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Editorial

Role of Twin Studies in Pulmonary and Respiratory Medicine

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Editorial

Some chronic pulmonary diseases are the leading cause of death worldwide, especially Chronic Obstructive Pulmonary Disease (COPD), asthma, occupational lung diseases and pulmonary hypertension. The genetic versus environmental background of these disorders can be investigated with the study of twins. Moreover, twins are getting more and more popular in pulmonary twin research as well due to the increasing interest towards epigenetic studies.

Twin studies estimate the influence of genetic, shared and unshared environmental influences by comparing the concordance rates or intra-class correlations in Monozygotic (MZ) and Dizygotic (DZ) twins. As known, MZ twins are genetically identical and share nearly 100% of their germ line sequence variation, whereas DZ twins are brother and sisters born together and share on average 50% of germ line sequence variants only [1]. In addition, MZ and DZ twins are usually exposed to very similar environmental factors in early development due to the same intrauterine environment and postnatal exposures.

Lung function has been thoroughly investigated by twin researchers worldwide and a moderate to strong heritability has been revealed which underlines the importance of screening of high-risk individuals with positive family history of reduced lung function and reflects the physiological condition of the lung and airways [2,3]. Genome-wide linkage and association studies have identified a number of genes and genetic loci associated with pulmonary function, such as novel candidate genes TMEM132C, UNC93A and TTLL2 in a northeast Asian population [4]. Pulmonary risk factors, such as smoking have been also studied and found to be not clearly environmental but also moderately genetically influenced [5]. Our working group has demonstrated that, similarly to tobacco smoking, secondhand smoke sensitivity itself is also moderately heritable [6]. Gene-Environmental (GxE) interactions have been also documented, indicating how lifestyle and other environmental factors change the heritability estimates. For example, the strong genetic influence on the variability of measured to expected FEV1 ratio is strongly modified by an interaction with tobacco smoking [7].

Asthma phenotypes have been also thoroughly studied with twins suggesting that many genes are involved in the pathogenesis of asthma [8]. A Danish twin study has shown that the individual variation in asthma symptom severity is weakly influenced by genetic factors (24%), and environmental factors explain the main part of the variation [9]. A Puerto Rican recently published twin study demonstrated an increasing contribution of genetic influence and decreasing contribution of shared environmental effects to liability for physician-diagnosed asthma and asthma medication use between ages 1 and 3 years [10]. Not only cross-sectional, but also longitudinal twin studies can be performed which contribute to the knowledge of the age related expression of genes in any respiratory traits, such as asthma [8]. Intermediate phenotypes of asthma, elevated levels of exhaled nitric oxide and airway hyper responsiveness is also heritable in 60% and 30%, respectively [11].

A meta-analysis of risk estimates for lung cancer in twins has shown an increased lung cancer risk associated with having an affected relative [12]. Risk appeared to be greater with earlier age of onset of the disease and with multiple affected family members, suggesting that lung cancer risk is in part heritable [12].

Beyond lung function latest techniques in respiratory medicine have been also applied in twins, such as electronic nose which can distinguish various disorders by analyzing exhaled Volatile Organic Compound (VOC) pattern [13]. Univariate quantitative hereditary modeling revealed that hereditary background did not influence the VOC pattern but shared environment determined most of the variance [13].

Large twin registries with thousands of twins make it possible to study heritability of diseases with relatively low prevalence. For instance, a large Danish twin research assessed 13,649 twins by questionnaire and found that chronic bronchitis is moderately (25% to 55%) heritable, particularly in women [14].

If two heritable phenotypes have a significant phenotypic correlation between them, twin studies are able to determine if this correlation is related to genetic or environmental factors. For instance, the same Danish large study investigated whether to what extent comorbidity between type 2 diabetes and chronic bronchitis and COPD is explained by shared genetic or environmental factors [15]. That study found a moderate genetic correlation (33% to 43%) between these diseases indicating an increased risk of type 2 diabetes in patients with chronic bronchitis or COPD [15].

In the recent years, great emphasis has been put on monozygotic twin pairs discordant for chronic diseases aiming to assess the role of epigenetic factors in the development of a disease. These twin pairs are ideal tool for such study because disease affected twin has different epigenetic drift as the unaffected twin. Epigenetic alterations, such as DNA methylation and histone acetylation which are defined as all heritable changes in gene expression that are not related to changes in the underlying DNA sequence, are the most

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important gene regulatory factors which can be modified by certain environmental factors, e.g., maternal diet, smoking, microbiome, xenobiotics exposure, stress and other lifestyle factors. This epigenetic variation is cell-, tissue- and organ specific. These monozygotic twin pairs discordant for pulmonary diseases contribute to explore their individual variability. The Swedish Twin study On Prediction and Prevention of Asthma (STOPPA) is a recent, ongoing initiative to identify environmental and genetic/epigenetic factors as determinants for asthma [16]. Asthma discordant twin pairs are investigated and various biospecimens (blood, urine feces and saliva) are collected in order to identify biomarkers, find candidates for drug development and prevent of asthma and allergic disease [16]. Albeit this kind of studies are lacking in the literature, this discordant twin study design will have an outstanding importance in the future in various respiratory disease as well. For example, emerging evidence has demonstrated the importance of epigenetics in the pathogenesis of pulmonary arterial hypertension [17] and pulmonary metastases [18]. In a study of 65 pulmonary metastases resected from 12 patients (5 with sarcoma and 7 with adrenocortical carcinoma) found that the patient-specific epigenetic clonality may be exploited for precision therapies targeting aberrant cancer-testis or tumor suppressor gene expression and PRC-2 may be a shared target for epigenetic therapy of pulmonary metastases [18]. The importance of understanding the epigenetic alterations involved in the pathogenesis of pulmonary diseases is essential for the development of novel and more effective treatments via novel targets and signaling pathways related to disease [17].

The new initiative of International Network of Twin Registries [19] promotes collaboration of twin researchers worldwide to expand the resources of twin registries in order to find enough number of discordant monozygotic twin pairs for rare diseases, such as in case of various pulmonary disorders. This collaboration will also make it possible to follow-up these twin pairs over time to investigate the within-pair epigenetic drift changes.

In summary, twin studies have revealed the genetic versus environmental variation in numerous respiratory and pulmonary diseases and associated risk factors. Moreover, gene-environment interactions and genetic covariance between various genotypes can be also estimated using twins. Epigenetic twin studies will unravel the underlying epigenetic changes associated with respiratory risk factor biomarkers, identify of those at risk for early-life interventions to aid to alter the risk trajectory and potentially reduce chronic pulmonary disease incidence later in life.

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