Multi-omics analysis identifies a novel glucocorticoid response-associated locus near *BIRC3*

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Introduction

Inhaled corticosteroids (ICS) are commonly used for the treatment of asthma. They exert anti-inflammatory effects via modulation of gene transcription following their binding to glucocorticoid receptor (GR) transcription factors. The largest ICS response genome-wide association study (GWAS) to date based on 2672 asthma patients treated with ICS from GSK clinical trials found little evidence that common genetic variants underlie differences in lung function observed after 8-12 weeks of ICS use [1]. We integrated the results of this GWAS with glucocorticoid response-related ChIP-Seq and transcriptomic data to identify novel loci that may contribute to ICS response.

Methods

ICS response-associated variant selection. Summary statistics of ICS response GWAS [1] were obtained from GSK. Variants nominally associated with ICS response (n=820; p-value $<10^{-4}$) and those in linkage disequilibrium with them (n=3664; r2 ≥0.8 based on 1000 Genomes phase 3 genotype data of European ancestry populations) were selected.

ChIP-Seq data analysis. Publicly available GR ChIP-Seq datasets of glucocorticoid response in three airway structural cell types, airway smooth muscle cells (ASM), BEAS-2B and A549 cell lines, were analyzed with the brocade pipeline (https://github.com/HimesGroup/brocade) [2]. GR-binding sites with glucocorticoid response element (GRE) motifs were identified by the FIMO tool within the MEME suite (http://meme-suite.org/tools/fimo).

Transcriptomic data analysis. Twenty publicly available transcriptomic datasets of glucocorticoid response involving 11 cell types were analyzed with the RAVED pipeline (https://github.com/HimesGroup/raved) [3].

eQTL data analysis. Selected GWAS variants were searched in GTEx v8 datasets across lung, whole blood and skeletal muscle tissues.

Results

Of 4484 selected GWAS SNPs, 29 were located within GR-binding sites that had significantly increased GR occupancy with glucocorticoid exposure in at least one cell type (q-value <0.05). One locus near the gene baculoviral IAP repeat containing 3 (*BIRC3*) , a known apoptosis inhibitor that protects airway epithelial cells exposed to pro-inflammatory cytokines, was of particular interest given that four of the 29 SNPs were located in GR-binding sites within 20kb of the *BIRC3* transcription start site in the three airway cell types considered **[Figure 1A]**. Of the four *BIRC3* SNPs, one was within and one was near putative GRE motifs of identified GR-binding sites **[Figure 1A]**. *BIRC3* had significantly increased gene expression in response to glucocorticoid exposure in eight of eleven cell types considered (q-value <0.05) **[Figure 1B]**. The SNP rs2846858, with the smallest p-value of 4.35×10^{-5}, is a *BIRC3* eQTL in blood, lung and skeletal muscle tissues **[Figure 1A]**.

Conclusions

Multi-omics data suggests that a nominally associated ICS response GWAS locus near *BIRC3* should be prioritized for further functional studies of glucocorticoid responses.

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Bibliography

[1] Mosteller M, *et al*. *J Allergy Clin Immunol*. (2017). **[2]** Diwadkar A, *et al*. *AMIA Annu Symp Proc.* (2019). **[3]** Kan M, *et al*. *AMIA Annu Symp Proc.* (2018).

Figure 1. ChIP-Seq and ICS response GWAS results near the *BIRC3* locus..

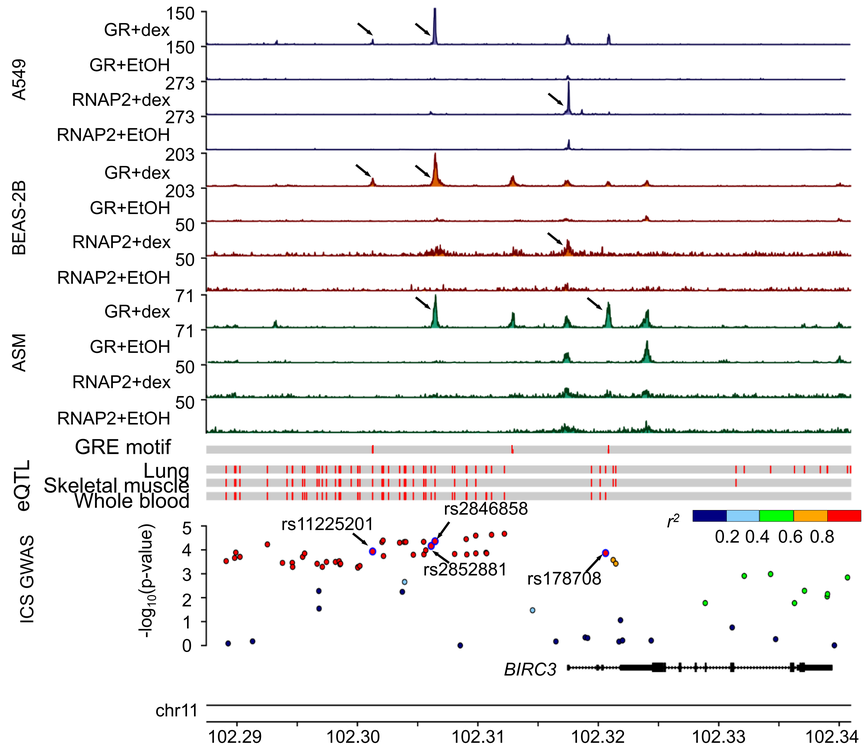

Figure 2. Differential expression results for *BIRC3* in various tissues exposed to glucocorticoids versus control.

GEO ID	Tissue	Treatment	Q-value
GSE115830	BEAS-2B	Bud 100nM 2h	9.27E-07
GSE115830	BEAS-2B	Bud 100nM 6h	8.61E-08
GSE115830	BEAS-2B	Bud 100nM 18h	9.56E-08
GSE115830	BEAS-2B	Bud 100nM 1h	4.01E-05
GSE55877	chALL	Dex 100nM 6h	4.80E-02
GSE55876	chALL	Dex 100nM 6h	7.21E-03
GSE17307	A549	Dex 100nM 6h	4.37E-02
GSE1815	BE	Dex 100nM 8h	5.49E-01
GSE3040	LEC	Dex 1uM 16h	5.59E-01
SRP098649	ASM	Bud 100nM 18h	9.12E-22
GSE46448	U2OS	Dex 100nM 4h	2.29E-02
GSE22152	chALL	Dex 100nM 6h	4.15E-03
GSE4917	MCF10A-Myc	Dex 1uM 24h	1.65E-01
GSE4302	BE	Inhaled Flu 1000ug daily	1.20E-01
GSE83233	BE	Inhaled Bud 1600ug once	3.86E-03
GSE34313	ASM	Dex 1uM 24h	8.70E-03
SRP033351	ASM	Dex 1uM 18h	3.09E-01
GSE44248	LCL	Dex 1uM 16h	5.95E-03
GSE13168	ASM	Fluticasone 10nM 0.5h	2.94E-01
GSE84992	myotubes	Prednisolone 1uM 48h	6.79E-01
GSE87000	MACRO	Dex 100nM 6h	5.83E-01
GSE79077	MACRO	Dex 100nM 20h	5.07E-02
GSE61880	MACRO	Dex 100nM 10h	2.16E-02