96–2.00). The ORs in each clinical study ranged from 0.61 (HZA106827) (N=616) to 4.42 (FFA112059), which is one of two smallest clinical trials, N=143 (Table 1). Meta-analysis of the influence of rs37973 on subject placement within response quartile across all seven clinical studies, revealed similar results to the subject level pooled data, suggesting a non-significant trend towards lower ICS response in *GLCCI1* rs37973 GG homozygotes, compared to AA homozygotes (P=0.11, OR 1.32, 95% CI 0.94–1.87). In order to closely mimic the analyses of Tantisira *et al* [5], change in trough FEV_1 was also regressed against age, sex and height. All analyses in our sample were repeated using these covariates; there were no qualitative differences between the two sets of results.

Asthma is currently estimated to affect ~315 million people worldwide[6]. A robust genetic predictor of ICS response in asthma patients would provide clinical value[7] as inter-individual variability in ICS treatment response is commonly observed. Tantisira *et al* [5] reported an association (P=0.0007) in a pooled analysis between *GLCCI1* rs37973 and ICS treatment response as measured over 4–8 weeks in 935 white non-Hispanic adults and children, and an OR of 2.36 in a subject level pooled analysis evaluating subject placement with response quartiles. In this larger sample set, n=1,916, drawn from seven clinical studies, we did not confirm *GLCCI1* rs37973 as a predictor of ICS response. However, the discrepant outcomes might have been due to various factors: the GSK studies were clinical trials specifically designed with FEV_1 change as the primary endpoint for all studies except one, whereas those of Tantisira were designed around a range of other primary endpoints, including lung growth, time to treatment failure and the percentage of asthma control days; paediatric study participants were only included in the initial Tantisira[5] cohort; and the duration of ICS treatment at the time of FEV_1 assessment varied between the two evaluations. Further genetic studies will be required to fully elucidate the potential role of *GLCCI1* in ICS treatment response in asthma patients.

Acknowledgments

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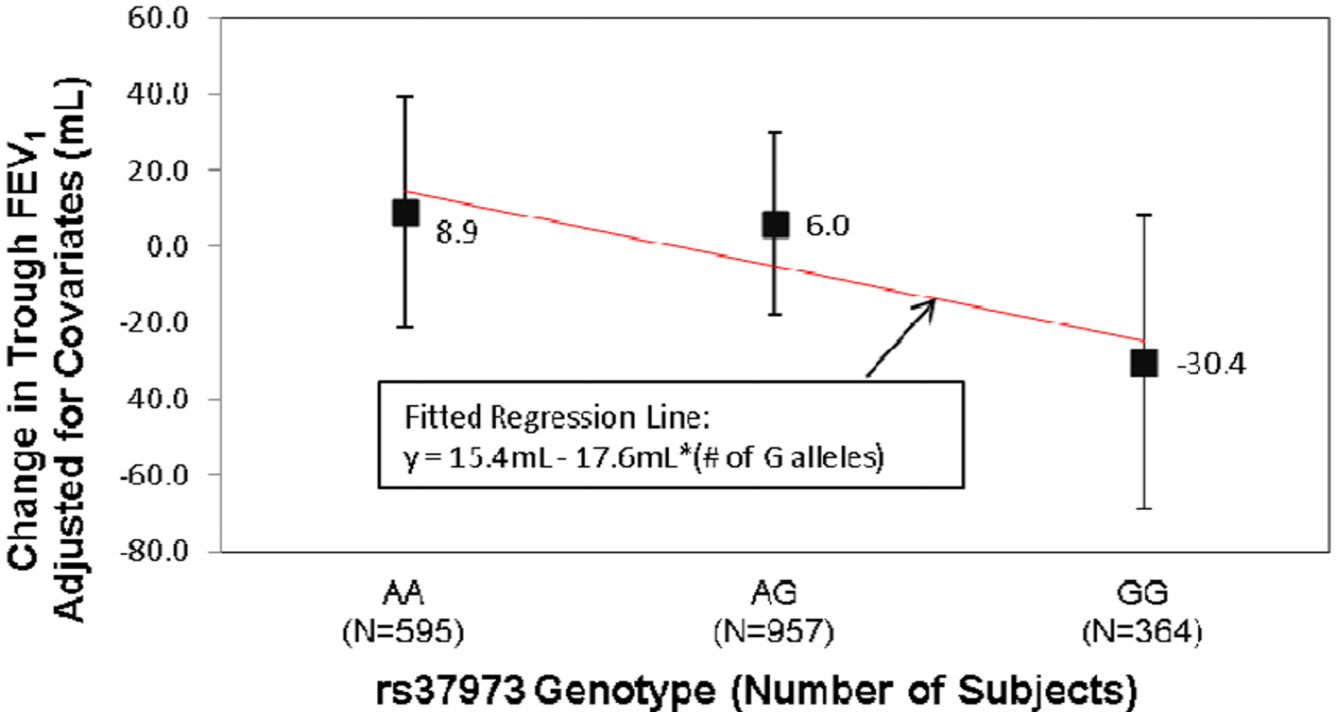

FIGURE 1.
GLCCI1 rs37973 genotype does not significantly influence steroid response in 1,916 asthma patients

TABLE 1

Baseline, demographic and steroid response characteristics in seven GSK-sponsored clinical studies

	Clinical Studies						
	FFA109684	**FFA109685**	**FFA109687**	**FFA112059**	**HZA106827**	**HZA106829**	**HZA106837**
Clinical Phase	**PIIb**	**PIIb**	**PIIb**	**PIIIa**	**PIIIa**	**PIIIa**	**PIIIa**
N	255	225	259	143	142	284	616
Age (years)	48.5 ± 13	42.1 ± 17.3	41.3 ± 15.9	42.4 ± 16.1	42.4 ± 16.0	47.3 ± 13.7	43.9 ± 16.5
Age of Onset (Years)	29.9 ± 17.9	25.0 ± 18.8	25.7 ± 18.5	25.3 ± 16.9	30.6 ± 18.5	33.6 ± 17.5	29.6 ± 18.1
FEV_1 at baseline (L)	2.3 ± 0.6	2.4 ± 0.6	2.4 ± 0.7	2.4 ± 0.7	2.3 ± 0.6	2.2 ± 0.7	2.3 ± 0.7
FEV_1 at baseline (% of predicted)	68.8 ± 11.5	73.7 ± 11.1	70.9 ± 12.2	72.5 ± 11.9	69.1 ± 10.4	66.3 ± 11.8	71.9 ± 10.5
Run-In period	28 day	28 day	28 day	4 weeks	4 weeks	4 weeks	2 weeks
Treatment on Run-In	ICS	ICS	non-CS	ICS	Asthma controller	ICS	FP or ICS
Sex (% female)	56.5	59.6	58.7	55.9	63.4	59.5	66.2
Height (cm)	168.7 ± 9.5	168.3 ± 9.6	168.6 ± 10.1	168.8 ± 10.4	167.6 ± 9.0	167.9 ± 9.9	166.2 ± 9.7
FF subject numbers	199	182	210	71	142	142	616
FF dose(s) mcg QD	200, 400, 600, 800	100, 200, 300, 400	25, 50, 100, 200	100	100	200	100
FP subject numbers	56	43	49	72	NA	142	NA
FP dose(s) mcg BD	500	250	100	250	NA	500	NA
Change FEV_1 *	0.18 ± 0.35	0.20 ± 0.42	0.29 ± 0.40	0.15 ± 0.36	0.33 ± 0.46	0.20 ± 0.44	0.19 ± 0.39
ANCOVA Parameter Estimate**	0.000 ± 0.030	−0.017 ± 0.036	−0.018 ± 0.033	−0.034 ± 0.043	0.008 ± 0.050	−0.007 ± 0.035	−0.031 ± 0.022
ANCOVA Estimate P value	1.00	0.64	0.57	0.43	0.87	0.85	0.16
GG to GA/AA Odds Ratio†	1.62	1.24	1.61	4.00	0.63	1.08	1.33
95% confidence interval	0.62–4.42	0.50–3.10	0.62–4.41	1.22–15.7	0.20–1.87	0.51–2.29	0.73–2.48
P value	0.33	0.65	0.33	0.02	0.40	0.85	0.35

*FEV_1 change was calculated as the pre-dose FEV_1 measurement taken during at the clinic visit while still on-treatment minus the pre-dose FEV_1 measurement taken on the first day of treatment

**Analysis of covariance estimate of the rs37973 per-allele effect for each copy of the “G” allele, ± the standard error of the estimate. Model included five clinical covariates in addition to rs37973 coded as 0, 1, or 2.

†Ratio of the odds of being in the lowest quartile of response (defined as change in FEV1, adjusted for five clinical covariates) given genotype GG relative to the odds given genotype GA or AA.