Pharmacogenomic associations of adverse drug reactions in asthma: systematic review and research prioritization

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## Abstract

A systematic review of pharmacogenomic studies capturing adverse drug reactions (ADRs) related to asthma medications was undertaken, and a survey of Pharmacogenomics in Childhood Asthma (PiCA) consortia members conducted. Studies were eligible if genetic polymorphisms were compared with suspected ADR(s) in a patient with asthma (primary or secondary outcome). Five studies met the inclusion criteria. Polymorphisms were associated with changes in lung function (ADRB2 rs1042713) with SABA/LABA, adrenal suppression (PDGFD rs591118) with inhaled corticosteroids, and both decreased bone mineral density (RADGEF5 rs6461639) and accretion (TBCD rs9896933, TUBG1 rs2074439), with oral corticosteroids. Two of these polymorphisms were replicated in an independent population within the discovery manuscript, none have been replicated beyond the original publication. PiCA members from15 institutions, across eight countries prioritised tachycardia (SABA/LABA), adrenal suppression/crisis and growth suppression (corticosteroids), sleep/behaviour disturbances (leukotriene receptor antagonists), and nausea and vomiting (theophylline) for inclusion in future pharmacogenomic studies of asthma.

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## Introduction

Asthma is a common chronic condition, affecting over 230 million people worldwide 1-3. The management of asthma is guided by national and international evidence based guidelines 4, 5, but there is inter-individual variability in treatment response. This variation may be related to several factors, including adherence, disease subtype and severity, and environmental factors. In addition, the genetic composition of each patient has been evidenced to play a key role in the different treatment responses in asthma 6-8. Evidence in pharmacogenomic studies of asthma medication efficacy in children performed to date have identified polymorphisms with current clinical utility 9.

However, the overall effectiveness of a medicine is a balance between the intended benefits and potential risks. Adverse drug reactions (ADRs) in asthma patients also need to be considered. The medications used in asthma have a well described set of ADRs associated with their use (Table 1). In adult patients, ADRs are responsible for 6.5% of all admissions, while 14.7% of adult inpatients experience an ADR 10, 11. For paediatrics, 3% of all admissions are related to ADRs 12, while over 17% of all paediatric inpatients experience one or more ADR 13. For asthmatic patients, ADRs represent a significant burden, reducing their quality of life, and extract an economic cost on healthcare systems worldwide 14, 15.

There is inter-individual variability in the type and severity of ADR experienced by patients. Factors such as adherence, and disease subtype influence this, but genomic factors are also important 16, with several genetic polymorphisms having been associated with severe ADRs 17, 18. For example with Carbamazepine and Steven Johnson Syndrome (SJS) in Han Chinese patients, the odds ratio for developing SJS for individuals with the HLA-B\*1502 allele compared to normal controls was 895 (95% CI, 50-15,869)17. Information from the US and EU regulators has been updated to reflect these findings 19, 20.

While the effect size of genetic factors in pharmacogenomic studies is often larger than that seen many in disease studies21, large cohorts may still be required (depending on the specificity of the phenotype), and independent population replication of findings is essential if findings are to be adopted into clinical practice to ensure generalizability of findings 22. International consortia, utilising the data from multiple groups, have been developed to facilitate this process 23. Within asthma, the pharmacogenomics in childhood asthma (PiCA) consortia is well established, containing multiple cohorts from studies around the world 24.

Our aim was to undertake a systematic review of pharmacogenomic studies of ADRs related to asthma medications across the entire population. In addition, in collaboration with the PiCA consortia, to survey active research groups in this area to establish which ADRs should be prioritised within future asthma pharmacogenomic research.

Table 1. List of adverse drug reactions for asthma drug classes(adapted from BNFc 25)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Short Acting B2 Agonist** | **Long Acting B2 Agonist** | **Corticosteroids** | **Leukotrienes** | **Theophylline** |
| Arrhythmias | Arrhythmias | Adrenal crisis | Abdominal Pain | Arrhythmias |
| Fine tremor | Arthralgia | Adrenal suppression | Abnormal dreams | CNS stimulation |
| Headache | Fine tremor | Aggression/ behavioural changes | Aggressive behaviour | Convulsions |
| Hyperglycaemia | Headache | Candidiasis | Agitation/ Anxiety | Diarrhoea |
| Hypersensitivity reactions | Hyperglycaemia | Cushing’s syndrome | Dizziness | Gastric irritation |
| Hypokalaemia | Hypersensitivity reactions | Hyperglycaemia | Hallucinations | Headache |
| Lactic acidosis  | Hypokalaemia | Hypertension | Headache | Hypokalaemia |
| Muscle cramps | Muscle cramps | Reduced growth velocity | Hyperkinesia | Hypotension |
| Nausea | Nausea | Reduced mineral bone density  | Sleep disturbances | Nausea and vomiting  |
| Rash | Rash |  | Thirst | Tachycardia  |
| Sleep/ behaviour disturbance | Sleep/ behaviour disturbance |  |  |  |
| Tachycardia | Tachycardia |  |  |  |

## Methodology

A systematic review of current evidence investigating adverse drug reactions of asthma medications in pharmacogenomic studies was undertaken. A protocol was submitted to the PiCA consortia before commencing.

### Search

Electronic databases, Medline, EMBASE and CINAHL, were searched up till January 2018 to locate eligible studies, using the terms “asthma”, “pharmacogenomics” and “asthma medication”. A list of asthma medication for inclusion in the search strategy was extracted from the British National Formulary for Children (BNFC) with both generic and brand names included (see supplementary file for full search strategy). No limit was placed on language, publication date or age of study population. References of included studies were analysed to locate any additional relevant studies of interest.

### Study Selection

Two reviewers (CK and DH), independently screened titles and abstracts for inclusion, removed duplicates, analysed full text for eligibility and collectively completed data extraction. Disagreements between the two reviewers were discussed and resolved mutually.

Both randomised control trials (RCTs) and observational studies were included. Studies were deemed eligible if genetic or genomic analysis were undertaken, the researchers examined a drug used in asthma treatment and if ADRs were stated. Adverse drug reactions were included if stated as either a primary or a secondary outcome of the study. An ADR was classified according to the WHO definition ‘A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function’26. A list of the top ADRs for each class of asthma medication is shown in Table 1 25, 27. Studies had to state the specific ADRs related to asthma medications and were excluded if ADRs were stated to be seen but no report produced with data. An asthma exacerbation was classified as a failure of medication efficacy rather than an ADR.

### Quality assessment and analysis

Methodological quality assessment was undertaken of the included studies: the Newcastle-Ottawa Quality Assessment Scale 28 was used for cohort and case-control studies, and the Cochrane Risk of Bias tool for RCTs 29. Results were extrapolated into a pre-determined data table, and a qualitative analysis was then conducted on the extracted data, with each asthma medication then individually reported.

### PiCA survey

An online survey was undertaken of PiCA consortia members to establish if this review had identified all possible pharmacogenomic studies analysing ADRs and asthma. In addition, the survey collated responses regarding the importance of capturing ADRs in future studies, and which ADRs’ members felt should be investigated in the future. Participants of the survey ranked their top three ADR for each drug from a pre-determined list (extrapolated from the BNFc25), the results were then ranked in order based on number of responses.

## Results

There were 1409 results after removal of duplicates generated from the search strategy, but of these, only three were eligible for inclusion 30-32. From the survey sent, two additional studies were subsequently discovered 33, 34 (Figure 1). Adverse events such as decreased efficacy or increased asthma exacerbations were reported in some papers, but since they were pre-specified outcomes, these were not included as ADRs in the systematic review. Within the eligible studies, three used ADRs as an endpoint of their studies. Four included studies were randomised control trials 30, 31, 33, 34, and one was a cohort study 32. All included studies had a low risk of bias (see supplementary file). Two of the studies were undertaken in the United Kingdom with the other three having been carried out in the USA. The overall sample size of the studies was 1457 participants. Of these, only 100/1457 (6.9%) were adults with asthma, while 1357/1457 (93.1%) were paediatric patients. The characteristics of the included studies are shown in Table 2.

Figure 1. Review flowchart showing screening and inclusion of studies

One study examined ADRs with inhaled short acting beta-2 agonists (SABA) 30, one analysed long acting beta-2 agonists (LABA) 31, three studies examined the use of corticosteroids 32-34, while no studies have examined ADRs occurring with either leukotriene receptor antagonists (LTA) or theophylline. For the SABA and LABA studies, candidate gene approaches were applied 30, 31, whereas in the three corticosteroid studies, genome-wide association studies (GWAS) were used 32-34.

Table 2. Characteristics of included studies. SABA: short acting beta-2 agonist. LABA: Long acting beta-2 agonist. RCT: Randomised controlled trial. GWAS: genome wide association study

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Study**  | **Drug** | **Asthma Severity**  | **Study Design and number of participants**  | **Method of gene identification** | **Ethnicity (number recruited)** | **Age range recruited years (mean)** |
| Israel 2004 30 | Inhaled SABA  | Mild asthma | RCT, 78 | Candidate gene | White (56), Black (15), Hispanic (6), Other (11) | 18-55yrs (31 years) |
| Tan 1997 31 | Inhaled LABA  | Moderately severe asthma | RCT, 22 | Candidate gene | Not stated | Range not given (38 years) |
| Park 2015 33 | Oral corticosteroids  | Mild to moderate asthma | RCT, 489 | GWAS | Caucasian | 5-12yrs (8.8 years) |
| Park 2017 34  | Oral corticosteroids  | Mild to moderate asthma | RCT, 461 | GWAS | Caucasian  | 5-12yrs (8.8 years) |
| Hawcutt 2018 32 | Inhaled +/- Oral Corticosteroids | All severities | Cohort study, 407  | GWAS | Caucasian | 5-18 (11.6 years) |

When analysing the genes identified in the studies (Table 3), the two candidate gene studies 30, 31 examined the association of rs1042713, located at the beta-2 adrenergic receptor gene (*ADRB2*). In contrast, the platelet derived growth gene (*PDGFD*), the rap guanine nucleotide exchange factor 5 (*RAPGEF5*), the tubulin folding cofactor D (*TBCD*), and the tubulin gamma 1 (*TUBG1*) genes were all identified through GWAS 32-34.

Table 3. Adverse drug reaction for each SNP in included studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Drug**  | **Adverse Drug Reaction** | **Associated SNP & Gene** | **Effect of SNP in discovery cohort** | **P-value or OR value if available** | **Replication cohort (Y/N) and effect(s) (p-value)** |
| Inhaled Albuterol 30 | Decrease in PEFR | rs1042713,*ADBR2* | 23L/min improvement of PEFR on discontinuation of Albuterol in Arg16/Arg16 group  | p-value=0.0162 | N |
| Inhaled Formoterol 31 | Desensitization to bronchodilator effects  | rs1042713,*ADBR2* | Homozygous Gly16/Gly16 patients exhibited greater desensitization, measured using FEV1, and FEF25-75  | p-value<0.05 | N |
| Oral prednisone 33 | Decreased bone mineral accretion | rs9896933,*TBCD* | Decreased bone mineral accretion  | p-value= 3.15x10-8 in GWAS | N |
| Oral prednisone 33 | Decreased bone mineral accretion | rs2074439,*TUBG1* | Decreased bone mineral accretion  | p-value= 2.74x10-4 in GWAS | N |
| Oral prednisone 34 | Decrease in BMD-z score | rs6461639,*RAPGEF5* | One of top 100 SNPs but did not achieve genome wide significance in discovery cohort | p-value=1.88x10-5 | Y. Statistically significant decrease BMD-z score in paediatric ALL cohort (p=0.016) |
| Inhaled corticosteroids +/- additional corticosteroids 32 | Adrenal suppression (peak cortisol <350nmol/L) | rs591118,*PDGFD* | Increased risk of adrenal suppression  | OR 7.32, 95% CI 3.15-16.99 | Increased risk of adrenal suppression in paediatric asthma cohort (OR 3.86, 95% CI 1.19–12.50) and adult COPD cohort (OR 2.41, 95% CI 1.10-5.28). Meta-analysis of all 3 cohorts achieved genome wide significance. |
| *ALL: acute lymphoblastic leukaemia. FEV1: forced expiratory volume in 1 second. FEF25-75: forced expiratory flow at 25-75% of pulmonary volume. PEFR: Peak expiratory flow rate. BMD: Bone mineral density. GWAS: genome wide association study. COPD: Chronic Obstructive Pulmonary Disease. SNP: Single Nucleotide Polymorphism. CI: confidence interval* |

Regarding the ADRs from SABA use, one study30 of 78 adults found that if participants had the homozygous Arg16/Arg16 allele then the peak expiratory flow was lower when on albuterol compared to placebo, with the peak expiratory flow rate being 23L/min better when albuterol was stopped. However, when this was replaced with ipratropium bromide, an anti-muscarinic, this group of participants had higher peak flow rates than when on albuterol or placebo.

For LABAs, one study31 of 22 adults found that participants with the homozygous Gly16/Gly16 genotypes had lower maximum FEV1, maximum FEF25-75, 6hr FEV1 and 6h FEF25-75 values compared to the Arg16/Arg16 genotype when given formoterol.

With inhaled corticosteroids, one study32 of 407 children (ages 5-18 years) from the PASS (Pharmacogenetics of Adrenal Suppression with Inhaled Steroids) study evaluated the association with ADRs. They found that SNP rs591118, located in the vicinity of the *PDGFD* gene, was associated with a higher risk of adrenal suppression (odds ratio (OR) in the paediatric asthma replication cohort = 3.86, 95% CI (1.19–12.50)).

For oral corticosteroids, two studies33, 34 examined children aged 5-12 years in the CAMP (Childhood Asthma Management Program) trial, evaluating the effect of prednisone on bone mineral density (BMD) z-scores and bone mineral accretion (BMA). SNP rs6461639 was significantly associated with a decrease in BMD z-scores in the ALL (acute lymphoblastic leukaemia) replication cohort33 (p-value=0.016). Two SNPs were found to worsen BMA with increased prednisone dosage, rs989633 (p-value 3.15x10-8) and rs207439 (p-value 2.74x10-4)33.

Independent population replication was undertaken in two of the studies that examined corticosteroid ADRs 32, 34. Additional publications validating further replication of these polymorphisms were not currently identified, although three of the manuscripts identified were less than three years old.

### Survey results

All members of the PiCA network were invited to take participate. Twenty PiCA members completed the survey, representing 15 institutes from the consortia in 67% of participating countries. 95% identified ADRs as an area that should be captured in pharmacogenomic studies, and 80% of respondents agreed that only a small percentage of studies currently assessed this area. The survey respondents undertook a prioritization exercise to establish the ADRs for each asthma medication they believe should be subject to further pharmacogenomics research. The results of this prioritization exercise are shown in table 4 (ranked in order of highest priority to lowest). The most important ADRs by consensus for each drug class varied; for beta 2 agonists (SABA or LABA) it was tachycardia, for corticosteroids it was both adrenal suppression/crisis and reduced growth, for leukotriene receptor antagonists it was sleep/behaviour disturbances, and for theophylline it was nausea and vomiting. Not all participants completed the survey for ADRs of each drug. For theophylline, 39% reported that the drug was no longer used in current asthma treatment.

Table 4. ADR's from survey and number of people who prioritized each

|  |  |  |  |
| --- | --- | --- | --- |
| **Beta 2 agonists** | **Corticosteroids** | **Leukotriene receptor antagonists** | **Theophylline** |
|  Tachycardia (14) | Adrenal suppression crisis (11) | Sleep/behaviour disturbances (12) | Nausea and vomiting (9) |
|  Arrhythmias (9) | Reduced growth (11) | Headache (7)  | Arrhythmias (7) |
|  Fine Tremor (8) |  Candidiasis (4) | Nausea and vomiting (5) |  Headache (5) |
|  Hypokalaemia (6) |  Hyperglycaemia (4) |  Tachycardia (3) |  Tachycardia (4) |
| Tachypnoea (4) | Sleep/behaviour disturbances (3) | Hypersensitivity reactions (2) |  Sleep/behaviour disturbances (3) |
| Lactic acidosis (3) |  Bone complications (3) | Rash (2) | Hypokalaemia (2) |
| Nausea and vomiting (3) | Fine Tremor (2) |  Fine Tremor (1) |  Tachypnoea (2) |
| Headache (2) | Headache (2) | Abdominal pain (1) |  Fine tremor (2) |
| Asthma exacerbation (2) | Nausea and vomiting (2) | Hypokalaemia (1) |  Lactic acidosis (1) |
| Hyperglycaemia (2) | Rash (1) |  Lactic acidosis (1) |  Hyperglycaemia (1) |
| Sleep/behaviour disturbances (1) | Asthma Exacerbation (1) | Candidiasis (1) | Rash (1) |
| Tachyphylaxis (1) |  | Dizziness (1) | CNS problems (1) |
|  |  | Agitation/anxiety (1) |  |
|  |  | Infection/immunosuppression (1) |  |
|  |  | Asthma Exacerbation (1) |  |

## Discussion

This is the first systematic review of genetic variants and adverse reactions of asthma. This systematic review has identified six distinct ADRs that have been evaluated across five asthma pharmacogenomic studies. However, these represent only a small subset of the overall pharmacogenomic research in asthma. The lack of studies considering ADRs in adult asthma populations was particularly striking. In addition, there is a lack of replication, with only two studies including independent population replication cohorts within the publication. In both studies, these replication cohorts successfully replicated the associations with individual polymorphisms identified in the discovery cohort.

Asthma is a disease that is particularly suitable for personalised therapy to either select efficacious medicines or avoid harms, as there are several medications that could be used in a given patient. While at a population level, these medications may be considered to have wide therapeutic indexes, there may be individuals who are particularly susceptible to the harms they can cause. It is therefore important that both the most important benefits and harms are identified and studied in pharmacogenomic studies.

The survey of PiCA consortia members supported future pharmacogenomic research into ADRs in asthma, and prioritised ADRs for each anti-asthma medication class. Of the fifty ADRs identified in the BNFc (Table 1), only three have been captured to date in pharmacogenomic studies. Of the ADRs that were captured in previous studies, only one (adrenal suppression) was ranked highly in the prioritisation exercise. The ADRs related to SABA/LABA medications were not the ones prioritised in the survey, and no data were identified for either leukotriene receptor antagonists or theophylline.

A minority of participants in the prioritisation exercise commented about whether frequency of asthma exacerbations is an ADR for beta-2 agonists, corticosteroids and LTAs. Increased exacerbations could be an ADR, but could also be the result of treatment failure, originating from either non-responsive disease, non-adherence or in the case of SABAs or LABAs, poor inhalation technique. The protocol for the systematic review therefore excluded these *a priori.* However, we note the core outcome set for childhood asthma does include risk of hospitalization secondary to asthma exacerbations. Reviewing the literature, asthma exacerbations have been defined as adverse events rather than ADRs in previous pharmacogenomic studies 6, 35, 36. A study of children with asthma who were on ICS plus LABA identified an increase in asthma exacerbations of 52% in those homozygous for the Arg16/Arg16 allele of *ADRB2* 35. Desensitization to these medications may also occur. This was considered for the included studies examining lung function, but they were included as either the lung function was worse than placebo 30or there was no placebo to compare against 31. Exacerbations are however included in the results of the prioritisation exercise, where the respondents were able to complete the ADRs of their choice.

A limitation of this study is that, as for any systematic review, the quality of the data produced is dependent on the quality of existing publications, and there were a paucity of eligible papers covering a range of drugs and ADRs. These studies all had relatively small sample sizes, and the diversity of ADRs identified precluded meta-analysis. However, the identification and prioritisation of ADRs by members of the PiCA consortia is a positive indicator that future pharmacogenomic studies may include more ADRs as well as markers of efficacy.

## Conclusion

Few pharmacogenomic studies of ADRs in asthma have been undertaken. None of these studies have been externally replicated, although one has only just been published. Future pharmacogenomic studies in asthma should collect relevant ADR data as well as markers of efficacy. Drug specific ADR priorities have been established to guide researchers.

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### Supplementary Files

Supplementary information is available at *The Pharmacogenomics Journal*’s website.

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### Figures

*Figure 1:* Prisma Flowchart of Studies

### Tables

*Table 1:* List of adverse drug reactions for asthma drug classes

*Table 2:* Characteristics of included studies

*Table 3:* Adverse drug reaction for each SNP in included studies

*Table 4:* ADR’s from survey and number of people who prioritized them