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Re-analysis of DNA methylationin genes associated with bronchial asthma

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Motivation and Aim: To study the variability of gene methylation patterns, which in our previous studies showed associations with bronchial asthma and tuberculosis (which are dystrophic diseases), we re-analyzed two datasets GSE104471 and GSE59339 from the public repository of functional genomic data Gene Expression Omnibus (GEO) [1]. The goal of the study was to compare DNA methylation level associated with bronchial asthma genes in different groups.

Methods and Algorithms: The GSE104471 dataset was received by I.V. Yang et al. (2017) comparing methylation profiles (Illumina 450k) in peripheral blood mononuclear cells (PBMC), nasal and bronchial epithelium in 12 patients with allergic bronchial asthma and 12 healthy individuals without asthma: all white non-smoking adults are non-Hispanic [2]. The GSE59339 dataset was received by L.P. Gunawardhana et al. (2014) at studying the profile of DNA methylation (Illumina Infinium Methylation27) in blood monocytes in adult patients with eosinophilic asthma (EA; $n = 21$), paucigranulocytic asthma (PGA; $n = 22$), neutrophilic asthma (NA; $n = 9$) and healthy individuals ($n = 10$). Over half (67 %) of NA patients were ex-smokers [3].

The analyzed target genes are divided into 3 subgroups: 1) associated with asthma/tuberculosis (13 genes (*IFNG, SOCS5, TNFB, TNFRSF1B, PIAS3, PIASY, CXCL10, ATM, NBN, MRE11, MLH1, PMS2, TP53BP1*), were considered in all groups comparison of GSE104471 and GSE59339 datasets); 2) interesting from the point of view of atopy (14 genes (*TNF, IL13, IL4, IL4R, TGFB1, MS4A2, HLA-DRB1, HLA-DQB1, CD14, LTC4S, IL10, TLR2, CTLA4, HLA-DQA1*), were considered in all groups comparisons of the GSE104471 data set and in the comparison groups of the GSE59339 set, including eosinophilic asthma); 3) interesting from the point of view of syntropy of asthma and diseases of the cardiovascular system (7 genes (*ANG, RNASE4, LOC105376244, TLR4, AL160272.2, ABTB2, CAT*) were considered in the comparison groups of the GSE59339 set, including neutrophilic and paucigranulocytic asthma).

Results: Only *MRE11* out of the target genes, was included in the list of Top 50 differentially methylated genes (DMG) when comparing eosinophilic and paucigranulocytic asthma ($p = 0.00028$), however, the introduction of a correction for multiple comparisons makes these differences statistically insignificant (adj. $p = 0, 49$). Significant differences in the level of DNA methylation of target genes, taking into account the FDR correction, were obtained only when comparing methylation between asthma patients and healthy individuals – in both nasal and bronchial epithelial cells. In bronchial epithelial cells, for 8 genes (*MRE11, MLH1, TP53BP1, TNF, TGFB1, HLA-DRB1, HLA-DQB1, CD14*), which were analyzed for this pair of comparisons using the GSE104471 dataset, there is information on the level of methylation of 175 CpG-sites,

differential methylation was shown with $p < 0.05$ – for 41, with pFDR < 0.05 – for 6 CpG-sites: 3 in the *MLH1* gene, one each in the *TNF, TGFB1*, and *HLA-DRB1* genes. In nasal epithelial cells, information on differences in methylation levels is available for 103 CpG-sites in 11 genes (*ATM, TP53BP1, IFNG, LTA, TNFRSF1B, PIAS3, IL4R, TGFB1, CD14, LTC4S, TLR2*), differential methylation is shown with $p < 0,05$ – for 39 sites in these genes, with *p*FDR < 0.05 – for 18.

In PBMC, it was possible to analyze the information on 228 CpG-sites in 13 genes (*ATM, MLH1, MRE11, PMS2, TP53BP1, IL13, IL4, TGFB1, HLA-DRB1, HLA-DQB1, TLR2, CTLA4, HLA-DQA1*). Differential methylation is recorded at $p < 0.05$ – for 18 sites in the 11 genes studied (except for *IL13* and *IL4*), with *p*FDR < 0.05 all differences do not reach a significant level.

When analyzing the GSE59339 dataset after the FDR correction, no statistically significant differences were found for any of the CpG-sites of the target genes. However, without an FDR test, differences in methylation are detected in all types of comparisons. Thus, compared with the control, differences in the level of methylation were revealed for eosinophilic AD – at two sites (in the *MRE11* and *LTA* genes), for neutrophilic asthma – at two sites (*MLH1, TLR4*), for paucigranulocytic – at two sites (*LTA, ANG*); when comparing the forms of asthma, depending on the types of inflammation, differences were found between eosinophilic asthma and neutrophilic asthma – by loci in the *MLH1* and *SOCS5* genes, between eosinophilic asthma and paucigranulocytic asthma – by the CpG-site in the *MRE11* gene, between neutrophilic asthma and paucigranulocytic asthma – by sites in the *MRE11* and *SOCS5* genes.

Conclusion: The data obtained as a result of reanalysis on differences in the level of DNA methylation of a number of genes associated with bronchial asthma indicate the potential significance of epigenetic modifications in predisposition to this pathology.

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References

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