Identification of new potential targets for treatment of coinciding asthma and hypertension

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Hypertension and asthma are serious disorders affecting millions of people worldwide. Both diseases are leading to decreased quality of life, increased mortality and both require special treatment plan. In adult patients these diseases are comorbid, what means that people, developed one disease have elevated risk of developing another one.

Hypertension, or persistently raised blood pressure is observed from every fifth to every third adult individual and its prevalence is growing together with age of cohort [1]. Hypertension causes other cardiovascular diseases, including heart failure and stroke. In addition to age, other risk factors of hypertension are lack of physical activity, obesity, excessive consumption of sodium, alcohol and tobacco usage and family history of hypertension. Blood pressure is typical multifactorial trait. Twin studies show that heritability of blood pressure is between 48 to 60% [2]. More than 50 genetic risk variants associated with hypertension were detected in genome-wide association studies (GWAS) [3]. Although some Mendelian forms

of hypertension were reported [4,5], its pathogenesis is not fully understood. Among the systems which dysregulation can lead to hypertension are renin-angiotensin system, aldosterone system, sympathetic nervous system and regulation of blood vessels endothelium. Asthma is chronic respiratory disease affecting more than 230 millions people and responsible for 380000 death in 2015, according to WHO estimates [6]. Asthma is characterized by recurrent wheezing, coughing, difficulties to breath in the result of bronchial spasms and inflammation of airways. Similar to hypertension, asthma seems to be the result of complex interactions between genetic and environmental (exposure to allergens, tobacco, air pollution) risk factors. Some factors can trigger asthma attack or worsen its symptoms, e.g. cold, stress, physical exercises and usage of non-steroid anti-inflammatory drugs (NSAIDs). It is important to note, that asthma is phenotypically heterogeneous, it is classified by age of onset, severity, frequency of attacks, type of inflammation and response to chemicals [7]. Two major types of asthma are childhood-onset, with first manifestation in early childhood and late-onset asthma starting later in life [7]. First type is allergic and have a tendency to co-occur with other immunological disorders e.g. dermatitis or food allergies. Adult asthma is less frequent, but more severe, it is not developing through allergy-related mechanism and has hypertension among comorbidities [8]. However, it is not clear whether treatment of asthma improves hypertension or vise versa. Understanding causal direction and mechanism of observed comorbidity of adult asthma and hypertension is necessary to propose new approaches for efficient management of both pathologies. Therefore the aim of this work is unraveling molecular reasons and detection of genes potentially responsible for this comorbidity.

In general, comorbidity between two phenotypes can be explained by common etiology, e.g. shared susceptibility variants, pathways or environmental factors, predisposing for both diseases. Comorbidity between asthma and hypertension could be the result of abnormal regulation of smooth muscle, endothelium or immune system. Previous works proposed genes that are involved in pathogenesis of both diseases and could be responsible for

comorbidity, for instance *ADRB1* and ADRB2 [9], Rho and Rho kinase [10]. Some variants in these genes can potentially have protective effect e.g. SLC26A4 variant [11].

As some examples of shared asthma- and hypertension-associated genes were in literature, we decided first to compose comprehensive lists of shared genes automatically. We obtained genes, associated with asthma and hypertension from OpenTargets [12] and HuGE Navigator [13] and got lists of 1364 and 796 genes respectively. As we focused on late-onset asthma, we excluded from asthma genes set those genes, that were associated with childhood asthma and its comorbidities such as eczema or allergy and only 866 genes remained. These two gene sets were tested for disease ontology (DO) terms enrichment, as nor OpenTargets, neither HuGe Navigator explicitly use it. Finally, we got the list of 108 genes that included (i) genes from the intersection of asthma and hypertension sets and (ii) genes, associated with one disease and linked with another one according to DO. Gene ontology terms enriched in this gene set were “vascular process in circulatory system” and ”regulation of blood vessel size”. All unions and intersections of gene sets were performed in TargetMine [14].

Example of hypertension and adult asthma is especially interesting, because in addition to a number of shared genes, some anti-hypertensive drugs, may provoke asthma attack, while some anti-asthmatics can worsen hypertension. For instance, beta-blockers, used to control blood pressure can stimulate asthma attack. Corticosteroids used to treat asthma can elevate blood pressure in the result their action on kidneys, leading to enhanced liquid retention. These examples have led us to idea that genes targeted or perturbed by drugs causing side effects similar to asthma and hypertension are also potentially involved into pathogenesis. Therefore, from SIDER [15], we retrieved all the drugs that have side effects, such as asthma and/or hypertension, or having at least one of these two conditions among contraindications. Automatically extracted lists comprised 137 and 261 drugs, which worsening or provoke asthma and hypertension respectively, but after manual curation, only 67 and 62 drugs remained, what shows very high rate of false mappings in SIDER. Interestingly, 6 of those drugs induced both asthma and hypertension. Genes targeted by these drugs may be involved

in the development of both condition and give us a key for understanding this comorbidity. Information about drug targets was extracted from DrugBank [16]. Further, in order to determine genes expressions that are perturbed in response to anti-asthmatic and anti-hypertensive drugs, we will extract from dSigDB [17] genes differentially expressed in response to each of selected drugs. We will highlight genes whose expression was frequently changed after treatment with anti-asthma drugs, anti-hypertension or both.

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