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Understanding the role of genetics in comorbidity

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Motivation and Aim: The pattern of diseases in humans is heterogeneous, which is manifested by various combinations of diseases, including comorbidities associated with a common pathogenetic mechanism, as well as diseases that rarely manifest together at the phenotypic level. According to the concept of syntropy/dystropy or often/rare co-existence diseases, the accumulation of cases of comorbidity in families indicates the non-random connection between diseases in individuals and their relatives, and the importance of genes called syntropic/dystropic respectively, which determine their mutual development [1]. We know little about genes involved in the comorbidity of bronchial asthma with other diseases for example of cardiovascular continuum, with special attention to the mechanisms that might underlie a relationship between them.

Methods and Algorithms: We studied in the capacity of the syntropy model of arterial hypertension, coronary heart disease, myocardial infarction, obesity, type 2 diabetes mellitus and bronchial asthma as a significantly more common comorbidity among patients. We focus on cis/trans-eQTL of the genes involved in complex interconnection as a reason for syntropy of bronchial asthma with cardiovascular diseases identified previously using bioinformatics approaches [2, 3]. Genotyping of cis/trans-eQTL was performed using MALDI-TOF mass spectrometry in patients with bronchial asthma combined with cardiovascular/metabolic disorders as well as practically healthy individuals.

Results: Bronchial asthma in combination with cardiovascular/metabolic disorders was linked with particular genetic variants affecting gene expression mainly *CAT, TLR4, ELF5, ABTB2, UTP25, TRAF3IP3, NFKB1, LOC105377347, C1orf74* and *IRF6*. Only rs11590807 which regulate expression of the *UTP25, IRF6, TRAF3IP3, RP1-28O10.1* genes was associated with all studied comorbid phenotype of bronchial asthma and diseases of the cardiovascular continuum. Additionally we established the specificity of the associations of the cis/trans-eQTL in the development of time-ordered comorbidities. The rs1010461 variant, which regulates the expression of *RNASE4* and *ANG* genes, is linked with cardiovascular diseases as the first phenotype of this comorbidity with bronchial asthma. The rs769214, rs11032700, rs11032699, rs484214, and rs480575 variants, which regulate the expression of *CAT* gene, are associated with bronchial asthma as the first phenotype of comorbidity.

Conclusion: We identified the cis/trans-eQTL that are involved in the pathogenesis of bronchial asthma and cardiovascular/metabolic diseases, and may also contribute to the comorbidity of these diseases. The cis/trans-eQTL affecting the expression of many genes can serve as potential biological markers of complex causal relationships between bronchial asthma and cardiovascular/metabolic disorders.

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