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Editorial Open Access

Realizing Personalized Medicine in Asthmatic Children Requires Large-Scale Collaboration

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Editorial

Although asthma treatment is effective in many children, there is large variability in the response as evidenced by improved symptom control, reduced exacerbations and lung function improvement. A study by the National Heart, Lung, and Blood Institute's Childhood Asthma Research and Education Network detailed the responses of 144 children with mild-to-moderate asthma to 8-weeks of treatment with inhaled corticosteroids (ICS) in a randomized cross-over design [1,2]. A large variation in lung function improvement from baseline was found [1]. Change in asthma-controlled days showed a similarly wide distribution, varying between an increase of seven asthma-controlled days per week to a decrease of four asthma-controlled days per week [2]. One mechanism for heterogeneity in treatment response seems likely to be due to genetic variations within the asthma population [3]. These genetic variants may be due to either innate differences in underlying disease subtype all manifesting clinically as asthma or to pharmacokinetic or pharmacodynamics influences on drug level or target. Candidate gene approaches and, to a lesser extent, whole-genome association studies have identified several genetic loci associated with poor treatment response or severe asthma, including FCER2 (coding for a low-affinity immunoglobin E (IgE) receptor, also known as CD23) [4,5], the 17q21 locus [6-8], and GLCCI1 (encoding glucocorticoid-induced transcript 1 protein) [9]. This might have implications for the treatment of asthma and suggests that we should move to a personalized (or stratified) approach guided by both clinical and genetic cues (i.e. pharmacogenetics) to benefit children with asthma. The benefits would be in terms of improvement of both drug efficacy and also drug safety of existing drugs. The potential of pharmacogenomics for optimizing treatment in childhood asthma is reflected in the results of the recent small randomized clinical trial by Lipworth and colleagues [10]. The study showed that asthmatic children homozygous for the variant genotype of ABDR2 seem to benefit more from a leukotriene antagonist (LTRA) than from a long-acting beta (2)-agonist (LABA) as add on treatment to ICS.

Need of Large Meta-Analyses

Based on the inter-individual heterogeneity combined with intra-individual repeatability of asthma treatment responses, it was estimated that 60-80% of the observed variance in treatment responses might be due to genetic differences [3,11]. Current identified genetic variants comprise only a small portion of the estimated heritability of asthma treatment responses. This could mean that the current applied methods of studying genomic variations are inefficient (i.e. studies are underpowered, searching methods are inadequate). Large scale meta-analyses can provide more insight on the current state of evidence for certain markers, but require collaboration. In addition, single biomarker approaches to phenotype asthma are increasingly regarded to be inaccurate and outdated. There is a need for large scale studies which combine multiple known biomarkers (genetic, but also non-genetic) in an integrated systems medicine approach to develop treatment algorithms [12].

Children are Not Small Adults

Most pharmacogenomics studies have focused on adults. We do have to realize that the biological factors influencing treatment response in children might differ from adults. It has been shown that inflammatory phenotypes differ between asthmatic children and adults [13]. These patterns may influence response to anti-inflammatory treatment. Furthermore, clinical trials in asthmatic adults could not demonstrate a modifying effect of ADRB2 Arg16 genotype on LABA treatment outcome [14,15], suggesting that the effect of ADRB2 might be restricted to LABA response in childhood-onset disease [16,17]. In addition, a recent GWAS analysis identified a SNP influencing FBXL7 expression to be associated with improvement in asthma symptoms in response to ICS [18]. This association was found in two independent pediatric asthma cohorts, but failed to be replicated in an adult asthmatic population. A large scale meta-analysis for the genetic markers identified in studies with asthmatic children is currently lacking.

Consensus on Outcome Definitions

The definition of response also needs to be taken into account. Poor response to treatment can be defined by various measurements, such as lack of improvement of lung function upon treatment, persistent airway hyperresponsiveness despite treatment, uncontrolled symptoms, or severe exacerbations despite treatment. The definition of response seems to influence the genetic profiles underlying that response phenotype [19]. Exacerbation-prone asthma is a different asthma phenotype compared to poorly controlled asthma [20], and children with limited symptoms can be prone to severe exacerbations [19]. Pharmacogenomics analyses should take into account different outcome phenotypes and consensus needs to be reached on uniform definition of response. Primary outcomes need to be patient focused (e.g. symptoms, exacerbations, quality of life), secondary outcomes can include health economic outcomes and physiological measures.

PiCA Consortium

In order to bring the field of personalized medicine in asthma further the Pharmacogenomics in Childhood Asthma (PiCA) consortium was initiated in 2014. This newly founded consortium has already brought together 20 studies (birth cohorts, asthma cohorts and clinical trials) with in total almost 15.000 asthmatic children. PiCA studies have genetic, medication exposure and treatment outcome data available (cross-sectional or longitudinally), or can obtain these data in asthmatic children in a short time-frame. The consortium covers the whole broad spectrum of asthmatics (from mild to severe) and aims to represent the global pediatric asthma population. First PiCA meta-analyses are in the startup phase and the active PiCA network welcomes new collaborators. If we want a future in which personalized medicine is part of clinical practice in childhood asthma, we need to collaborate.

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