Journal of Applied Biomedicine xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Applied Biomedicine

journal homepage: www.elsevier.com/locate/jab

Review Article

Hits and defeats of genome-wide association studies of atopy and asthma

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ARTICLE INFO

Article history:
Received 16 November 2016
Received in revised form 7 March 2017
Accepted 7 March 2017
Available online xxx

Keywords:
GWAS
Asthma
Atopy
Gene-environment
Epigenetics
Farming

ABSTRACT

Atopy and asthma are complex conditions, recognised as outcomes in which both genes and environment play crucial role. Large number of disease associated loci have been identified within GWAS approach over last years and the knowledge of pathobiology of asthma and allergy has widened substantially. However still the results achieved are difficult to interpret. Most markers have no clear function on and expound small portion of heritability. The "missed heritability" could be hidden in the gene-by environment interactions. The most know environmental factor which interacts with asthma and atopy is farming. The common link between genes and environment could be epigenetics.

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Introduction

Asthma and allergic atopic conditions are complex traits, recognised as outcomes in which both genes and environment play an important role. The family studies with segregation analysis and twin studies brought the evidences of heritability, but the increase in the prevalence could not be explained by genetic drift. Thus the importance of an environmental component is commonly in focus. Asthma is believed to be also triggered by developmental factors early in life, which currently are poorly recognised. An example of that relationship is correlation of asthma at 10 years with reduced lung function at birth (Håland et al., 2006). Similarly genes implicated in foetal lung development have been showed to influence asthma susceptibility and treatment response (Sharma et al., 2015).

Different environmental exposures have been taken into account as impacting allergy – urban vs. rural living, farm vs. non-farm, change of diet, increased air pollution, reduced infections, parasite exposure and increased use of antibiotics. They can be considered as components of well-known hygiene hypothesis. The umbrella term "hygiene" or "the lack of hygiene" is currently replaced by biodiversity. Biodiversity hypothesis implicates that reduced biodiversity has negative consequences as a reduced immune tolerance to "harmless" allergens. Immunomodulatory role of saprophytic bacteria has been recognised as a main

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http://dx.doi.org/10.1016/j.jab.2017.03.002

Please cite this article in press as: H. Danielewicz, Hits and defeats of genome-wide association studies of atopy and asthma, J. App. (2017), http://dx.doi.org/10.1016/j.jab.2017.03.002

Nomenclature

ADA1	Adenosine deaminase 1
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif 9
AP5B1	Adaptor related protein complex 5 beta 1 subunit
ASB3	Ankyrin repeat and SOCS box containing 3
BCAP	B-Cell adapter for phosphoinositide 3-Kinase
C11orf30	EMSY, BRCA2 interacting transcriptional repressor
CARD4	Caspase recruitment domain family member 4
CDH17	Cadherin 17
CEP68	Centrosomal protein 68
CLEC16A	C-Type lectin domain family 16 member a
COL18A1	Collagen type XVIII alpha 1
COL29A1	Collagen type XXIX alpha 1
CTNNA3	Catenin alpha 3
DAD1	Defender against cell death 1
DENND1B	DENN domain containing 1B
DEXI	Dexi homolog
EFHC1	EF-Hand domain containing 1
FCER1A	High affinity immunoglobulin epsilon receptor alpha-subunit
FLG	Filaggrin
FNDC3A	Fibronectin type III domain containing 3A
FOXA1	Forkhead box A1
FOXB1	Forkhead box B1
GAB1	GRB2 associated binding protein 1
GATA2	GATA binding protein 2
GLCCI1	Glucocorticoid induced 1
GSD1A	Glucose-6-phosphatase catalytic subunit
GSDMA	Gasdermin A
GSDMB	Gasdermin B
GWAS	Genome-wide association study
HERC2	HECT and RLD domain containing E3 ubiquitin protein ligase 2
HIF-1α	Hypoxia inducible factor 1 alpha subunit
HLA-DPB1	Major histocompatibility complex, class II, DP beta1
HLA-DQ	Major histocompatibility complex, class II, DQ
IKZF2	IKAROS family zinc finger 2
IKZF3	IKAROS family zinc finger 3
IL13	Interleukin 13
IL18R1	Interleukin 18 receptor 1
IL1RL1	IL-33 receptor
IL2RA	Interleukin 2 receptor subunit alpha
IL2RB	Interleukin 2 receptor subunit beta
IL4	Interleukin 4
IL5	Interleukin 5
IL33	Interleukin 33
KIF3A	Kinesin family member 3A
LPP	LIM domain containing preferred translocation partner in lipoma
LRRC32	Leucine rich repeat containing 32
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MAP3K5	Mitogen-activated protein kinase 5
MICA	MHC class I polypeptide-related sequence A
MLLT3	MLLT3, super elongation complex subunit
MRPL4	Mitochondrial ribosomal protein L4
MYB	MYB proto-oncogene, transcription factor
MYC	V-Myc avian myelocytomatosis viral oncogene homolog
NFATC2	Nuclear factor of activated T-Cells 2
NF-KB	Nuclear factor kappa B
NOD1	Nucleotide binding oligomerization domain containing 1
ODZ3	Alias TENM3 teneurin transmembrane protein 3
ORMDL3	ORMDL sphingolipid biosynthesis regulator 3
OVOL1	Ovo like zinc finger 1
OXA1L	Oxidase (Cytochrome C) assembly 1-Like
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase catalytic subunit alpha
PLCL1	Phospholipase C like 1
PTGER4	Prostaglandin E receptor 4
PYHIN1	Pyrin and HIN domain family member 1
RAD50	RAD50 double strand break repair protein
RORA	RAR related orphan receptor A
SgK493	Sugen kinase 493 (Protein kinase domain containing, cytoplasmic PKDCC)
SH2B3	SH2B adaptor protein 3
SLC25A46	Solute carrier family 25 member 46
SLC6A15	Solute carrier family 6 member 15
SMAD3	SMAD family member 3
SNP	Single nucleotide polymorphism
STAT6	Signal transducer and activator of transcription 6
TBCD	Tubulin folding cofactor D
TMEM232	Transmembrane protein 232
TMTC2	Transmembrane and tetratricopeptide repeat containing 2
TNIP1	TNFAIP3 interacting protein 1
TNS1	Tensin 1
TSLP	Thymic stromal lymphopoietin
TTC6	Tetratricopeptide repeat domain 6
USP38	Ubiquitin specific peptidase 38
WDR36	WD repeat domain 36
ZBTB10	Zinc finger and BTB domain containing 10

benefit of biodiversity. Last findings in that subject emphasise the role of farming in the richness of microbiome composition and diversity (Birzele et al., 2017; Depner et al., 2017).

Studying genes – genome-wide association study GWAS

Essential number of genetic studies has been conducted in order to find out the potential genetic risk associated with allergic conditions. In GWAS, which is relatively new approach, genome scan is used in the hypothesis independent manner, which allows to identify multiply candidate genes for complex diseases. In the statistical analysis a test for the association between common genetic variants spread throughout the whole genome is performed. Contrary, well known, candidate gene strategy is hypothesis driven – based on the current knowledge in the area. The problems associated with that kind of research are frequent discrepancies between studies, some caused by population stratification or small sample size. Furthermore, this kind of analysis doesn't allow discovering novel genes or molecular pathways.

Single nucleotide polymorphism is one of the most common type of variation within human genome, which occurs in the population with frequency of at least 1%. SNP appears with an average of 1 per 300 bases, so it is estimated that approximately there are 10 million variants per single genome with 3 billion nucleotides. Some of SNPs are localised around the genes, influencing the variation in the amount or the function of a protein (International HapMap Consortium, 2003). According to current dbSNP database (NIH) there are 154.2 million SNPs in total, with the number increasing every year https://www.ncbi.nlm.nih.gov/dbvar/content/org_summary/. Due to haplotype structure of

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