Updates on the COPD gene list

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Abstract: A genetic contribution to develop chronic obstructive pulmonary disease (COPD) is well established. However, the specific genes responsible for enhanced risk or host differences in susceptibility to smoke exposure remain poorly understood. The goal of this review is to provide a comprehensive literature overview on the genetics of COPD, highlight the most promising findings during the last few years, and ultimately provide an updated COPD gene list. Candidate gene studies on COPD and related phenotypes indexed in PubMed before January 5, 2012 are tabulated. An exhaustive list of publications for any given gene was looked for. This well-documented COPD candidate-gene list is expected to serve many purposes for future replication studies and meta-analyses as well as for reanalyzing collected genomic data in the field. In addition, this review summarizes recent genetic loci identified by genome-wide association studies on COPD, lung function, and related complications. Assembling resources, integrative genomic approaches, and large sample sizes of well-phenotyped subjects is part of the path forward to elucidate the genetic basis of this debilitating disease.

Keywords: COPD, genetics, lung function, candidate genes, genome-wide association study

Introduction

Chronic obstructive pulmonary disease (COPD) is the third-leading cause of worldwide mortality and is predicted to remain a major public health problem in the near future.1,2 It is characterized by airflow limitations that occur in approximately 10% of adults aged ≥ 40 years.3 Cigarette smoking is the primary risk factor. However, only a fraction of smokers (~20%) develop the disease, and host differences in susceptibility are thus persuasive. The author has previously reviewed the genetics of COPD and COPD-related phenotypes.4 The current review aims to: (1) update this publication, (2) provide a comprehensive literature overview on the genetics of COPD, (3) highlight the most promising findings during the last few years, and ultimately (4) provide an updated COPD gene list.

Chronic obstructive pulmonary disease candidate-gene studies

A systematic review of the literature was conducted in order to provide a comprehensive overview of genes associated with COPD and related phenotypes. PubMed was searched using the string “genetics and COPD” on January 5, 2012. All titles and abstracts were reviewed for inclusion. The goal was to obtain all publications testing genetic variants in humans for association with COPD and related phenotypes (ie, spirometric
measurements, emphysema, chronic bronchitis, lung-function decline, etc). Population-based, case-control, and family studies were included. The author attempted to include all reported articles without quality assessment or exclusion criteria based on sample size or other criteria. The search for relevant publications was complemented using the list of references in relevant manuscripts and the COPD genetic association compendium. Readers are welcome to contact the author for any articles missed in the current review.

A large number of candidate gene–association studies were conducted to identify the COPD-susceptibility genes. Table 1 provides a comprehensive overview of the genes associated with COPD and related phenotypes using this genetic approach. Supplementary Table 1 presents additional genes tested but showing lack of association with COPD and related phenotypes. Most genes in these tables were studied because of their potential role in the pathobiology of COPD, but some also represent follow-up genes originally identified from genome-wide linkage and association studies. Genes are presented in alphabetical order. Single studies and meta-analyses testing each gene are indicated. An attempt was made to classify each article as supportive or not of a given gene based on the conclusions provided by the authors. Single genetic markers, haplotypes, or combinations of variants associated with COPD, COPD severity, COPD-related phenotypes, or complications were considered as positives. Table 1 aims to provide an exhaustive list of publications for any given gene.

A total of 192 genes are summarized in Table 1 and Supplementary Table 1. Figure 1 illustrates these genes based on the number of publications supporting the association with COPD phenotypes. Briefly, 86 genes are supported by one study, 36 genes by two to five studies, 15 genes by six to ten studies, and seven genes by more than ten studies. The latter seven genes include ADRB2, TGFBI, TNF, GSTM1, GSTP1, SERPINA1, and EPHXI. Note that Figure 1 must be interpreted with caution. Replication of genotype–phenotype associations is the gold standard to identify genes conferring susceptibility. However, the number of supportive studies is not necessarily an indication that a gene is consistently replicated. Figure 2 illustrates the relationship between the number of studies supporting and not supporting the list of COPD genes. It seems that genes replicated many times in COPD are simply the most popular genes studied. For example, the author found 20 studies supporting TNF as a COPD-susceptibility gene. However, lack of association between this gene and COPD phenotypes was found in 20 other studies (Table 1). Considering publication bias, candidate genes associated with COPD are not consistently replicated and the overall results are rather inconclusive. In fact, excluding SERPINA1 (encoding the alpha-1 antitrypsin protein), none of the other genes are well-proven susceptibility genes for COPD. Perhaps the most convincing candidate COPD genes up to now are those less studied but consistently replicated, such as SOD3. Many of the most studied COPD genes have now been investigated in meta-analyses.

Meta-analyses
A number of meta-analyses have been conducted to identify genes robustly associated with COPD and lung function. So far, meta-analyses have been conducted for genes involved in the following pathways: inflammation (IL4, IL6, IL13, IL1B, IL1RN, LTA, TNF, and TGFBI), protease/antiprotease (MMP9, TIMP2, and SERPINA3), oxidative stress (GSTM1, GSTP1, GSTT1, EPXH1, SOD2, and SOD3), and others (ACE and ADRB2). These studies and their main outcomes are summarized by gene in Table 1. Among these genes, GSTM1 was consistently associated with COPD in more than one meta-analysis. This is also true for TNF, but only in Asian populations. In contrast, other genes have not been supported in meta-analyses conducted so far, including GSTT1, IL1B, IL6, and MMP9. The other genes considered in meta-analyses were either reported in only one study or showed conflicting results across studies (Table 1).

As genetic data accumulates, more genes and polymorphisms will be considered in meta-analyses. Combining the findings of an increasing number of studies will allow pooled analyses in more homogenous subgroups based on ethnicity, smoking history, emphysema vs airway type of COPD, and others. These subgroup analyses are likely to be important in finding susceptibility genes for COPD. Ongoing activities gathering genetic data in the field of COPD are important. For example, a web application summarizing candidate-gene studies was recently established. At the time of publication, this database included 108 genetic-association studies, including population-based and case-control studies but excluding family-based studies. Seventy-two genes were studied, focusing strictly on single-marker biallelic polymorphisms. A total of 27 genetic variants were found to be reported in three or more independent study populations and summarized into a meta-analysis. Four genes were found to carry a single genetic variant significantly associated with COPD, being GSTM1, TGFBI, TNF, and SOD3. It should be noted that this COPD genetic-association compendium has not been updated since April 2010 and does not include...
| Symbol | Name | Chromosome | References | Single studies | Meta-analyses |
|--------|------|------------|------------|----------------|---------------|
|        |      |            |            | Positive | Negative | Positive | Negative |
| A2M    | Alpha-2-macroglobulin | 12 | 51 | | |
| ABCC1  | ATP-binding cassette, sub-family C (CFTR/MRP), member 1 | 16 | 52–54 | | |
| ACE    | Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 | 17 | 55–60 | 61,62 | 5 |
| ADAM33 | ADAM metallopeptidase domain 33 | 20 | 63–68 | 69,70 | | |
| ADRB2  | Adrenergic, beta-2, receptor, surface | 5 | 71–82 | 83 | 5,83 |
| ALOX5AP| Arachidonate 5-lipoxygenase-activating protein | 13 | | 84 | |
| AQP5   | Aquaporin 5 | 12 | | 85,86 | |
| BCL2   | B-cell CLL/lymphoma 2 | 18 | | 87 | |
| BDKRB2 | Bradykinin receptor B2 | 14 | | 88 | |
| CASP10 | Caspase 10, apoptosis-related cysteine peptidase | 2 | | 89 | |
| CAT    | Catalase | 11 | | 90 | 91,92 |
| C5L5   | Chemokine (C-C motif) ligand 5 (RANTES) | 17 | | 93 | 79 |
| CCR2   | Chemokine (C-C motif) receptor 2 | 3 | | 94 | |
| CD14   | CD14 molecule | 5 | | 95,96 | |
| CD40   | CD40 molecule, TNF receptor superfamily member 5 | 20 | | 97 | |
| CD63   | CD63 molecule | 12 | | 98 | |
| CD86   | CD86 molecule | 3 | | 99 | |
| CDC6   | Cell division cycle 6 homolog (S cerevisiae) | 17 | | 100 | |
| CDKN1A | Cyclin-dependent kinase inhibitor 1A (p21, Cip1) | 6 | | 101 | |
| CFTR   | Cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) | 7 | | 102–108 | 109,110 |
| CHI3L1 | Chitinase 3-like 1 (cartilage glycoprotein-39) | 1 | | 111 | |
| CHRNA3 | Cholinergic receptor, nicotinic, alpha 3 (neuronal) | 15 | | 26,30,31, 112,113 | |
| CHRNA5 | Cholinergic receptor, nicotinic, alpha 5 (neuronal) | 15 | | 26,30,31, 112,113 | |
| CLCA1  | Chloride channel accessory 1 | 1 | | 114 | |
| COL4A3 | Collagen, type IV, alpha 3 (Goodpasture antigen) | 2 | | 115 | |
| CRP    | C-reactive protein, pentraxin-related | 1 | | 116 | 117–119 |
| CSF2   | Colony stimulating factor 2 (granulocyte-macrophage) | 5 | | 120 | 121 |
| CSF3   | Colony stimulating factor 3 (granulocyte) | 17 | | 121 | |
| CTLA4  | Cytotoxic T-lymphocyte-associated protein 4 | 2 | | 99,122,123 | |
| CTSS   | Cathepsin S | 1 | | 124 | |
| CYBA   | Cytochrome b-245, alpha polypeptide | 16 | | 125 | |
| CYP1A1 | Cytochrome P450, family 1, subfamily A, polypeptide 1 | 15 | | 125–128 | 129,130 |
| CYP1A2 | Cytochrome P450, family 1, subfamily A, polypeptide 2 | 15 | | 129,131 | 125,128 |
| CYP2E1 | Cytochrome P450, family 2, subfamily E, polypeptide 1 | 10 | | 127,132 | 130 |
| CYP2F1 | Cytochrome P450, family 2, subfamily F, polypeptide 1 | 19 | | 133 | |
| CYP3A5 | Cytochrome P450, family 3, subfamily A, polypeptide 5 | 7 | | 134 | |
| DEFB1  | Defensin, beta 1 | 8 | | 135,136 | 137 |
| DEFB4A | Defensin, beta 4A | 8 | | 138 | |
| EDN1   | Endothelin 1 | 6 | | 139–141 | 142,143 |
| EDNRB  | Endothelin receptor type B | 13 | | 143 | |

(Continued)
Table 1 (Continued)

| Symbol | Name                                                                 | Chromosome | References |
|--------|----------------------------------------------------------------------|------------|------------|
|        |                                                                      |            | Single studies | Meta-analyses |
|        |                                                                      |            | Positive | Negative | Positive | Negative |
| **ELN**| Elastin (supravalvular aortic stenosis, Williams–Beuren syndrome)   | 7          | 144,145    | 146,147   |          |          |
| **EPHX1**| Epoxide hydrolase 1, microsomal (xenobiotic)                      | 1          | 77,83,130, 127,168–174 | 146–167 | 175 | 5,8,176 |
| **ESR1**| Estrogen receptor 1                                                | 6          | 146,147,151 | 155,187   |          |          |
| **FAM13A**| Family with sequence similarity 13, member A                      | 4          | 26         |          |          |          |
| **FGF10**| Fibroblast growth factor 10                                      | 5          | 178        |          |          |          |
| **GC** | Group-specific component (vitamin D binding protein)               | 4          | 179–186    | 146,147,151 |          |          |
| **GCLC**| Glutamate-cysteine ligase, catalytic subunit                        | 4          | 188        | 172,189   |          |          |
| **GCLM**| Glutamate-cysteine ligase, modifier subunit                        | 1          | 190        | 172,188   |          |          |
| **GSTCD**| Glutathione S-transferase, C-terminal domain containing            | 4          | 191        |          |          |          |
| **GSTM1**| Glutathione S-transferase M1                                      | 1          | 127,148,161, 90,130,146,147 | 164,165, | 151,169,203–206 |          |
| **GSTO1**| Glutathione S-transferase omega 1                                  | 10         | 207        |          |          |          |
| **GSTO2**| Glutathione S-transferase omega 2                                  | 10         | 207        |          |          |          |
| **GSTP1**| Glutathione S-transferase pi 1                                    | 11         | 77,90,146, 69,127,130,147 | 8,213 | 5,214 |          |
| **GSTM1**| Glutathione S-transferase theta 1                                 | 22         | 127,165,193, 90,130,148,161 | 196–198 | 164,169,194, | 204–206 | 199–201,203 |
| **HCK** | Hemopoietic cell kinase                                            | 20         | 215        |          |          |          |
| **HHIP** | Hedgehog interacting protein                                      | 4          | 26,191,216 |          |          |          |
| **HLA** | Classical class 11 subregion of the MHC                            | 6          | 217,218    | 219,220   |          |          |
| **HMOX1**| Heme oxygenase (decycling) 1                                       | 22         | 130,151,166, 69,147,185 | 221–224 | 196,225 |          |
| **HTR4** | 5-hydroxytryptamine (serotonin) receptor 4                         | 5          | 191        |          |          |          |
| **IFNG**| Interferon, gamma                                                  | 12         | 226–228    |          |          |          |
| **IL1A**| Interleukin 1, alpha                                              | 2          | 227        |          |          |          |
| **IL1B**| Interleukin 1, beta                                                | 2          | 227,229–233 | 120,228, | 234–238 | 5,8 |          |
| **IL1RN**| Interleukin 1 receptor antagonist                                 | 2          | 231,232, 228,230, | 234,235 | 236–238 |          |
| **IL2** | Interleukin 2                                                      | 4          | 227        |          |          |          |
| **IL27**| Interleukin 27                                                     | 16         | 239        |          |          |          |
| **IL4** | Interleukin 4                                                      | 5          | 71,227,240 | 120,241,242 | 5 |          |
| **IL4R**| Interleukin 4 receptor                                             | 16         | 227,243    | 79,241    |          |          |
| **IL5** | Interleukin 5 (colony-stimulating factor, eosinophil)              | 5          | 244        |          |          |          |
| **IL6** | Interleukin 6                                                      | 7          | 118,228,234, 116,233, | 236,248 | 5,8 |          |
| **IL8** | Interleukin 8                                                      | 4          | 120        | 234,235,238, | 249,250 |          |
| **IL8RA**| Interleukin 8 receptor, alpha                                      | 2          | 251        | 120,146,147 |          |          |
| **IL8RB**| Interleukin 8 receptor, beta                                       | 2          | 250        | 120,146,147 |          |          |
| **CXCR2**| Interleukin 10                                                     | 1          | 149,227,235, 248,252–254 | 120,234,255 |          |          |
| **IL12B**| Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40) | 5          | 227        | 239        |          |          |

(Continued)
Table 1 (Continued)

| Symbol | Name                                                                 | Chromosome | References | Single studies | Meta-analyses |
|--------|----------------------------------------------------------------------|------------|------------|----------------|---------------|
|        |                                                                      |            |            | Positive | Negative | Positive | Negative |
| IL13   | Interleukin 13                                                       | 5          |            | 79,241,242,   |            | 71,120,238, | 5          |
|        |                                                                      |            |            | 256–261 | 243,262 |           |           |
| IL13RA1| Interleukin 13 receptor, alpha 1                                     | X          |            | 241      |            |            |            |
| IL1F   | Interleukin 17                                                       | 6          |            | 263      |            |            |            |
| IREB2  | Iron-responsive element binding protein 2                            | 15         |            | 26,30,47 |            |            |            |
| KCNMB1 | Potassium large conductance calcium-activated channel, subfamily M, beta member 1 | 5 | | 264 | | | |
| KEAP1  | Kelch-like ECH-associated protein 1                                  | 19         |            | 265      |            |            |            |
| LEP    | Leptin                                                              | 7          |            | 266      |            |            |            |
| LEPR   | Leptin receptor                                                      | 1          |            | 267      |            |            |            |
| LTA    | Lymphotoxin alpha (TNF superfamily, member 1)                        | 6          |            | 234,268–272 |            | 120,233,248, | 5          |
|        |                                                                      |            |            | 273–275 | | | |
| LTA4H  | Leukotriene A4 hydrolase                                            | 12         |            | 84       |            |            |            |
| LTB4   | Latent transforming growth factor beta binding protein 4             | 19         |            | 146,147 |            |            |            |
| MBL2   | Mannose-binding lectin (protein C) 2, soluble                         | 10         |            | 276,277 |            |            |            |
| MHC    | MHC class I polypeptide-related sequence B                           | 6          |            | 278      |            |            |            |
| MIR196A2| MicroRNA 196a-2                                                      | 12         |            | 279      |            |            |            |
| MIR499A| MicroRNA 499a                                                        | 20         |            | 279      |            |            |            |
| MMP1   | Matrix metalloproteinase 1 (interstitial collagenase)                | 11         |            | 146,280,281 |            | 69,128,147, | 151,282–285 |
|        |                                                                      |            |            | 128,202,281 |            | 69,147,151, | 280,283,285,287 |
|        |                                                                      |            |            | 288–290 | | | |
| MMP2   | Matrix metalloproteinase 2 (gelatinase A, 72 kDa gelatinase, 72 kDa type IV collagenase) | 16 | | 285 | | 69,281 | |
| MMP3   | Matrix metalloproteinase 3 (stromelysin 1, progelatinase)            | 11         |            | 286      |            | 128,287 | |
| MMP9   | Matrix metalloproteinase 9 (gelatinase B, 92 kDa gelatinase, 92 kDa type IV collagenase) | 20 | | 128,202,281 | 69,147,151, | 280,283,285,287 |
|        |                                                                      |            |            | 288–290 | | | |
| MMP12  | Matrix metalloproteinase 12 (macrophage elastase)                    | 11         |            | 280,283, | 69,146,147, | |
|        |                                                                      |            |            | 291,292 | | | |
| MMP14  | Matrix metalloproteinase 14 (membrane-inserted)                      | 14         |            | 293      |            |            |            |
| MSR1   | Macrophage scavenger receptor 1                                      | 8          |            | 137,294 |            |            |            |
| NAT2   | N-acetyltransferase 2 (arylamine N-acetyltransferase)                | 8          |            | 132      |            |            |            |
| NFE2L2 | Nuclear factor (erythroid-derived 2)-like 2                          | 2          |            | 265,295 |            |            |            |
| NFKBIB | Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, beta | 19 | | 185 | | | |
| NOS3   | Nitric oxide synthase 3 (endothelial cell)                           | 7          |            | 57,62,296,297 | | 149 | |
| NQO1   | NAD(P)H dehydrogenase, quinone 1                                     | 16         |            | 90       |            |            |            |
| NR3C1  | Nuclear receptor subfamily 3, group C, member 1 (glucocorticoid receptor) | 5 | | 298 | | 299 | |
| OGG1   | 8-oxoguanine DNA glycosylase                                         | 3          |            | 300      |            | 189      |            |
| OR4X1  | Olfactory receptor, family 4, subfamily X, member 1                  | 11         |            | 301      |            |            |            |
| PDE4D  | Phosphodiesterase 4D, cAMP-specific (phosphodiesterase E3 dunce homolog, drosophila) | 5 | | 302 | | | |
| PLAU   | Plasminogen activator, urokinase receptor                            | 19         |            | 303,304 |            |            |            |
| PPARG  | Peroxisome proliferator-activated receptor gamma                     | 3          |            | 163      |            |            |            |
| PTEN   | Phosphatase and tensin homolog                                      | 10         |            | 14       |            |            |            |
| PTGDR  | Prostaglandin D2 receptor (DP)                                       | 14         |            | 305      |            |            |            |
| PTGS2  | Prostaglandin-endoperoxide synthase 2                               | 1          |            | 306,307 |            |            |            |
| (COX2) | Prostaglandin G/H synthase and cyclooxygenase                       |            |            |            |            |            |            |
| SERPINA1| Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 1 | 14 | | 76,308–325 | 326–336 | | | (Continued)
Table 1 (Continued)

| Symbol | Name                                                                 | Chromosome | References                                                                 |
|--------|----------------------------------------------------------------------|------------|---------------------------------------------------------------------------|
|         |                                                                      |            | **Single studies** | **Negative** | **Meta-analyses** |
|         |                                                                      |            | Positive | Negative | Positive | Negative |
| SERPINA3 | Serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3 | 14         | 337–343 | 146,147,149 | 151,310,314 | 326,332,344 |
| SERPINE2 | Serpin peptidase inhibitor, clade E (nexin, plasminogen activator inhibitor type 1), member 2 | 2          | 77,146,149, 147,152,171 | 326,345–348 | 349,350 |
| SFTPA1  | Surfactant protein A1                                                  | 10         | 69,351 |
| SFTPA2  | Surfactant protein A2                                                  | 10         | 69 |
| SFTP8   | Surfactant protein B                                                   | 2          | 147,151,171, 69,77,146, 351–354 | 149,152,355 |
| SFTPC   | Surfactant protein C                                                   | 8          | 356 |
| SFTPD   | Surfactant protein D                                                  | 10         | 69,358,359, 151,351 |
| SIRT2   | Sirtuin 2                                                             | 19         | 185 |
| SLC6A4  | Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 | 17         | 360 |
| SLC1A1  | Solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1 | 2          | 361 |
| SMAD3   | SMAD family member 3                                                  | 15         | 362 |
| SMOC2   | SPARC related modular calcium binding 2                               | 6          | 363 |
| SOD2    | Superoxide dismutase 2, mitochondrial                                  | 6          | 364–366, 91,92,271 | 8 |
| SOD3    | Superoxide dismutase 3, extracellular                                  | 4          | 90,91,364, 367–370 | 8 |
| SOX5    | SRY (sex determining region Y)-box 5                                  | 12         | 371 |
| STAT1   | Signal transducer and activator of transcription 1, 91 kDa            | 2          | 185 |
| STAT3   | Signal transducer and activator of transcription 3 (acute-phase response factor) | 17         | 372 |
| STAT6   | Signal transducer and activator of transcription 6, interleukin-4 induced | 12         | 79 | 241 |
| STIP1   | Stress-induced-phosphoprotein 1                                       | 11         | 373 |
| TBXA2R  | Thromboxane A2 receptor                                                | 19         | 244,374 |
| TGFB1   | Transforming growth factor, beta 1                                    | 19         | 69,77,146, 30,149,151, 147,238, 171,383, 375–382 |
| TGFB3   | Transforming growth factor, beta receptor III                          | 1          | 190 |
| TIMP1   | TIMP metalloproteinase inhibitor 1                                     | X          | 285, 69 |
| TIMP2   | TIMP metalloproteinase inhibitor 2                                     | 17         | 146,385,386, 147,151,387 | 5 |
| TLRA    | Toll-like receptor 4                                                  | 9          | 388,389, 96,271 |
| TNF     | Tumor necrosis factor (TNF superfamily, member 2)                     | 6          | 11,149,151, 83,120,146, 234,238,250, 147,155,230, 262,268, 233,333,250, 270–272, 248,269, 390–398, 273–275, 399–403 |
| TNS1    | Tensin 1                                                              | 2          | 191 |
| TP53    | Tumor protein p53                                                      | 17         | 101,307 |
| (p53)   |                                                                      |            |                |
| TRPV4   | Transient receptor potential cation channel, subfamily V, member 4     | 12         | 404 |
| TSLP    | Thymic stromal lymphopoietin                                          | 5          | 405 |
| VDR     | Vitamin D (1,25-dihydroxyvitamin D3) receptor                        | 12         | 406–408 | 409 |
| VEGFA   | Vascular endothelial growth factor A                                   | 6          | 410 |
| XRCC1   | X-ray repair complementing defective repair in Chinese hamster cells 1 | 19         | 300 |
| XRCC5   | X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining) | 2          | 412 |
FEV testing. The strongest genetic association signals with vital capacity (FVC) ratio after correction for multiple loci, none was significantly associated with forced lung function traits in the general populations of diverse origins or in cohorts of patients with respiratory diseases.

A systematic replication study of genes associated with lung function was recently conducted in the SpiroMeta Consortium. A literature search identified 104 publications reporting a positive association with lung-function traits in the general populations of diverse origins or in cohorts of patients with respiratory diseases. A total of 130 genes and 48 intergenic regions were studied in 20,288 individuals. Among the 16,936 genotyped or imputed single-nucleotide polymorphisms (SNPs) in these loci, none was significantly associated with forced expiratory volume in one second (FEV₁) or FEV₁/FVC ratio after correction for multiple testing. The strongest genetic association signals with FEV₁ were observed in ever-smokers in the SERPINA1 and PDE4D genes.

Smaller-scale studies testing multiple genes were also conducted in China. First, 170 asthmatic cases and 347 controls were evaluated for 119 SNPs in 98 genes for association with lung function. After correction for multiple testing, none of the SNPs was significantly associated with lung function (ie, FEV₁, FVC, or FEV₁/FVC). The strongest association was observed between rs320995 (Phe309Phe) in CYSLTR1 and FEV₁/FVC ($P = 0.0004$). Second, 1,261 SNPs in 380 candidate genes for cancer or other human diseases were tested for association with COPD in 53 cases and 107 controls with in-home coal exposure. A total of 22 genes were associated with COPD risk, but only PTEN was significant after correction for multiple testing. Considering the small sample sizes, the results of these studies must be replicated before reaching firm conclusions.

Figure 1 Candidate genes associated with chronic obstructive pulmonary disease (COPD) or related phenotypes. Notes: The upper part shows a histogram of the number of COPD susceptibility genes based on the number of publications supporting a significant genetic association. The lower part shows the corresponding genes in each bar. Official gene symbols are indicated. The number of publications that are supportive is indicated in parentheses. References are provided in Table 1 for genes supported by at least one publication and in Supplementary Table 1 for genes tested but not supported.

**Multi-gene-association studies**

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**Genome-wide association studies on COPD**

Table 2 summarizes COPD susceptibility loci identified by genome-wide association (GWA) studies. The results of the first GWA study on COPD were published in 2009. The GWA study was conducted in a case-control cohort of...
COPD locus was identified on chromosome 19q13, which was confirmed in this extended GW A study. In addition, a new group of candidate genes for chronic obstructive pulmonary disease was identified (ie, CHRNA3/CHRNA5/IREB2, HHIP, and FAM13A). These genes were studied in the ECLIPSE, NETT-NAS, Norway, and COPDGene studies. The latest GWA study on COPD was performed using 3499 cases and 1922 controls regrouping from the multicenter Evaluation of COPD Longitudinally to Normative Aging Study (NAS), as well as cases and controls from the Framingham Heart Study. In 2007, Wilk et al reported the first GW A study on lung function in approximately 1200 individuals. The study was conducted as part of the Framingham Heart Study. Association tests were performed on 70,987 autosomal SNPs and for ten spirometry phenotypes. No SNP was associated with lung-function phenotypes using stringent criteria for genome-wide significance, but suggestive evidence of association was provided for a nonsynonymous coding SNP in exon 5 of the GTO2 gene. In 2009, a larger GW A study from the Framingham Heart Study was performed in 7691 participants. Interestingly, the 4q31-HHIP COPD locus harbored the RAB4B, EGLN2, MIA, and CYP2A6 genes. It was estimated that the four GW A-nominated COPD loci accounted for ~5% of the total variance of the sibling relative risk of COPD.

Two of the four genome-wide associated loci found in COPD – 15q25 and 19q13 – were previously associated with cigarettes smoked per day and cotinine levels, suggesting that the risk alleles are acting through smoking behavior. Further studies support this hypothesis on 15q25. In fact, previous studies suggested that sequence variants on chromosome 15q25 confer risk of smoking-related lung diseases (ie, COPD and lung cancer) through its effect on tobacco addiction. This is consistent with the lack of association between the 15q25 locus and lung cancer among never-smokers. In contrast, other evidence argues against this hypothesis, showing weak or no evidence that the 15q25 locus directly influences smoking behavior, and no appreciable variation in the risk of lung cancer across smoking categories, and significant effect of the 15q25 locus on smoking-related diseases after adjustment for smoking exposure. Multiple distinct loci affecting both smoking behavior and lung cancer were reported on 15q25. It is still unknown whether genes located at any of these loci are causally involved in the pathogenesis of COPD and lung cancer or the effect is mediated by changing smoking behavior. Risk alleles on chromosome 15q25 were shown to modulate the mRNA expression levels of the CHRNA5 gene in the brain and lung tissues as well as the expression of CHRNA5 and IREB2 genes in sputum. The regulation of genes in primary disease tissues, such as lung and sputum, suggests a direct effect of 15q25 genes on COPD susceptibility. More functional studies are needed to find the causal alleles and genes on 15q25 as well as to disentangle their impact on correlated traits associated with this chromosomal region.

**GWA studies on lung function**

In 2007, Wilk et al reported the first GW A study on lung function in approximately 1200 individuals. The study was conducted as part of the Framingham Heart Study. Association tests were performed on 70,987 autosomal SNPs and for ten spirometry phenotypes. No SNP was associated with lung-function phenotypes using stringent criteria for genome-wide significance, but suggestive evidence of association was provided for a nonsynonymous coding SNP in exon 5 of the GSTO2 gene. In 2009, a larger GW A study from the Framingham Heart Study was performed in 7691 participants.
Table 2 Susceptibility loci for chronic obstructive pulmonary disease (COPD) and related phenotypes identified by genome-wide association studies

| Reference     | Study* | Sample size (cases/controls) | Disease/trait | Platform (# SNPs) | Region (size) | Gene | Key SNPs |
|---------------|--------|------------------------------|---------------|-------------------|---------------|-------|----------|
| Pillai et al 15 | Norway | 823/810                      | COPD          | Illumina (Human Hap550) | 15q25         | CHRNA3, CHRNA5 | rs8034191, rs1051730 |
|               | ICGN   | 1891                         |               |                   |               |       |          |
|               | NETT-NAS | 389/472                     |               |                   |               |       |          |
|               | EOCOPD | 949                          |               |                   |               |       |          |
| Cho et al 19  | Norway | 2940/1380                    | COPD          | Illumina (Human Hap550 or Quad610) | 15q25         | CHRNA3, CHRNA5, IREB2 | rs1062980, rs1828591, rs13118928, rs7671167, rs1903003 |
|               | NETT-NAS | 2940/1380                    |               |                   |               |       |          |
|               | ECLIPSE | 1764/178                     | COPD          | Illumina (Human Hap550, Quad610, or Omni1 Quad) | 15q25         | CHRNA3, CHRNA5, IREB2 | rs964516, rs7671167, rs13141641, rs13118928, rs11858836, rs13180 |
|               | GenKOLS | 373/435                      |               |                   |               |       |          |
|               | COPDGene | 863/808                      |               |                   |               |       |          |
|               | ICGN   | 983 probands/1876 siblings   |               |                   |               |       |          |
| Wilk et al 17 | FHS    | 1059–1222                    | Ten spirometry phenotypes | Affymetrix (70,987) | 10q25         | GSTO2 | rs156697 |
| Wilk et al 18 | FHS    | 7691                         | FEV1/FVC      | Affymetrix (500 K + 50 K) | 4q31  | HHIP | rs13147758 |
| Repapi et al 40 | SpiroMeta Consortium | 20,288                     | FEV1, and FEV1/FVC | Affymetrix and Illumina (2.5 million) | 4q31 | HHIP | rs12504628 |
| Hancock et al 37 | CHARGE Consortium | 20,890                     | FEV1/FVC     | Affymetrix and Illumina (2,515,866) | 2q36 | PID1 | rs1435867 |
|               | SpiroMeta consortium | 16,178                     |               |                   |               |       |          |

(Continued)
was associated with percent predicted FEV$_1$/FVC ratio. This locus was confirmed in a second set of participants from the Family Heart Study (n = 835).

In January 2010, two articles reported GWA studies for lung function.$^{39,40}$ First, Repapi et al$^{40}$ performed a GWA study on FEV$_1$ and FEV$_1$/FVC ratio in the SpiroMeta consortium (20,288 individuals of European ancestry). They have also followed up the best associated SNPs in 32,184 additional individuals. Overall, they have identified five novel genome-wide significant loci for pulmonary function,
being 2q35 (TNS1), 4q24 (GSTCD), and 5q33 (HTR4) for FEV₁, and 6p21 (AGER) and 15q23 (THSD4) for FEV₁/FVC. Second, Hancock et al²⁹ conducted a GWA study on the same two clinically important pulmonary function measures in the CHARGE consortium consisting of 20,890 participants of European ancestry. They identified significant associations with FEV₁/FVC ratio for SNPs located in seven previously unrecognized loci: 6q24 (GPR126), 5q33 (ADAM19), 6p21 (AGER and PPT2), 4q22 (FAM13A), 9q22 (PTCH1), 2q36 (PID1), and 5q33 (HTR4). For FEV₁, one new locus annotated by three genes (INTS12, GSTCD, and NPNT) on 4q24 was identified. 4q24 (GSTCD), 5q33 (HTR4) and 6p21 (AGER) were common in both consortia, ie, SpiroMeta and CHARGE. The previously reported 4q31 locus located upstream of the HHIP gene associated with FEV₁ and FEV₁/FVC ratio was also confirmed in these consortia.

More recently, a larger GWA study of FEV₁ and FEV₁/FVC ratio was reported, comprising more than 48,000 individuals of European ancestry and followed up for replication in more than 46,000 individuals.⁴¹ Ten out of eleven loci previously reported by the SpiroMeta and CHARGE consortia were replicated in this extended GWA study. Only PID1 on 2q36 was not replicated. More interestingly, 16 new loci were identified, including twelve loci for FEV₁/FVC, three for FEV₁, and one for both traits. Thus, 26 loci were associated with lung function in this GWA study. Together, these loci explain 3.2% of the additive polygenic variance for FEV₁/FVC and 1.5% of the variance for FEV₁.

The first GWA study on lung-function decline was recently reported.⁴² Briefly, genome-wide analyses on FEV₁ and FEV₁/FVC decline were conducted in 2677 nonasthmatics and 1441 asthmatics separately. The top hits were then replicated in 10,858 nonasthmatic and 1138 asthmatic participants. Decline of FEV₁ and FEV₁/FVC ratio was evaluated during a follow-up examination period of roughly 10 years in these participants. No SNP reached genome-wide significance in the discovery set. However, one locus on chromosome 13q14.3 containing the DLEU7 gene was strongly associated with FEV₁ decline in nonasthmatics from the discovery set and confirmed in the replication set. A strong association signal was also reported on 8p22 harboring the TUSC3 gene for FEV₁/FVC decrease in asthmatics, but not validated in the replication set. Many loci previously associated with cross-sectional lung function in GWA studies described above were replicated with baseline lung function in either asthmatic or nonasthmatic subjects. However, few GWAS-nominated lung-function loci were associated with lung-function decline, suggesting different genetic mechanisms governing baseline lung function and decline with age. In addition, this study showed the genetic heterogeneity of lung-function decline between subjects with and without asthma. Table 2 summarizes lung-function susceptibility loci identified by GWA studies.

**GWA studies on COPD-related phenotypes**

Other GWA studies were reported on COPD-related phenotypes. Emphysema is an important feature of COPD and varies considerably between patients. A recent GWA study was performed on emphysema measures by computed tomography scan and defined by radiologist qualitative scores and quantitative assessments of low-attenuation areas.⁴³ The qualitative scores obtained in 1557 patients from the ECLIPSE study and 432 subjects from the Norway cohort led to the identification of an emphysema locus on chromosome 12p11.2. The most strongly associated SNP is located in the BICD1 gene, known to be involved in regulating telomere length. The ECLIPSE, Norway, and NETT studies were also used to perform a GWA study on COPD-related cachexia phenotypes, including body mass index and fat-free mass index.⁴⁴ Cachexia occurs in approximately 10% of patients with COPD and is associated with increased mortality. The GWA study on body mass index and fat-free mass index in patients with COPD identified a single susceptibility locus that harbored the FTO gene, the most robust gene associated with obesity. Whether FTO acts through obesity or directly affects lung function remains to be elucidated.

GWA studies on COPD, lung function, and related phenotypes provided strong and consistent evidence of genetic susceptibility loci. These studies also highlight the large number of participants required to identify reproducible genetic loci. So far, GWA studies have identified only a small fraction of the genetic variants contributing to COPD risk, related complications, and lung-function variability. GWA studies on larger sample sizes, especially for COPD, will be required to identify the genetic factors underpinning COPD and related phenotypes. Large international efforts are under way to increase sample sizes and use more comprehensive molecular phenotyping (eg, gene expression in the lung) to elucidate the genetic component of COPD.⁴⁵,⁴⁶ It should be emphasized that the causal genes and genetic variants of all these newly discovered loci by GWA studies remain to be identified. More integrative genomic approaches will be required for these purposes. Different study designs testing rare and copy-number variants as well as gene-smoking interaction are also needed.
Integrative genomic approaches

More studies are being conducted using integrative genomic approaches in order to identify COPD susceptibility genes. For example, the IREB2 gene was identified by combining gene expression in human lungs and genetic association in COPD cohorts.47 In this study, lung specimens were obtained from patients undergoing lung nodule resection, and gene expression was compared between 15 COPD and 18 non-COPD patients using whole-genome gene-expression arrays. A total of 889 SNPs found in the 62 genomic regions containing genes differentially expressed between patients with or without COPD were tested for association with COPD and lung function. Seventy-one SNPs nominally associated ($P \leq 0.05$) with COPD in the NETT-NAS study were followed up for replication in the EOCOPD study. A gene-based replication was then completed to confirm genetic association between genetic variants in the IREB2 gene and lung function. Overall, the IREB2 gene was shown to be upregulated in lung specimens of COPD patients and to contain genetic variants associated with COPD. Gene expression in a larger number of lung specimens will be required to test whether COPD-associated SNPs in the IREB2 gene influence the expression of its gene product.

Although Table 2 shows the major susceptibility loci identified by GWA studies, many additional loci were borderline significant in these studies. Many true positives are likely to be missed by this approach owing to the stringent threshold used to control for false-discovery rates. Different weighting methods and SNP-prioritization strategies are currently used to find true-positive signals from previous GWA studies. For example, the FGF7 gene was recently identified as a COPD susceptibility locus by weighting GWA analysis on regions of conserved homozygosity haplotype in subjects affected with COPD compared to unaffected subjects.48 As mentioned previously,49 further studies reanalyzing genome-wide SNP datasets with weighting methods based on function annotations (eg, coding variants or regions) or prior knowledge (eg, candidate genes or genome-wide linkage studies) will be required. Similarly, ongoing lung expression quantitative trait loci (eQTLs) mapping data50,46 are likely to leverage the impact of previous GWA studies on COPD by providing a list of SNPs that regulate gene expression in relevant tissues. SNPs associated with gene expression will provide crucial functional information to understand the molecular changes introduced by the susceptibility DNA variants. The identification of SNPs associated with both disease traits and quantitative transcript levels of one or more genes in relevant tissues will highlight the most likely causal gene within the susceptibility loci and the functional SNPs that are prime candidates to be directly involved in the pathogenesis of COPD.

Conclusion

Elucidating the genetic component of COPD and lung function turned out to be a challenging task. Major resources and collaborative efforts will be required to achieve our goal. In this review, the author provides an updated list of COPD genes and a summary of GWAS results conducted during the last few years. It is hoped that the gene list can be used by investigators to replicate or refute susceptibility genes of COPD. As eluded above, this gene list can also be used to reanalyze GWA data by prioritizing genes previously associated with COPD or related phenotypes or enter into more global gene network and causality analyses. Owing to the challenge faced by the genetic community, large collections of patients well characterized for COPD phenotypes are ongoing to identify the genuine COPD genes. A lumping and splitting strategy is an old idea in the field of genetics of complex traits50 that will certainly be essential in the field of COPD. Pooling resources (ie, lumping) is required to obtain proper sample sizes, but is likely to increase heterogeneity. These larger sample sizes, however, provide the opportunity to subdivide (ie, splitting) the pooled data into more homogeneous subgroups where the molecular defects are more likely to be similar. Accordingly, not only the genetic community but the entire spectrum of experts managing and treating patients with COPD will be required to provide samples, precise phenotypes, and expertise to search for the underlying genetic mechanisms. In parallel, complementary multidimensional genomic data in relevant tissues (eg, lung eQTLs) will be crucial to uncover causal genes and genetic variants that contribute to COPD and to discover new molecular targets for prevention, diagnosis, and treatment.

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References

1. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet. 1997;349(9064):1498–1504.
2. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med. 2007;176(6):532–555.

3. Halbert RJ, Natoli JL, Gano A, Badamarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523–532.

4. Bossé Y. Genetics of chronic obstructive pulmonary disease: a succinct review, future avenues and prospective clinical applications. Pharmacogenomics. 2009;10(4):655–667.

5. Castaldi PJ, Cho MH, Cohn M, et al. The COPD genetic association compendium: a comprehensive online database of COPD genetic associations. Hum Mol Genet. 2010;19(3):526–534.

6. Chanock SJ, Manolio T, Boehnke M, et al. Replicating genotype-phenotype associations. Nature. 2007;447(7145):655–660.

7. Hu G, Yao W, Zhou Y, et al. Meta- and pooled analyses of the effect of glutathione S-transferase M1 and T1 deficiency on chronic obstructive pulmonary disease. Int J Tuberc Lung Dis. 2008;12(12):1474–1481.

8. Smolonska J, Wijmenga C, Postma DS, Boezen HM. Meta-analyses on suspected chronic obstructive pulmonary disease genes: a summary of 20 years’ research. Am J Respir Crit Care Med. 2009;180(7):618–631.

9. Zhan F, Wang J, Wei SZ, et al. TNF-308 gene polymorphism is associated with COPD risk among Asian: meta-analysis of data for 6,118 subjects. Mol Biol Rep. 2011;38(13):219–227.

10. Zhang S, Wang C, Xi B, Li X. Association between the tumour necrosis factor-alpha-308G/A polymorphism and chronic obstructive pulmonary disease. Respirology. 2011;16(1):107–115.

11. Gingo MR, Silveira LJ, Miller YE, et al. Tumour necrosis factor gene polymorphisms are associated with COPD. Eur Respir J. 2008;31(5):1005–1012.

12. Obeidat M, Wain LV, Shrine N, et al. A comprehensive evaluation of potential lung function associated genes in the SpiroMeta general population sample. PLoS One. 2011;6(5):e193382.

13. Hong X, Zhou H, Tsai HJ, et al. CysteinyI leukotriene receptor 1 gene variation and risk of asthma. Eur Respir J. 2009;33(1):42–48.

14. Hosgood HD 3rd, Menashe I, He X, Chanock S, Lan Q. PTEN identified as important risk factor of chronic obstructive pulmonary disease. Respir Med. 2009;103(12):1866–1870.

15. Pillai SG, Ge D, Zhu G, et al. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. PLoS Genet. 2009;5(3):e1000421.

16. Amos CI, Wu X, Broderick P, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet. 2008;40(5):616–622.

17. Thorogirsson TE, Geller F, Sulem P, et al. A variant associated with nicotine dependence and lung cancer maps to nicotinic acetylcholine receptor subunit genes on chromosome 15q25.1. The COPD genetic association studies influence different disease-related phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182(12):1498–1505.

18. Wang Y, Broderick P, Matakidou A, Eisen T, Houlston RS. Role of 5p15.33 (TERT-CLPTM1L) 6p21.33 and 15q25.1 (CHRNA5-CHRNA3) variation and lung cancer risk in never-smokers. Carcinogenesis. 2010;31(2):234–238.

19. Spitz MR, Amos CI, Dong Q, Lin J, Wu X. The CHRNA5-A3 region on chromosome 15q24-25.1 is a risk factor both for nicotine dependence and for lung cancer. J Natl Cancer Inst. 2008;100(21):1552–1556.

20. Landi MT, Chatterjee N, Yu K, et al. A genome-wide association study of lung cancer identifies a region of chromosome 5p15 associated with risk for adenocarcinoma. Am J Hum Genet. 2009;85(5):679–691.

21. Chappell SL, Daly L, Lotya J, et al. The role of IREB2 and transforming growth factor-beta-1 variant in COPD: a replication case-control study. BMC Med Genet. 2011;12:24.

22. Saconne NL, Curlerhouse RC, Schwantes-An TH, et al. Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. PLoS Genet. Aug 2010;6(8):e1001053.

23. Broderick P, Wang Y, Vijayakrishnan J, et al. Deciphering the impact of common genetic variation on lung cancer risk: a genome-wide association study. Cancer Res. 2009;69(16):6633–6641.

24. Wang JC, Cruchaga C, Saconne NL, et al. Risk for nicotine dependence and lung cancer is conferred by mRNA expression levels and amino acid change in CHRNA5. Hum Mol Genet. 2009;18(16):3125–3135.

25. Wang JC, Gruca R, Cruchaga C, et al. Genetic variation in the CHRNA5 gene affects mRNA levels and is associated with risk for alcohol dependence. Mol Psychiatry. 2009;14(5):501–510.

26. Falabella FS, Galvan A, Frullanti E, et al. Transcript deregulation at the 15q25 locus in association with lung adenocarcinoma risk. Clin Cancer Res. 2009;15(5):1837–1842.

27. Qiu W, Cho MH, Riley NJ, et al. Genetics of sputum gene expression in chronic obstructive pulmonary disease. PLoS One. 2011;6(9):e24395.

28. Wilk JB, Walter RE, Laramie JM, Gottlieb DJ, O’Connor GT, Framingham Heart Study genome-wide association: results for pulmonary function measures. BMC Med Genet. 2007;8 Suppl 1:S8.

29. Wilk JB, Chen TH, Gottlieb DJ, et al. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet. 2009;5(3):e1000429.

30. Hancock DB, Eijgelsheim M, Wilk JB, et al. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. Nat Genet. 2010;42(1):45–52.

31. Repapi E, Sayers I, Wain LV, et al. Genome-wide association study identifies five loci associated with lung function. Nat Genet. 2010;42(1):36–44.

32. Soler Artigas M, Loth DW, Wain LV, et al. Genome-wide association and large-scale follow up identifies 16 new loci influencing lung function. Nat Genet. 2011;43(11):1082–1090.

33. Imboden M, Bouzigon E, Curjucic I, et al. Genome-wide association study of lung function decline in adults with and without asthma. J Allergy Clin Immunol. 2012;129(5):1218–1228.

34. Kong X, Cho MH, Anderson W, et al. Genome-wide association study identifies BICD1 as a susceptibility gene for emphysema. Am J Respir Crit Care Med. 2011;183(1):43–49.

35. Wan ES, Cho MH, Boutaoui N, et al. Genome-wide association analysis of body mass in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2011;45(2):304–310.
65. van Diemen CC, Postma DS, Aulchenko YS, et al. Novel strategy to identify genetic risk factors for COPD severity: a genetic isolate. *Eur Respir J*. 2010;35(4):768–775.

66. Sadeghnejad A, Ohar JA, Zheng SL, et al. Adam33 polymorphisms are associated with COPD and lung function in long-term tobacco smokers. *Respir Res*. 2009;10:21.

67. Wang X, Li L, Xiao J, et al. Association of ADAM33 gene polymorphisms with COPD in a northeastern Chinese population. *BMC Med Genet*. 2009;10:132.

68. Schedel M, Depner M, Schoen C, et al. The role of polymorphisms in ADAM33, a disintegrin and metalloprotease 33, in childhood asthma and lung function in two German populations. *Respir Res*. 2006;7:91.

69. van Diemen CC, Postma DS, Aulchenko YS, et al. Novel strategy to identify genetic risk factors for COPD severity: a genetic isolate. *Eur Respir J*. 2010;35(4):768–775.

70. Pabst S, Pizarro Tourn C, Giliissen A, et al. ADAM33 gene polymorphisms in chronic obstructive pulmonary disease. *Eur J Med Res*. 2009;14 Suppl 4:177–181.

71. Hegab AE, Sakamoto T, Saitoh W, et al. Polymorphisms of IL4, IL13, and ADRB2 genes in COPD. *Chest*. 2004;126(6):1832–1839.

72. Ho Li, Harn HJ, Chen CJ, Tsai NM. Polymorphism of the beta(2)-adrenoceptor in COPD in Chinese subjects. *Chest*. 2001;120(5):1483–1499.

73. Joos L, Weir TD, Connell JE, et al. Polymorphisms in the beta2 adrenergic receptor and bronchodilator response, bronchial hyperresponsiveness, and rate of decline in lung function in smokers. *Thorax*. 2005;58(5):703–707.

74. Kim WJ, Oh YM, Sung J, et al. CT scanning-based phenotypes vary with ADRB2 polymorphisms in chronic obstructive pulmonary disease. *Respir Med*. 2009;103(1):98–103.

75. Vaccia G, Schwabe K, Duck R, et al. Polymorphisms of the beta2 adrenoceptor gene in chronic obstructive pulmonary disease. *Thorax*. 2009;64(1):3–10.

76. Papatheodorou A, Makrythanasis P, Kaliakatsos M, et al. Development of novel microarray methodology for the study of mutations in the SERPINA1 and ADRB2 genes – their association with obstructive pulmonary disease and disseminated bronchiectasis in Greek patients. *Clin Biochem*. 2010;43(1–2):43–50.

77. Kim WJ, Hoffman E, Reilly J, et al. Association of COPD candidate genes with computed tomography emphysema and airway phenotypes in severe COPD. *Eur Respir J*. 2011;37(1):39–43.

78. Matheson MC, Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ. Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults. *J Hum Genet*. 2006;51(11):943–951.

79. Leung TF, Chan IH, Wong GW, et al. Association between candidate gene polymorphism and lung function growth in Chinese asthmatic children. *Clin Exp Allergy*. 2007;37(10):1480–1486.

80. Turner SW, Khoo SK, Laing IA, et al. Beta2 adrenergic receptor Arg16Gly polymorphism, airway responsiveness, lung function and asthma in infants and children. *Clin Exp Allergy*. 2004;34(7):1043–1048.

81. Summerhill E, Leavitt SA, Gidley H, Parry R, Solway J, Ober C. Beta(2)-adrenergic receptor Arg16Gly polymorphism is associated with reduced lung function, but not with asthma, in the Hutterites. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):599–602.

82. Silverman EK, Kwiatkowski DJ, Sylvia JS, et al. Family-based association analysis of beta2-adrenergic receptor polymorphisms in the childhood asthma management program. *J Allergy Clin Immunol*. 2003;112(5):870–876.

83. Brogger J, Steen VM, Eiken HG, Gulsvik A, Bakke P. Genetic association between COPD and polymorphisms in TNF, ADRB2 and EPHX1. *Eur Respir J*. 2006;27(4):682–688.

84. Holloway JW, Barton SJ, Holgate ST, Rose-Zerilli MJ, Sayers I. The role of LTA4H and ALOX5AP polymorphism in asthma and allergy susceptibility. *Allergy*. 2008;63(8):1046–1053.

85. Ning Y, Ying B, Han S, Wang B, Wang X, Wen F. Polymorphisms of aquaporin5 gene in chronic obstructive pulmonary disease in a Chinese population. *Swiss Med Wkly*. 2008;138(39–40):573–578.

86. Hansel NN, Siddhaye V, Rafalski NM, et al. Aquaporin 5 polymorphisms and rate of lung function decline in chronic obstructive pulmonary disease. *PLoS One*. 2010;5(12):e14226.
87. Mata M, Takabatake N, Inoue S, et al. Intronic single-nucleotide polymorphisms in Bcl-2 are associated with chronic obstructive pulmonary disease severity. *Respirology*. 2007;12(1):34–41.

88. Hopkinson NS, Elefteriou KI, Payne J, et al. +9/+9 Homozygosity of the bradykinin receptor gene polymorphism is associated with reduced fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr*. 2006;83(4):912–917.

89. Smith AK, Lange LA, Ampleford EJ, Meyers DA, Bleeker ER, Howard TD. Association of polymorphisms in CASP10 and CASP8 with FEV1/FVC and bronchial hyperresponsiveness in ethnically diverse asthmatics. *Clin Exp Allergy*. 2008;38(11):1738–1744.

90. Korytina GF, Akhmadishina LZ, Tselousova OS, Zagidullin SZ, Viktorova TV. Polymorphism of the genes for antioxidant defense enzymes and their association with the development of chronic obstructive pulmonary disease in the population of Bashkortostan. *Genetika*. 2009;45(7):967–976. Russian.

91. Young RF, Hopkins R, Black PN, et al. Functional variants of anti-oxidant genes in smokers with COPD and in those with normal lung function. *Thorax*. 2006;61(5):394–399.

92. Mak JC, Ho SP, Yu WC, et al. Polymorphisms and functional activity in superoxide dismutase and catalase genes in smokers with COPD. *Eur Respir J*. 2007;30(4):684–690.

93. Hizawa N, Makita H, Nasuhara Y, et al. Functional single nucleotide polymorphisms of the CCL5 gene and nonemphysematous phenotype in COPD patients. *Eur Respir J*. 2008;32(2):372–378.

94. Al-Abdulhadi SA, Al-Rabia MW. Association and preferential transmission of the CCR2+64I polymorphism with absence of asthma in high-risk families. *Saudi Med J*. 2008;29(12):1711–1718.

95. Zhou H, Alexis NE, Almond M, et al. Influence of C-159T SNP of the CD4+ T cell receptor gene in patients with disseminated bronchiectasis. *Hum Genet*. 2009;125(5):228–233.

96. LeVan TD, Von Essen S, Romberger DJ, et al. Polymorphisms in the CD14 gene associated with pulmonary function in farmers. *Am J Respir Crit Care Med*. 2005;171(7):773–779.

97. Liu Y, Liang WB, Gao LB, Wang YY, Zhang L. Association of CD40-1CT polymorphism in the 5’-untranslated region and chronic obstructive pulmonary disease. *Clin Chim Acta*. 2009;408(1–2):56–59.

98. Zhang XZ, Pare PD, Sandford AJ. PMN degranulation in relation to CD63 expression and genetic polymorphisms in healthy individuals and COPD patients. *Int J Mol Med*. 2007;19(5):817–822.

99. Liu Y, Liang WB, Gao LB, et al. CTLA4 and CD86 gene polymorphisms and susceptibility to chronic obstructive pulmonary disease. *Hum Immunol*. 2010;71(11):1141–1146.

100. Takabatake N, Toriyama S, Igarashi A, et al. Novel polymorphism in CDC6 is associated with the decline in lung function of ex-smokers in COPD. *Biochem Biophys Res Commun*. 2009;381(4):912–917.

101. Lee YL, Chen W, Tsai WK, et al. Polymorphisms of p53 and p21 genes in chronic obstructive pulmonary disease. *J Lab Clin Med*. 2006;147(5):228–233.

102. Bombieri C, Benetazzo M, Saccomani A, et al. Complete mutational screening of the CFTR gene in 120 patients with pulmonary disease. *Hum Genet*. 1998;103(6):718–722.

103. Dumur V, Lafitte JJ, Gervais R, et al. Abnormal distribution of cystic fibrosis delta F508 allele in adults with chronic bronchial hypersecretion. *Lancet*. 1990;335(8701):1340.

104. Gervais R, Lafitte JJ, Dumur V, et al. Sweat chloride and delta F508 mutation in chronic bronchitis or bronchiectasis. *Lancet*. 1993;342(8877):997.

105. Piganiot PF, Bombieri C, Benetazzo M, et al. CFTR gene variant IVS8-5T in disseminated bronchiectasis. *Am J Hum Genet*. 1996;58(4):889–892.

106. Poller W, Faber JP, Scholz S, Olek K, Muller KM. Sequence analysis of the cystic fibrosis gene in patients with disseminated bronchiectatic lung disease. Application in the identification of a cystic fibrosis patient with atypical clinical course. *Klin Wochenschr*. 1991;69(14):657–663.
127. Korytina GF, Yanbaeva DG, Babenkova LI, Etkina EI, Victorova TV. Genetic polymorphisms in the cytochromes P-450 (1A1, 2E1), microsomal epoxide hydrolase and glutathione S-transferase M1, T1, and P1 genes, and their relationship with chronic bronchitis and relapsing pneumonia in children. J Mol Med. 2005;83(9):700–710.

128. Cheng SL, Yu CJ, Yang PC. Genetic polymorphisms of cytochrome p450 and matrix metalloproteinase in chronic obstructive pulmonary disease. Biochem Genet. 2009;47(7–8):591–601.

129. Korytina GF, Akhmadishina LZ, Kochetova OV, Zagidullin SZ, Victorova TV. Association of cytochrome P450 genes polymorphisms (CYP1A1 and CYP1A2) with the development of chronic obstructive pulmonary disease in Bashkortostan. Mol Biol (Mosk). 2008;42(1):32–41. Russian.

130. Budhi A, Hiyama T, Ozdemir T, Bilgen T, Tosun O, Keser I. The effect of CYP1A2 gene polymorphisms on theophylline metabolism and chronic obstructive pulmonary disease in Turkish patients. BMB Rep. 2010;43(8):530–534.

131. Uslu A, Ogus C, Ozdemir T, Bilgen T, Tosun O, Keser I. The effect of CYP1A2 gene polymorphisms on theophylline metabolism and chronic obstructive pulmonary disease in Turkish patients. BMB Rep. 2010;43(8):530–534.

132. Arif E, Vibhuti A, Alam P, et al. Association of CYP2E1 and NAT2 gene polymorphisms with chronic obstructive pulmonary disease. Clin Chim Acta. 2007;382(1–2):37–42.

133. Korytina GF, Akhmadishina LZ, Victorova TV. The CYP1B1 and CYP2F1 genes polymorphisms frequency in three ethnic groups of Bashkortostan and chronic obstructive pulmonary disease patients. Mol Biol (Mosk). 2010;44(1):33–41. Russian.

134. Seo T, Pahwa P, McDuffie HH, et al. Genetic association analysis of COPD-related traits on chromosome 8p. Am J Respir Cell Mol Biol. 2005;33(4):535–536.

135. Matsushita I, Hasegawa K, Nakata K, Yasuda K, Tokunaga K, Keicho N. Association between cytochrome P450 3A5 polymorphism and the lung function in Saskatchewan grain workers. Pharmacogenet Genomics. 2008;18(6):487–493.

136. Hu RC, Xu YJ, Zhang ZX, Ni W, Chen SX. Correlation of HDEFB1 polymorphism and susceptibility to chronic obstructive pulmonary disease in Chinese Han population. Chin Med J (Engl). 2004;117(11):1637–1641.

137. Matsuhashi T, Hasegawa K, Nakata K, Yasuda K, Tokunaga K, Keicho N. Genetic variants of human beta-defensin-1 and chronic obstructive pulmonary disease. Biochem Biophys Res Commun. 2002;291(1):17–22.

138. Hersh CP, Demco DL, Raby BA, et al. Genetic linkage and association analysis of COPD-related traits on chromosome 8p. COPD. 2006;3(4):189–194.

139. Janssens W, Nuutten H, Dupont LJ, et al. Genomic copy number determines functional expression of beta-defensin 2 in airway epithelial cells and associates with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182(2):163–169.

140. Samposnas F, Antonacciopoulou A, Spathis D, et al. Positive association between two polymorphic sites (+134 ins/A delA and G198T) of the endothelin-1 gene and chronic obstructive pulmonary disease. A case-control study. Respir Med. 2010;104(1):114–120.

141. Kaparitano A, Argyropoulou E, Eftimidis G, Flordellis C, Spirooulis K. Decline in FEV1 related to genetic polymorphisms (+138 ins/A delA and Lys198Asn) of the endothelin-1 gene in COPD. A pilot study. Eur Rev Med Pharmacol Sci. 2010;14(8):705–719.

142. Kaparitano A, Samposnas F, Lykouras D, et al. Association of ET-1 genes with COPD phenotypes in a Caucasian population. Monaldi Arch Chest Dis. 2011;75(2):126–131.

143. Samposnas F, Lykouras D, Drakatos P, Moschopoulou A, Spirooulis K, Karkoulias K. Endothelin-1 polymorphisms involved in impaired exercise tolerance in COPD patients. A pilot study. Eur Rev Med Pharmacol Sci. 2011;15(2):123–128.

144. Taille C, Guencougo A, Almolii A, et al. ETB receptor polymorphism is associated with airway obstruction. BMC Pulm Med. 2007;7:5.

145. Kelleher CM, Silverman EK, Broekelmann T, et al. A functional mutation in the terminal exon of elastin in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2005;33(4):355–362.

146. Cho MH, Ciulla DM, Klanderman BJ, et al. Analysis of exonic elastin variants in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol. 2009;40(6):751–755.

147. DeMeo DL, Hersh CP, Hoffman EA, et al. Genetic determinants of emphysema distribution in the national emphysema treatment trial. Am J Respir Crit Care Med. 2007;176(1):42–48.

148. Hersh CP, DeMeo DL, Lazarus R, et al. Genetic association analysis of functional impairment in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2006;173(9):977–984.

149. Cheng SL, Yu CJ, Chen CJ, Yang PC. Genetic polymorphism of epoxide hydrolase and glutathione S-transferase in COPD. Eur Respir J. 2004;23(6):818–824.

150. DeMeo DL, Campbell EJ, Barker AF, et al. IL10 polymorphisms are associated with airflow obstruction in severe alpha-antitrypsin deficiency. Am J Respir Cell Mol Biol. 2008;38(1):114–120.

151. Hang J, Zhou W, Wang X, et al. Microsomal epoxide hydrolase, endotoxin, and lung function decline in cotton textile workers. Am J Respir Crit Care Med. 2005;171(2):165–170.

152. Hersh CP, Demco DL, Lange C, et al. Attempted replication of reported chronic obstructive pulmonary disease candidate gene associations. Am J Respir Cell Mol Biol. 2005;33(1):71–78.

153. Sandford AJ, Chagani T, Weir TD, Connett JE, Anthonisen NR, Pare PD. Susceptibility genes for rapid decline of lung function in the lung health study. Am J Respir Crit Care Med. 2001;163(2):469–473.

154. Smith CA, Harrison DJ. Association between polymorphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. Lancet. 1997;350(9078):630–633.

155. Viibhuti A, Arif E, Deepak D, Singh B, Qadar Pasha MA. Genetic polymorphisms of GSTP1 and mEPHX correlate with oxidative stress markers and lung function in COPD. Biochem Biophys Res Commun. 2007;359(1):136–142.

156. Xiao D, Wang C, Du MJ, et al. Association between polymorphisms in the microsomal epoxide hydrolase (mEH) gene and chronic obstructive pulmonary disease. Zhonghua Yi Xue Za Zhi. 2003;83(20):1782–1786. Chinese.

157. Xiao D, Wang C, Du MJ, et al. Relationship between polymorphisms of genes encoding microsomal epoxide hydrolase and glutathione S-transferase P1 and chronic obstructive pulmonary disease. Chin Med J (Engl). 2004;117(5):661–667.

158. Yoshikawa M, Hiyama K, Ishioka S, Maeda H, Maeda A, Yamakido M. Microsomal epoxide hydrolase genotypes and chronic obstructive pulmonary disease in Japanese. Int J Mol Med. 2005;15(2):443–448.

159. Zidzik J, Slaba E, Joppa P, et al. Glutathione S-transferase and microsomal epoxide hydrolase gene polymorphisms and risk of chronic obstructive pulmonary disease in Slovak population. Croat Med J. 2008;49(2):182–191.

160. Lakhkar R, Denden S, Knani J, et al. Microsomal epoxide hydrolase gene polymorphisms and susceptibility to chronic obstructive pulmonary disease in the Tunisian population. Genet Test Mol Biomarkers. 2010;14(6):857–863.

161. Denys G, Poliska S, Csanaky E, et al. Analyses of association between PPAR gamma and EPHX1 polymorphisms and susceptibility to COPD in a Hungarian cohort, a case-control study. BMC Med Genet. 2010;11:152.

162. Lakhkar R, Denden S, Mouhamed MH, et al. Correlation of EPHX1, GSTP1, GSTM1, and GSTT1 genetic polymorphisms with antioxidative stress markers in chronic obstructive pulmonary disease. Exp Lung Res. 2011;37(4):195–204.
165. Lakhdar R, Denden S, Knaani J, et al. Combined analysis of EPHX1, GSTP1, GSTM1 and GSTT1 gene polymorphisms in relation to chronic obstructive pulmonary disease risk and lung function impairment. *Dis Markers*. 2011;30(5):253–263.

166. Fu WP, Sun C, Dai LM, Yang LF, Zhang YP. Relationship between COPD and polymorphisms of HOX-1 and mEPH in a Chinese population. *Oncol Rep*. 2007;17(2):483–488.

167. Rodriguez F, Jardi R, Costa X, et al. Detection of polymorphisms at exons 3 (Tyr113→His) and 4 (His139→Arg) of the microsomal epoxide hydrolase gene using fluorescence PCR method combined with melting curves analysis. *Anal Biochem*. 2002;308(1):120–126.

168. Matheson MC, Raven J, Walters EH, Abramson MJ, Ellis JA. Microsomal epoxide hydrolase is not associated with COPD in a community-based sample. *Hum Biol*. 2006;78(6):705–717.

169. Yim JJ, Park GY, Lee CT, et al. Genetic susceptibility to chronic obstructive pulmonary disease in Koreans: combined analysis of polymorphic genotypes for microsomal epoxide hydrolase and glutathione S-transferase M1 and T1. *Thorax*. 2000;55(2):121–125.

170. Zhang R, Zhang A, He Q, Lu B. Microsomal epoxide hydrolase gene polymorphism and susceptibility to chronic obstructive pulmonary disease in Han nationality of North China. *Zhonghua Nei Ke Za Zhi*. 2002;41(1):11–14. Chinese.

171. Foreman MG, DeMeo DL, Hersh CP, et al. Polymorphic variation in surfactant protein B is associated with COPD exacerbations. *Eur Respir J*. 2008;32(4):938–944.

172. Chappell S, Daly L, Morgan K, et al. Genetic variants of microsomal epoxide hydrolase and glutathione-cysteine ligase in COPD. *Eur Respir J*. 2008;32(4):931–937.

173. Siedlinski M, Postma DS, Smit HA, Boezen HM. No effects of EPHX1 polymorphisms on the level or change of FEV1 in the general population. *Eur Respir J*. 2009;33(2):446–449.

174. Takeyabu K, Yamaguchi E, Suzuki I, Nishimura M, Hizawa N. Association of Gc-globulin gene polymorphism and susceptibility to COPD and diffuse panbronchiolitis. *Hum Genet*. 1997;99(6):822–826.

175. Hu G, Shi Z, Hu J, Zou G, Peng G, Ran P. Association between polymorphic genotypes of glutathione S-transferases and COPD in the Turkish population. *Respirology*. 2006;44(7–8):307–319.

176. Gilliland FD, Wain LV, Repapi E, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med*. 2011;184(7):786–795.

177. Baranowa O, Perriot J, Albuissier E, et al. Peculiarities of the GSTM1 0/0 genotype in French heavy smokers with various types of chronic bronchitis. *Respirology*. 2007;12:1–20.

178. Hersh CP, Hansel NN, Barnes KC, et al. Transforming growth factor-beta receptor-3 is associated with pulmonary emphysema. *Am J Respir Cell Mol Biol*. 2009;41(4):324–331.

179. Soler Artigas M, Wain LV, Repapi E, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med*. 2011;184(7):307–319.

180. Calikoglu M, Tamer L, Ates Aras N, Karakas S, Erkan B. The association between polymorphic genotypes of glutathione S-transferases and COPD in the Turkish population. *Hum Genet*. 2004;116(4):171–179.

181. Bakke PS, Zhu G, Gulsvik A, et al. Candidate genes for COPD in two large data sets. *Eur Respir J*. 2011;37(2):255–263.

182. Shen LH, Zhang XM, Su DJ, et al. Association of vitamin D binding protein variants with susceptibility to chronic obstructive pulmonary disease. *J Int Med Res*. 2010;38(3):1093–1098.

183. Korytina GF, Akhmadishina LZ, Ianaeva DG, Viktorova TV. Genotypes of vitamin D-binding protein (DBP) in patients with chronic obstructive pulmonary disease and healthy population of Republic Bashkortostan. *Mol Biol (Mosk)*. 2006;40(2):231–238. Russian.

184. Siedlinski M, Postma DS, van Diemen CC, Blokstra A, Smit HA, Boezen HM. Lung function loss, smoking, vitamin C intake, and polymorphisms of the glutamate-cysteine ligase genes. *Am J Respir Crit Care Med*. 2008;178(1):13–19.

185. Liu S, Li B, Zhou Y, Zhong N, Ran P Genetic analysis of CC16, OGG1 and GCLC polymorphisms and susceptibility to COPD. *Respirology*. 2007;12(1):29–33.

186. Takeyabu K, Yamaguchi E, Suzuki I, Nishimura M, Hizawa N. Association of Gc-globulin gene polymorphism and susceptibility to COPD and diffuse panbronchiolitis. *Hum Genet*. 1997;99(6):822–826.

187. Calikoglu M, Tamer L, Ates Aras N, Karakas S, Erkan B. The association between polymorphic genotypes of glutathione S-transferases and COPD in the Turkish population. *Respirology*. 2006;44(7–8):307–319.

188. Gilliland FD, Gauderman WJ, Vora H, Rappaport E, Dubeau L. Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth. *Am J Respir Crit Care Med*. 2002;166(5):710–716.

189. Harrison DJ, Cantlay AM, Rae F, Lamb D, Smith CA. Frequency of glutathione S-transferase M1 deletion in smokers with emphysema and lung cancer. *Hum Exp Toxicol*. 1997;16(7):356–360.

190. He JQ, Ruan J, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Antioxidant gene polymorphisms and susceptibility to a rapid decline in lung function in smokers. *Am J Respir Crit Care Med*. 2002;166(3):323–328.

191. Imboden M, Downs SH, Senn O, et al. Glutathione S-transferase polymorphisms modify lung function decline in the general population: SAPALDIA cohort study. *Respir Res*. 2007;8:2.

192. Faramawy MM, Mohammed TO, Hossaini AM, Kashem RA, Abu Rahma RM. Genetic polymorphism of GSTT1, GSTM1 and GSTM3 in COPD patients in a north Indian population. *Hum Genet*. 2004;116(4):131–134.

193. Calikoglu M, Tamer L, Ates Aras N, Karakas S, Erkan B. The association between polymorphic genotypes of glutathione S-transferases and COPD in the Turkish population. *Hum Genet*. 2004;116(4):131–134.

194. Bashkortostan. Lung function loss, smoking, vitamin C intake, and polymorphisms of the glutamate-cysteine ligase genes. *Am J Respir Crit Care Med*. 2008;178(1):13–19.

195. Liu S, Li B, Zhou Y, Zhong N, Ran P Genetic analysis of CC16, OGG1 and GCLC polymorphisms and susceptibility to COPD. *Respirology*. 2007;12(1):29–33.

196. Hersh CP, Hansel NN, Barnes KC, et al. Transforming growth factor-beta receptor-3 is associated with pulmonary emphysema. *Am J Respir Cell Mol Biol*. 2009;41(4):324–331.

197. Soler Artigas M, Wain LV, Repapi E, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med*. 2011;184(7):786–795.

198. Baranowa O, Perriot J, Albuissier E, et al. Peculiarities of the GSTM1 0/0 genotype in French heavy smokers with various types of chronic bronchitis. *Respirology*. 2007;12:1–20.
204. He JQ, Connnett JE, Anthonisen NR, Pare PD, Sandford AJ. Glutathione S-transferase variants and their interaction with smoking on lung function. *Am J Respir Crit Care Med*. 2004;170(4):388–394.

205. Mehrotra S, Sharma A, Kumar S, Kar P, Sardana S, Sharma JK. Polymorphism of glutathione S-transferase M1 and T1 gene loci in COPD. *Int J Immunogenet*. 2010;37(4):263–267.

206. Thakur H, Gupta L, Sobti RC, Janmeja AK, Seth A, Singh SK. Association of GSTM1/T1 genes with COPD and prostate cancer in north Indian population. *Mol Biol Rep*. 2011;38(3):1733–1739.

207. Vanbogaert DG, Wouters EF, Dentener MA, Spruit MA, Reynaert NL. Association of glutathione-S-transferase omega haplotypes with susceptibility to chronic obstructive pulmonary disease. *Free Radic Res*. 2009;43(8):738–743.

208. Ishii T, Matsuse T, Teramoto S, et al. Glutathione S-transferase P1 (GSTP1) polymorphism in patients with chronic obstructive pulmonary disease. *Thorax*. 1999;54(8):693–696.

209. Rodriguez F, de la Roza C, Jardi R, Schaper M, Vidal R, Miravitlles M. Glutathione S-transferase P1 and lung function in patients with alpha-1-antitrypsin deficiency and COPD. *Chest*. 2005;127(5):1537–1543.

210. Lakhdar R, Denden S, Knani J, et al. Relationship between glutathione S-transferase P1 polymorphisms and chronic obstructive pulmonary disease in a Tunisian population. *Genet Mol Res*. 2010;9(2):897–907.

211. Lu B, He Q. Correlation between exon5 polymorphism of glutathione S-transferase P1 gene and susceptibility to chronic obstructive pulmonary disease in northern Chinese population of Han nationality living in Beijing, China. *Zhonghua Nei Ke Za Zhi*. 2002;41(10):678–681. Chinese.

212. Yim JJ, Yoo CG, Lee CT, Kim YW, Han SK, Shim YS. Lack of association between glutathione S-transferase P1 polymorphism and COPD in Koreans. *Lung*. 2002;180(2):119–125.

213. Yan F, Chen C, Jing J, Li W, Shen H, Wang X. Association between polymorphism of glutathione S-transferase P1 and chronic obstructive pulmonary disease: a meta-analysis. *Respir Med*. 2010;104(4):473–480.

214. Zhong L, Zhang YP, Fu WP, Dai LM, Sun C, Wang YQ. The relationship between GSTP1 1105V polymorphism and COPD: a reappraisal. *Am J Respir Crit Care Med*. 2010;181(7):763–765.

215. Zhang X, Mahmudi-Azer S, Connnett JE, et al. Association of Hck protein with COPD. *Mol Biol Rep*. 2007;34(5):681–690.

216. Van Durme YM, Eijgelsheim M, Joos GF, et al. Hedgehog-interacting protein is a COPD susceptibility gene: the Rotterdam Study. *Eur Respir J*. 2010;36(1):89–95.

217. Keicho N, Tokunaga K, Nakata K, et al. Contribution of HLA genes to genetic predisposition in diffuse panbronchiolitis. *Am J Respir Crit Care Med*. 1998;158(3):846–850.

218. Sugiyama Y, Kudo H, Maeda H, Suzuki H, Takaku F. Analysis of HLA antigens in patients with diffuse panbronchiolitis. *Am Rev Respir Dis*. 1990;141(6):1459–1462.

219. Kasuga I, Hogg JC, Pare PD, et al. Role of genetic susceptibility to latent adenoviral infection and decreased lung function. *Respir Med*. 2009;103(11):1672–1680.

220. Kasuga I, Ruan J, Connnett JE, Anthonisen NR, Sandford AJ. Lack of association of human leukocyte antigen-β7 with COPD and rate of decline in lung function. *Respir Med*. 2005;99(12):1528–1533.

221. Aubier M, Guenegoau A, Benessiano J, Leynaert B, Boczkowski J, Neukirch F. Association of lung function decline with the microsatellite polymorphism in the heme oxygenase-1 gene promoter, in a general population sample. Results from the Longitudinal European Community Respiratory Health Survey (ECRHS-France). *Bull Acad Natl Med*. 2006;190(4–5):877–891. French.

222. Guenegoau A, Boczkowski J, Aubier M, Neukirch F, Leynaert B. Interaction between a heme oxygenase-1 gene promoter polymorphism and serum beta-carotene levels on 8-year lung function decline in a general population: the European Community Respiratory Health Survey (France). *Am J Epidemiol*. 2008;167(2):139–144.

223. Guenegoau A, Leynaert B, Benessiano J, et al. Association of lung function decline with the heme oxygenase-1 gene promoter microsatellite polymorphism in a general population sample. Results from the European Community Respiratory Health Survey (ECRHS), France. *J Med Genet*. 2006;43(8):e43.

224. Yamada N, Yamaya M, Oginaga S, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. *Am J Hum Genet*. 2000;66(1):187–195.

225. Tanaka G, Aminuddin F, Akhbar L, et al. Effect of heme oxygenase-1 polymorphisms on lung function and gene expression. *BMC Med Genet*. 2011;12:117.

226. He JQ, Burkett K, Connnett JE, Anthonisen NR, Pare PD, Sandford AJ. Interferon gamma polymorphisms and their interaction with smoking are associated with lung function. *Hum Genet*. 2006;119(4):365–375.

227. Trajkov D, Mrkovic-Stojkovic J, Petlickovski A, et al. Association of cytokine gene polymorphisms with chronic obstructive pulmonary disease in Macedonians. *Iran J Allergy Asthma Immunol*. 2009;8(1):31–42.

228. Hackett TL, Stefanovicz D, Aminuddin F, et al. Effect of gene environment interactions on lung function and cardiovascular disease in COPD. *Int J Chon Obstruct Pulmon Dis*. 2011;6:277–287.

229. Asada M, Yamaya M, Eibikara S, et al. Interleukin-β7 gene polymorphisms associated with COPD. *Chest*. 2005;128(2):1072–1073; author reply 1073.

230. Hegab AE, Sakamoto T, Sakai W, et al. Polymorphisms of TGFalpha, IL1beta, and IL1RN genes in chronic obstructive pulmonary disease. *Biochem Biophys Res Commun*. 2005;329(4):1246–1252.

231. Joos L, McIntyre L, Ruan J, et al. Association of IL-1beta and IL-1 receptor antagonist haplotypes with rate of decline in lung function in smokers. *Thorax*. 2001;56(11):863–866.

232. Lee JS, Kang YR, Park SH, et al. Polymorphisms in interleukin-1B and its receptor antagonist genes and the risk of chronic obstructive pulmonary disease in a Korean population: a case-control study. *Respir Med*. 2008;102(9):1311–1320.

233. Broekhuizen R, Grimbil RF, Howell WM, et al. Pulmonary cachexia, systemic inflammatory profile, and the interleukin ibeta-511 single nucleotide polymorphism. *Am J Clin Nutr*. 2005;82(5):1059–1064.

234. Danilko KV, Korytina GF, Akhmidishina LZ, Ianbaeva DG, Zagidullin SZ, Victorova TV. Association of cytokines genes (IL1, IL1RN, TNF, LTA, IL6, IL8, IL10) polymorphic markers with chronic obstructive pulmonary disease. *Mol Biol (Mosk)*. 2007;41(1):26–36. Russian.

235. Josyula AB, Kurzius-Spencer M, Littau SR, Yucesoy B, Fleming J, Burgess JL. Cytokine genotype and phenotype effects on lung function decline in firefighters. *J Occup Environ Med*. 2008;50(9):282–288.

236. Hsieh MH, Chong JW, Hwang JJ, et al. Lack of associations between several polymorphisms in cytokine genes and the risk of chronic obstructive pulmonary diseases in Taiwan. *Kaohsiung J Med Sci*. 2008;24(3):126–137.

237. Ishii T, Matsuse T, Teramoto S, et al. Neither IL-1beta, IL-1 receptor antagonist, nor TNF-alpha polymorphisms are associated with susceptibility to COPD. *Respir Med*. 2009;94(9):847–851.

238. Yucesoy B, Kurzius-Spencer M, Johnson VJ, et al. Association of cytokine gene polymorphisms with rate of decline in lung function. *J Occup Environ Med*. 2008;50(6):642–648.

239. Huang N, Liu L, Wang XZ, Liu D, Yin SY, Yang XD. Association of interleukin (IL)-12 and IL-27 gene polymorphisms with chronic obstructive pulmonary disease in a Chinese population. *DNA Cell Biol*. 2008;27(9):527–531.

240. Burchard EG, Silverman EK, Kondurakci LV, et al. Association between a sequence variant in the IL-4 gene promoter and FEV(1) in asthma. *Am J Respir Crit Care Med*. 1999;160(3):919–922.

241. Beghe B, Hall RP, Parker SG, et al. Polymorphisms in IL13 pathway genes in asthma and chronic obstructive pulmonary disease. *Allergy*. 2010;65(4):474–481.
242. van der Pouw Kraan TC, Kucukaycan M, Bakker AM, et al. Chronic obstructive pulmonary disease is associated with the -1055 IL-13 promoter polymorphism. Genes Immun. 2002;3(7):436–439.

243. He JQ, Connett JE, Anthonisen NR, Sandford AJ. Polymorphisms in the IL13, IL13RA1, and IL4RA genes and rate of decline in lung function in smokers. Am J Respir Cell Mol Biol. 2003;28(3):379–385.

244. Hong SJ, Lee SY, Kim HB, et al. IL-5 and thromboxane A2 receptor gene polymorphisms are associated with decreased pulmonary function in Korean children with atopic asthma. J Allergy Clin Immunol. 2005;115(4):758–763.

245. Cordoba-Lanus E, de-Torres JP, Lopez-Aguilar C, et al. Association of IL-6 gene polymorphisms and COPD in a Spanish population. Respir Med. 2008;102(12):1805–1811.

246. He JQ, Foreman MG, Shumansky K, et al. Associations of IL6 gene polymorphisms with chronic obstructive pulmonary disease and asthma. Zhonghua Yi Xue Za Zhi. 2004;84(6):594–598. Chinese.

247. Matheson MC, Ellis JA, Raven J, Walters EH, Abramson MJ. Association of IL8, CXCR2 and TNF-alpha polymorphisms and airway disease. J Hum Genet. 2006;51(3):196–203.

248. Seifart C, Dempfle A, Plagens A, et al. TNF-alpha-, TNF-beta-, IL-6-, and IL-10-promoter polymorphisms in patients with chronic obstructive pulmonary disease. Tissue Antigens. 2005;65(1):93–100.

249. Arinir U, Klein W, Rohde G, Stemmler S, Epplen JT, Schultze-Werninghaus G. Polymorphisms in the interleukin-8 gene in patients with chronic obstructive pulmonary disease. Electrophoresis. 2005;26(15):2888–2891.

250. Garcia L, Salzano M, Schmid LM, et al. Association of the -1055 IL-13 polymorphism in promoter regions with chronic obstructive pulmonary disease. Eur Respir J. 2005;26(1):28–33.

251. Stemmler S, Arinir U, Klein W, et al. Association of interleukin-8 receptor alpha polymorphisms with chronic obstructive pulmonary disease and asthma. Genes Immun. 2005;6(3):225–230.

252. Burruss JL, Fierro MA, Lantz RC, et al. Longitudinal decline in lung function: evaluation of interleukin-10 genetic polymorphisms in firefighters. J Occup Environ Med. 2004;46(10):1013–1022.

253. Hu RC, Xu YJ, Zhang ZX, Xie JG. Polymorphism of interleukin-10 gene promoter and its association with susceptibility to chronic obstructive pulmonary disease in Chinese Han people. Zhonghua Yi Xue Yi Chuan Xue Za Zhi. 2003;28(6):504–507. Chinese.

254. Lyon H, Lange C, Lake S, et al. IL10 gene polymorphisms are associated with asthma phenotypes in children. Genet Epidemiol. 2004;26(2):155–165.

255. He JQ, Shumansky K, Zhang X, Connett JE, Anthonisen NR, Sandford AJ. Polymorphisms of interleukin-10 and its receptor and lung function in COPD. Eur Respir J. 2007;29(6):1120–1126.

256. He B, Zhao MW, Ning LD, Jiang L, Yao WZ. The study of interleukin-13 gene polymorphism and its association with susceptibility to chronic obstructive pulmonary disease. Zhonghua Jie He He Hu Xi Za Zhi. 2004;27(8):529–532. Chinese.

257. Hu RC, Xu YJ, Zhang ZX. Study on the correlation of interleukin-13 polymorphism and susceptibility to chronic obstructive pulmonary disease in Chinese Han population. Zhonghua Lixue Xing Bing Bing Za Zhi. 2004;25(7):607–611. Chinese.

258. Sadeghnejad A, Meyers DA, Bottai M, Sterling DA, Bleeker ER, Ohr JA. IL13 promoter polymorphism 1112C/T modulates the adverse effect of tobacco smoking on lung function. Am J Respir Crit Care Med. 2007;176(8):748–752.

259. Liu SF, Chen YC, Wang CC, et al. IL13 polymorph (-1055) polymorphism associated with chronic obstructive pulmonary disease in Taiwanese. Exp Lung Res. 2009;35(10):807–816.

260. Kang MJ, Lee SY, Kim HB, et al. Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. Pharmacogenet Genomics. 2008;18(7):551–558.

261. Park HW, Lee JE, Kim SH, et al. Genetic variation of IL13 as a risk factor of reduced lung function in children and adolescents: a cross-sectional population-based study in Korea. Respir Med. 2009;103(2):284–288.
Hunninghake GM, Cho MH, Tesfaigzi Y, et al. MMP12, lung function, and COPD in high-risk populations. *Respir Res*. 2010;11:12:57.

Sanuto P, Casanova F, Biondi ML, Blasi F, Di Marco F, Centanni S. Stromelysin-1 polymorphism as a new potential risk factor in progression of chronic obstructive pulmonary disease. *Monaldi Arch Chest Dis*. 2009;71(1):15–20.

Schirmer H, Basso da Silva L, Teixeira PJ, Moreira JS, Moreira AL, Simon D. Matrix metalloproteinase gene polymorphisms: lack of association with chronic obstructive pulmonary disease in a Brazilian population. *Genet Mol Res*. 2009;8(3):1028–1034.

Ito I, Nagai S, Handa T, et al. Matrix metalloproteinase-9 promoter polymorphism associated with upper lung dominant emphysema. *Am J Respir Crit Care Med*. 2005;172(11):1378–1382.

Minematsu N, Nakamura H, Tateno H, Nakajima T, Yamaguchi K. Genetic polymorphism in matrix metalloproteinase-9 and pulmonary emphysema. *Biochem Biophys Res Commun*. 2001;289(1):116–119.

Zhou M, Huang SG, Wan HY, Li B, Deng WW, Li M. Genetic polymorphism in matrix metalloproteinase-9 and the susceptibility to chronic obstructive pulmonary disease in Han population of south China. *Chin Med J (Engl)*. 2004;117(10):1481–1484.

Huninghake GM, Cho MH, Tesfaigzi Y, et al. MMP12, lung function, and COPD in high-risk populations. *N Engl J Med*. 2009;361(27):2599–2608.

Haq I, Lowrey GE, Kalshke N, Johnson SR. Matrix metalloproteinase-12 (MMP-12) SNP affects MMP activity, lung macrophage infiltration and protects against emphysema in COPD. *Thorax*. 2011;66(11):970–976.

Saitoh W, Sakamoto T, Hegah AE, et al. MMP14 gene polymorphisms in chronic obstructive pulmonary disease. *Int J Mol Med*. 2006;17(4):621–626.

Ohar JA, Hamilton RF Jr, Zheng S, et al. COPD is associated with a macrophage scavenger receptor-1 gene sequence variation. *Chest*. 2010;137(5):1098–1107.

Hua CC, Chang LC, Tseng JC, Chu CM, Liu YC, Shieh WB. Functional haplotypes in the promoter region of transcription factor Nrf2 in chronic obstructive pulmonary disease. *Dis Markers*. 2010;28(3):185–193.

Arif E, Ahsan A, Vibhuti A, et al. Endothelial nitric oxide synthase gene variants contribute to oxidative stress in COPD. *Biochem Biophys Res Commun*. 2007;361(1):182–188.

Novoradovsky A, Brantly ML, Wacławiw MA, et al. Endothelial nitric oxide synthase as a potential susceptibility gene in the pathogenesis of emphysema in alpha1-antitrypsin deficiency. *Am J Respir Cell Mol Biol*. 1999;20(3):441–447.

Corvol H, Nathan N, Charlier C, et al. Glucocorticoid receptor gene polymorphisms associated with progression of lung disease in young patients with cystic fibrosis. *Respir Res*. 2007;8:88.

Schwabe K, Vaccia G, Duck R, Gillissen A. Glucocorticoid receptor gene polymorphisms and potential association to chronic obstructive pulmonary disease. *Eur J Med Res*. 2009;14 Suppl 4:210–213.

Yang SF, Xu YJ, Xie JG, Zhang ZX. hOGG1 Ser326Cys and XRCRC1 Arg399Gln polymorphisms associated with chronic obstructive pulmonary disease. *Chin Med J (Engl)*. 2009;122(8):960–966.

Takabatake N, Toriyama S, Takeishi Y, et al. A nonfunctioning single nucleotide polymorphism in olfactory receptor gene family is associated with the forced expiratory volume in the first second/forced vital capacity values of pulmonary function test in a Japanese population. *Biochem Biophys Res Commun*. 2007;364(3):662–667.

Homma S, Sakamoto T, Hegah AE, et al. Association of phosphodiesterase 4D gene polymorphisms with chronic obstructive pulmonary disease: relationship to interleukin 13 gene polymorphism. *Int J Mol Med*. 2006;18(5):933–939.

Stewart CE, Hall JP, Parker SG, et al. PLAUR polymorphisms and lung function in UK smokers. *BMC Med Genet*. 2009;10:112.

Barton SJ, Koppelman GH, Yonk JM, et al. PLAUR polymorphisms are associated with asthma, PLAUR levels, and lung function decline. *J Allergy Clin Immunol*. 2009;123(6):1391–1400.

Tsai YJ, Choudhry S, Kho J, et al. The PTGDR gene is not associated with asthma in 3 ethnically diverse populations. *J Allergy Clin Immunol*. 2006;118(6):1242–1248.

Wu L, Merrilees M, Young RP, Black PN. The cyclooxygenase-2-765C promoter polymorphism protects against the development of chronic obstructive pulmonary disease. *Respir Med*. 2011;105(3):506–510.

Arif E, Vibhuti A, Deepak D, Singh B, Siddiqui MS, Pasha MA. COX2 and p53 risk-alleles coexist in COPD. *Clin Chim Acta*. 2008;397(1–2):48–50.

Kwok JS, Lawton JW, Yew WW, Chau CH, Lee J, Wong PC. Protease inhibitor phenotypes and serum alpha-1-antitrypsin levels in patients with COPD: a study from Hong Kong. *Respirology*. 2004;9(2):265–270.

Hodgson I, Kalshke N. DNA polymorphisms of the human alpha 1 antitrypsin gene in normal subjects and in patients with pulmonary emphysema. *J Med Genet*. 1987;24(1):47–51.

Chappell S, Daly L, Morgan K, et al. Cryptic haplotypes of SERPINA1 confer susceptibility to chronic obstructive pulmonary disease. *Hum Mutat*. 2006;27(1):103–109.

Abbud RT, Rushton JM, Grzybowski S. Interrelationships between neutrophil elastase, serum alpha-, and -antitrypsin, lung function and chest radiography in patients with chronic airflow obstruction. *Am Rev Respir Dis*. 1979;120(1):31–40.

Barnett TB, Gottovi D, Johnson AM. Protease inhibitors in chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1975;111(5):587–593.

Bartmann K, Fokee-Achterrath M, Koch G, et al. Heterozygosity in the Pi-system as a pathogenetic cofactor in chronic obstructive pulmonary disease (COPD). *Eur J Respir Dis*. 1985;66(4):284–296.

Cox DW, Hoepner VH, Levison H. Protease inhibitors in patients with chronic obstructive pulmonary disease: the alpha-antitrypsin heterozygote controversy. *Am Rev Respir Dis*. 1976;113(5):601–606.

Dahl M, Nordestgaard BG, Lange P, Vestbo J, Tybjaerg-Hansen A. Molecular diagnosis of intermediate and severe alpha(1)-antitrypsin deficiency: MZ individuals with chronic obstructive pulmonary disease may have lower lung function than MM individuals. *Clin Chem*. 2001;47(1):56–62.

Dendran S, Haj Khelil A, Perrin P, et al. Alpha 1 antitrypsin polymorphism in the Tunisian population with special reference to pulmonary disease. *Pathol Biol (Paris)*. 2008;56(3):106–110.

Gupta J, Bhadopa DR, Lat MK, et al. Association of the PIM3 allele of the alpha-1-antitrypsin gene with chronic obstructive pulmonary disease. *Clin Biochem*. 2005;38(5):489–491.

Lieberman J, Winter B, Sastre A. Alpha 1-antitrypsin Pi-types in 965 COPD patients. *Chest*. 1986;89(3):370–373.

Matzen RN, Bader PI, Block WD. alpha-1-Antitrypsin deficiency in clinic patients. *Ann Clin Res*. 1977;9(2):88–92.

Poller W, Meisen C, Olek K. DNA polymorphisms of the alpha-1-antitrypsin gene region in patients with chronic obstructive pulmonary disease. *Eur J Clin Invest*. 1990;20(1):1–7.
321. Sandford AJ, Weir TD, Spinelli JJ, Pare PD. Z and S mutations of the alpha 1-antitrypsin gene and the risk of chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1986;134(3):545–551.

322. Dahi M, Tybjærg-Hansen A, Lange P, Vestbo J, Nordestgaard BG. Change in lung function and morbidity from chronic obstructive pulmonary disease in alpha 1-antitrypsin MZ heterozygotes: a longitudinal study of the general population. *Ann Intern Med*. 2002;136(4):270–279.

323. Klayton R, Fallat R, Cohen AB. Determinants of chronic obstructive pulmonary disease in patients with intermediate levels of alpha-antitrypsin. *Am Rev Respir Dis*. 1975;112(1):71–75.

324. Shigeoka JW, Hall WJ, Hyde RW, et al. The prevalence of alpha-antitrypsin heterozygotes (Pi MZ) in patients with obstructive pulmonary disease. *Am Rev Respir Dis*. 1976;114(6):1077–1084.

325. Fujimoto K, Ikeda S, Arai T, et al. Polymorphism of SERPINE2 gene is associated with pulmonary emphysema in consecutive autopsy cases. *BMJ Med Genet*. 2010;11:159.

326. Quint JK, Donaldson GC, Kumari M, Talmud PJ, Hurst JR. SERPINA1 polymorphism and chronic obstructive pulmonary disease among Japanese-American men. *Chest*. 1977;72(4):489–491.

327. Lochon B, Vercaigne D, Lochon C, et al. Pan-lobular emphysema: relationship with serum alpha-1-antitrypsin levels, Pi phenotype and the HLA system (author's transl). *Nouv Presse Med*. 1978;7(14):1167–1170. French.

328. Ostrow DN, Manfreda J, Dorman T, Cherniack RM. Alpha1-antitrypsin deficiency. *Am Rev Respir Dis*. 1976;114(6):1077–1084.

329. Baekvad-Hansen M, Tyljaerg-Hansen A, Nordestgaard BG. Surfactant protein C gene in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2011;184(4):418–424.

330. Shigeoka JW, Hall WJ, Hyde RW, et al. The prevalence of alpha-antitrypsin heterozygotes (Pi MZ) in patients with obstructive pulmonary disease. *Am Rev Respir Dis*. 1975;112(1):71–75.

331. Klayton R, Fallat R, Cohen AB. Determinants of chronic obstructive pulmonary disease in patients with intermediate levels of alpha-antitrypsin. *Am Rev Respir Dis*. 1975;112(1):71–75.

332. Shigeoka JW, Hall WJ, Hyde RW, et al. The prevalence of alpha-antitrypsin heterozygotes (Pi MZ) in patients with obstructive pulmonary disease. *Am Rev Respir Dis*. 1975;112(1):71–75.

333. Kim CH, Yim JJ, Yoo CG, et al. Alpha-antitrypsin genotypes in Korean patients with chronic obstructive pulmonary disease. *Respirology*. 2005;10(2):223–228.

334. Ishii T, Hagiwara K, Kamio K, et al. Involvement of surfactant protein-D in emphysema revealed by genetic association study. *Eur J Respir Dis*. 2010;129(3–4):131–136.

335. Ishii T, Kida K, Kurosaki H, Gemma A, Kida K. Association of surfactant protein B 121ins2 heterozygosity, reduced pulmonary function and COPD in 10,231 individuals. *Eur Respir J*. 2011;37(4):791–799.

336. Ishii T, Matsuse T, Teramoto S, et al. Association between alpha-1-antichymotrypsin polymorphism and susceptibility to chronic obstructive pulmonary disease. *Eur J Clin Invest*. 2000;30(6):543–548.

337. Sandford AJ, Chagani T, Weir TD, Pare PD. Alpha 1-antichymotrypsin mutations in patients with chronic obstructive pulmonary disease. *Dis Markers*. 1998;13(4):257–260.

338. Kalsheker NA, Hodgson IJ, Watkins GL, White JP, Morrison HM, Silverman EK. Genetic markers in chronic obstructive lung disease. *Chest*. 2007;131(9):2119–2124.

339. Lindmark BE, Arborelius M Jr, Eriksson SG. Pulmonary function and FEV1 decline in COPD. *Thorax*. 2001;56 Suppl:S9–S11.

340. Poller W, Faber JP, Scholz S, et al. Mis-sense mutation of alpha 1-antitrypsin gene associated with chronic lung disease. *Lancet*. 1992;339(8808):1538.

341. Poller W, Faber JP, Weidinger S, et al. A leucine-to-proline substitution causes a defective alpha 1-antichymotrypsin allele associated with familial obstructive lung disease. *Genomics*. 1993;17(3):740–743.

342. Samilchuk EI, Chuchalin AG. Mis-sense mutation of alpha 1-antichymotrypsin gene and chronic lung disease. *Lancet*. 1993;342(8871):624.

343. Ishii T, Matsuse T, Teramoto S, et al. Association between alpha-1-antichymotrypsin polymorphism and susceptibility to chronic obstructive pulmonary disease. *Eur J Clin Invest*. 2000;30(6):543–548.

344. Demeo DL, Mariani TJ, Lange C, et al. The SERPINE2 gene is associated with chronic obstructive pulmonary disease. *Am J Hum Genet*. 2006;78(2):253–264.

345. Luo G, Warren L, Aponte J, et al. The SERPINE2 gene is associated with chronic obstructive pulmonary disease in two large populations. *Am J Respir Crit Care Med*. 2007;176(2):167–173.

346. Sorheim IC, Gulsvik A. Genetics of chronic obstructive pulmonary disease: a case-control study in Bergen, Norway. *Clin Respir J*. 2008;2 Suppl 1:129–131.

347. Klayton R, Fallat R, Cohen AB. Determinants of chronic obstructive pulmonary disease in patients with intermediate levels of alpha-antitrypsin. *Am Rev Respir Dis*. 1975;112(1):71–75.

348. Shigeoka JW, Hall WJ, Hyde RW, et al. The prevalence of alpha-antitrypsin heterozygotes (Pi MZ) in patients with obstructive pulmonary disease. *Am Rev Respir Dis*. 1975;112(1):71–75.

349. Fujimoto K, Ikeda S, Arai T, et al. Polymorphism of SERPINE2 gene is associated with pulmonary emphysema in consecutive autopsy cases. *BMJ Med Genet*. 2010;11:159.

350. Quint JK, Donaldson GC, Kumari M, Talmud PJ, Hurst JR. SERPINA1 polymorphism and alpha 1-antitrypsin, exacerbation frequency and FEV1 decline in COPD. *Thorax*. 2011;66(5):418–424.

351. Guo X, Lin HM, Lin Z, et al. Surfactant protein gene A, B, and D marker alleles in chronic obstructive pulmonary disease of a Mexican population. *Eur Respir J*. 2001;18(3):482–490.

352. Hu R, Xu Y, Zhang Z. Surfactant protein B 1580 polymorphism is associated with susceptibility to chronic obstructive pulmonary disease in Chinese Han population. *J Huazhong Univ Sci Technolog Med Sci*. 2004;24(3):216–218, 238.

353. Seifart C, Plagens A, Brodziej D, Muller B, von Wichert P, Floros J. Surfactant protein B intron 4 variation in German patients with COPD and acute respiratory failure. *Dis Markers*. 2002;18(3):129–136.

354. Baekvad-Hansen M, Dahl M, Tybjærg-Hansen A, Nordestgaard BG. Surfactant protein-B 121ins2 heterozygosity, reduced pulmonary function, and chronic obstructive pulmonary disease in smokers. *Am J Respir Crit Care Med*. 2010;181(1):17–20.

355. Baekvad-Hansen M, Nordestgaard BG, Dahl M. Surfactant protein B polymorphisms, pulmonary function and COPD in 10,231 individuals. *Eur Respir J*. 2011;37(4):791–799.

356. Tsvetkova OA, Veselovskaya MV. Polymorphic variants of a surfactant protein C gene in patients with chronic obstructive pulmonary disease. *Ter Arkh*. 2007;79(9):65–69. Russian.

357. Baekvad-Hansen M, Nordestgaard BG, Tybjærg-Hansen A, Dahl M. Two novel mutations in surfactant protein-C, lung function and chronic obstructive lung disease. *Respir Med*. 2010;104(3):418–425.

358. Ishii T, Hagiwara K, Kamio K, et al. Involvement of surfactant protein-D in emphysema revealed by genetic association study. *Eur J Hum Genet*. 2012;20(2):230–235.

359. Foreman MG, Kong X, DeMeo DL, et al. Polymorphisms in surfactant protein-D are associated with chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2011;44(3):316–322.

360. Ishii T, Wakabayashi R, Kurosaki H, Gemma A, Kida K. Association of serotonin transporter gene variation with smoking, chronic obstructive pulmonary disease, and its depressive symptoms. *J Hum Genet*. 2011;56(1):41–46.

361. Kim EJ, Kim KM, Park SH, et al. SLC11A1 polymorphisms are associated with the risk of chronic obstructive pulmonary disease in a Korean population. *Biochem Genet*. 2008;46(7–8):506–519.
362. Yang T, Ying B, Song X, et al. Single-nucleotide polymorphisms in SMAD3 are associated with chronic obstructive pulmonary disease. Exp Biol Med (Maywood). 2010;235(5):599–605.

363. Wilk JB, Herbert A, Shoemaker CM, Gottlieb DJ, Karamohamed S. Secreted modular calcium-binding protein 2 haplotypes are associated with pulmonary function. Am J Respir Crit Care Med. 2007;175(6):554–560.

364. Siedlinski M, van Diemen CC, Postma DS, Vonk JM, Boezen HM. Superoxide dismutases, lung function and bronchial responsiveness in a general population. Eur Respir J. 2009;33(5):966–992.

365. Pietras T, Szerma M, Witusik A, et al. The sequence polymorphism of MnSOD gene in subjects with respiratory insufficiency in COPD. Med Sci Monit. 2010;16(9):CR427–CR432.

366. Bijlstra ST, Witusik A, Panek M, Galecki P, Szymraj J, Gorski P. Anxiety, depression and polymorphism of the gene encoding superoxide dismutase in patients with chronic obstructive pulmonary disease. Pol Merkur Lekarski. 2010;29(171):165–168. Polish.

367. Juul K, Tybjerg-Hansen A, Marklund S, Lange P, Nordestgaard BG. Genetically increased antioxidative protection and decreased chronic obstructive bronchitis. Am J Respir Crit Care Med. 2006;173(8):858–864.

368. Dahl M, Bowler RP, Juul K, Crapo JD, Levy S, Nordestgaard BG. Superoxide dismutase 3 polymorphism associated with reduced lung function in two large populations. Am J Respir Crit Care Med. 2007;176(9):906–912.

369. Ganguly K, Depner M, Fattman C, et al. Superoxide dismutase 3, extracellular (SOD3) variants and lung function. Physiol Genomics. 2009;37(3):260–267.

370. Sorheim IC, DeMeo DL, Washko G, et al. Polymorphisms in the superoxide dismutase-3 gene are associated with emphysema in COPD. COPD. 2010;7(4):262–268.

371. Heresh CP, Silverman EK, Gascon J, et al. SOX5 is a candidate gene for chronic obstructive pulmonary disease susceptibility and is necessary for lung development. Am J Respir Crit Care Med. 2011;183(11):1482–1489.

372. Litonjua AA, Tantisira KG, Lake S, et al. Polymorphisms in signal transducer and activator of transcription 3 and lung function in asthma. Respir Res. 2005;6:52.

373. Hawkins GA, Lazarus R, Smith RS, et al. The glucocorticoid receptor heterodimer gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. J Allergy Clin Immunol. 2009;123(6):1376–1383.

374. Leung TF, Tang NL, Lam CW, Li AM, Chan IH, Ha G. Thromboxane A2 receptor gene polymorphism is associated with the serum concentration of cat-specific immunoglobulin E as well as the development and severity of asthma in Chinese children. Pediatr Allergy Immunol. 2002;13(1):10–17.

375. Celenjo JC, Lange C, Raby BA, et al. The transforming growth factor-beta 1 (TGFBI) gene is associated with chronic obstructive pulmonary disease (COPD). Hum Mol Genet. 2004;13(15):1649–1656.

376. Ogawa E, Ruan J, Connell JE, Anthonisen NR, Pare PD, Sandford AJ. Transforming growth factor-beta 1 polymorphisms, airway responsiveness and lung function decline in smokers. Respir Med. 2007;101(5):938–943.

377. Su ZG, Wen FQ, Feng YL, Xiao M, Wu XL. Transforming growth factor-beta 1 gene polymorphisms associated with chronic obstructive pulmonary disease in Chinese population. Acta Pharmacol Sin. 2005;26(6):714–720.

378. van Diemen CC, Postma DS, Vonk JM, Bruinenberg M, Nolte IM, Boezen HM. Decorin and TGF-beta 1 polymorphisms and development of COPD in a general population. Respir Res. 2006;7:89.

379. Wu L, Chau J, Young RP, et al. Transforming growth factor-beta 1 genotype and susceptibility to chronic obstructive pulmonary disease. Thorax. 2004;59(2):126–129.

380. Ito M, Hanaoka M, Droma Y, et al. The association of transforming growth factor beta 1 gene polymorphisms with the emphysema phenotype of COPD in Japanese. Intern Med. 2008;47(15):1387–1394.

381. Liu DS, Li XO, Ying BW, et al. Effects of single nucleotide polymorphisms 869 T/C and 915 G/C in the exon 1 locus of transforming growth factor-beta 1 gene on chronic obstructive pulmonary disease susceptibility in Chinese. Chin Med J (Engl). 2010;123(4):390–394.

382. Arkwright PD, Laurie S, Super M, et al. TGF-beta 1 genotype and accelerated decline in lung function in patients with cystic fibrosis. Thorax. 2006;55(6):459–466.

383. Yoon HJ, Silverman EK, Lee HW, et al. Lack of association between COPD and transforming growth factor-beta 1 (TGFBI) genetic polymorphisms in Koreans. Int J Tuberc Lung Dis. 2006;10(5):504–509.

384. Gong Y, Fan L, Wan H, et al. Lack of association between the TGF-beta 1 gene and development of COPD in Asians: a case-control study and meta-analysis. Lung. 2011;189(3):213–223.

385. Hirano K, Sakamoto T, Uchida Y, et al. Tissue inhibitor of metalloproteinase-2 gene polymorphisms in chronic obstructive pulmonary disease. Eur Respir J. 2001;18(5):748–752.

386. Hegab AE, Sakamoto T, Uchida Y, et al. Promoter activity of human tissue inhibitor of metalloproteinase 2 gene with novel single nucleotide polymorphisms. Respiratory. 2005;10(1):27–30.

387. Hegab AE, Sakamoto T, Uchida Y, et al. Association analysis of tissue inhibitor of metalloproteinase 2 gene polymorphisms with COPD in Egyptians. Respir Med. 2005;99(1):107–110.

388. Speletas M, Merentiti V, Kostikas K, et al. Association of TLR4-T399I polymorphism with chronic obstructive pulmonary disease in smokers. Clin Dev Immunol. 2009;2009:620286.

389. Rohde G, Klein W, Ariniz U, et al. Association of the ASP299GLY TLR4 polymorphism with COPD. Respir Med. 2006;100(5):892–896.

390. Huang SL, Su CH, Chang SC. Tumor necrosis factor-alpha gene polymorphism in chronic bronchitis. Am J Respir Crit Care Med. 1997;156(5):1436–1439.

391. Kucukaycan M, Van Krugten M, Pennings HJ, et al. Tumor necrosis factor-alpha +489G/A gene polymorphism is associated with chronic obstructive pulmonary disease. Respir Res. 2002;3:29.

392. Papatheodorou A, Latsi P, Vrettou C, et al. Development of a novel microarray methodology for the study of SNPs in the promoter region of the TNF-alpha gene: their association with obstructive pulmonary disease in Greek patients. Clin Biochem. 2007;40(12):843–850.

393. Sakao S, Tatsuki K, Igarashi H, Shino Y, Shirasawa H, Kuriyama T. Association of tumor necrosis factor alpha gene promoter polymorphism with the presence of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;163(2):420–422.

394. Stankovic MM, Nestorovic AR, Tomovic AM, et al. TNF-alpha-308 promoter polymorphism in patients with chronic obstructive pulmonary disease and lung cancer. Neoplasma. 2009;56(4):348–352.

395. Saper E, Wood AM, Ahmad A, Stockley RA. Tumor necrosis factor-alfa [-alpha] rs361525 polymorphism is associated with increased local production and downstream inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;182(2):192–199.

396. Chen YC, Liu SF, Chin CH, et al. Association of tumor necrosis factor-alpha-863C/A gene polymorphism with chronic obstructive pulmonary disease. Lung. 2010;188(4):339–347.

397. Cordoba-Lanus E, Baz-Davila R, de-Torres JP, et al. TNFA-863 polymorphism is associated with a reduced risk of chronic obstructive pulmonary disease: a replication study. BMC Med Genet. 2011;12:132.

398. Keatings VM, Cave SJ, Henry MJ, et al. A polymorphism in the tumor necrosis factor-alpha gene promoter region may predispose to a poor prognosis in COPD. Chest. 2000;118(4):971–975.

399. Chappell S, Daly L, Morgan K, et al. Variation in the tumour necrosis factor gene is not associated with susceptibility to COPD. Eur Respir J. 2007;30(4):810–812.

400. Chierakul N, Wongwisutikul P, Vejaesya S, Chotvilaiwan K. Tumor necrosis factor-alpha gene promoter polymorphism is not associated with smoking-related COPD in Thailand. Respiratory. 2005;10(1):36–39.

401. Higham MA, Pride NB, Alikhan A, Morrell NW. Tumour necrosis factor-alpha gene promoter polymorphism in chronic obstructive pulmonary disease. Eur Respir J. 2000;15(2):281–284.
402. Sakao S, Tatsumi K, Igari H, et al. Association of tumor necrosis factor-alpha gene promoter polymorphism with low attenuation areas on high-resolution CT in patients with COPD. Chest. 2002;122(2):416–420.

403. Teramoto S, Ishii T, Ishii M, et al. Variation in the tumour necrosis factor-alpha gene is not associated with susceptibility to Asian COPD. Eur Respir J. 2008;31(3):682–683.

404. Zhu G, Gulsvik A, Bakke P, et al. Association of TRPV4 gene polymorphisms with chronic obstructive pulmonary disease. Hum Mol Genet. 2009;18(11):2053–2062.

405. Masuko H, Sakamoto T, Kaneko Y, et al. Lower FEV1 in non-COPD, nonasthmatic subjects: association with smoking, annual decline in FEV1, total IgE levels, and TSLP genotypes. Int J Chron Obstruct Pulmon Dis. 2011;6:181–189.

406. Janssens W, Bouillon R, Claes B, et al. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010;65(3):215–220.

407. Hopkinson NS, Li KW, Kehoe A, et al. Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. Am J Clin Nutr. 2008;87(2):385–390.

408. Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. Am J Respir Crit Care Med. 2004;170(10):1057–1065.

409. Shaheen SO, Jameson KA, Robinson SM, et al. Relationship of vitamin D status to adult lung function and COPD. Thorax. 2011;66(8):692–698.

410. Sharma S, Murphy AJ, Soto-Quiros ME, et al. Association of VEGF polymorphisms with childhood asthma, lung function and airway responsiveness. Eur Respir J. 2009;33(6):1287–1294.

411. Sakao S, Tatsumi K, Hashimoto T, et al. Vascular endothelial growth factor and the risk of smoking-related COPD. Chest. 2003;124(1):323–327.

412. Hersh CP, Pillai SG, Zhu G, et al. Multistudy fine mapping of chromosome 2q identifies XRCC5 as a chronic obstructive pulmonary disease susceptibility gene. Am J Respir Crit Care Med. 2010;182(5):605–613.
## Supplementary materials

### Table S1 Genes tested but showing lack of association with chronic obstructive pulmonary disease

| Symbol       | Name                                                                 | Chromosome | References |
|--------------|----------------------------------------------------------------------|------------|------------|
| AGER         | Advanced glycosylation end product-specific receptor                 | 6          | 1,2        |
| CASP8        | Caspase 8, apoptosis-related cysteine peptidase                      | 2          | 3          |
| CCL17 (TARC) | Chemokine (C-C motif) ligand 17                                      | 16         | 4          |
| CCL2         | Chemokine (C-C motif) ligand 2                                       | 17         | 5          |
| CFLAR        | CASP8 and FADD-like apoptosis regulator                              | 2          | 3          |
| COL6A5       | Collagen, type VI, alpha 5                                           | 3          | 6          |
| CXADR        | Coxsackie virus and adenovirus receptor                             | 21         | 7          |
| CYP1B1       | Cytochrome P450, family 1, subfamily B, polypeptide 1                | 2          | 8,9        |
| CYP2D6       | Cytochrome P450, family 2, subfamily D, polypeptide 6                | 22         | 10         |
| DCN          | Decorin                                                              | 12         | 11         |
| DNAJB1       | DnaJ (Hsp40) homolog, subfamily B, member 1                          | 19         | 12         |
| EDNRA        | Endothelin receptor type A                                           | 4          | 13         |
| FGA          | Fibrinogen alpha chain                                              | 4          | 14         |
| FGB          | Fibrinogen beta chain                                               | 4          | 14,15      |
| FGG          | Fibrinogen gamma chain                                              | 4          | 14         |
| FKB54        | FK506 binding protein 4, 59 kDa                                     | 12         | 12         |
| FKB55        | FK506 binding protein 5                                              | 6          | 12         |
| FLCN         | Foliculin                                                            | 17         | 16         |
| GABPA        | GA binding protein transcription factor, alpha subunit 60 kDa        | 21         | 17         |
| GPX1         | Glutathione peroxidase 1                                             | 3          | 18,19      |
| GSTM3        | Glutathione S-transferase mu 3 (brain)                               | 1          | 20         |
| HDAC2        | Histone deacetylase 2                                               | 6          | 1          |
| HDACS1       | Histone deacetylase 5                                               | 17         | 1          |
| HSP90AA1     | Heat shock protein 90 kDa alpha (cytosolic), class A member 1        | 14         | 12         |
| HSP90AB1     | Heat shock protein 90 kDa alpha (cytosolic), class B member 1        | 6          | 12         |
| HSPA1A       | Heat shock 70 kDa protein 1A                                          | 6          | 21         |
| HSPA1B       | Heat shock 70 kDa protein 1B                                          | 6          | 21         |
| HSPA1I       | Heat shock 70 kDa protein 1-like                                     | 6          | 21         |
| HSPA8        | Heat shock 70 kDa protein 8                                           | 11         | 12         |
| IL1I         | Interleukin 11                                                       | 19         | 1          |
| IL13RA2      | Interleukin 13 receptor, alpha 2                                     | X          | 22         |
| ITGB5        | Integrin, beta 5                                                     | 3          | 7          |
| JAK3         | Janus kinase 3                                                       | 19         | 1          |
| KCND2        | Potassium voltage-gated channel, Shal-related subfamily, member 2    | 7          | 1          |
| MAPK3K       | Mitogen-activated protein kinase kinase 5                            | 6          | 1          |
| MIR146a      | MicroRNA 146a                                                        | 5          | 23         |
| MRPL44       | Mitochondrial ribosomal protein L4                                   | 2          | 24         |
| ORMDL3       | ORM1-like 3 (S cerevisiae)                                           | 17         | 25         |
| PTGES3       | Prostaglandin E synthase 3 (cytosolic)                               | 12         | 12         |
| RARRES2      | Retinoic acid receptor responder (tazarotene induced)                | 7          | 1          |
| SCGB1A1      | Secretoglobin, family 1A, member 1 (uteroglobin)                     | 11         | 26         |
| SOD1         | Superoxide dismutase 1, soluble                                      | 21         | 18,27      |
| TBX21        | T-box 21                                                             | 17         | 28         |
| THSD4        | Thrombospondin, type I, domain containing 4                          | 15         | 2          |
| TLR2         | Toll-like receptor 2                                                 | 4          | 29,30      |
| TLR6         | Toll-like receptor 6                                                 | 4          | 31         |
| TNFRSF1A     | Tumor necrosis factor receptor superfamily, member 1A               | 12         | 32         |
| TNFRSF1B     | Tumor necrosis factor receptor superfamily, member 1B              | 1          | 32         |
References

1. Bakke PS, Zhu G, Gulsvik A, et al. Candidate genes for COPD in two large data sets. *Eur Respir J* 2011;37(2):255–263.

2. Soler Artigas M, Wain LV, Repapi E, et al. Effect of five genetic variants associated with lung function on the risk of chronic obstructive lung disease, and their joint effects on lung function. *Am J Respir Crit Care Med.* 2011;184(7):786–795.

3. Smith AK, Lange LA, Ampleford EJ, Meyers DA, Bleecker ER, Howard TD. Association of polymorphisms in CASP10 and CASP8 with FEV1/FVC and bronchial hyperresponsiveness in ethnically diverse asthmatics. *Clin Exp Allergy.* 2008;38(11):1738–1744.

4. Leung TF, Chan IH, Wong GW, et al. Association between candidate genes and lung function growth in Chinese asthmatic children. *Clin Exp Allergy.* 2007;37(10):1480–1486.

5. Liu SF, Wang CC, Fang WE, Chen YC, Lin MC. MCP1-2518 polymorphism and chronic obstructive pulmonary disease in Taiwanese men. *Exp Lung Res.* 2010;36(5):277–283.

6. Harazin M, Parwez Q, Petrasch-Parwez E, et al. Variation in the heterocomplex gene STIP1 is associated with improved lung function. *Exp Lung Res.* 2009;25(6):685–694.

7. Kasuga I, Hogg JC, Pare PD, et al. Role of genetic susceptibility to latent adenoviral infection and decreased lung function. *Respir Med.* 2009;103(11):1672–1680.

8. Kaur-Knudsen D, Nordestgaard BG, Tybjaerg-Hansen A, Bojesen SE. CYP1B1 genotype and risk of cardiovascular disease, pulmonary disease, and cancer in 50,000 individuals. *Pharmacogenet Genomics.* 2009;19(9):638–649.

9. Korytina GF, Akhmadishina LZ, Viktorova TV. Polymorphism of the genes for antioxidant defense enzymes and their association with the development of chronic obstructive pulmonary disease in the population of Bashkortostan. *Genetika.* 2009;45(7):967–976. Russian.

10. Arif E, Vibhuti A, Alam P, et al. Association of CYP2E1 and NAT2 gene polymorphisms frequency in three ethnic groups of diverse asthmatics. *Am J Respir Crit Care Med.* 2010;181(4):441–447.

11. van Diemen CC, Postma DS, Vonk JM, Bruinenberg M, Nolte IM, Howard TD. Association of polymorphisms in three ethnically diverse populations. *Clin Respir J.* 2008;184(7):786–795.

12. Hawkins GA, Lazarus R, Smith RS, et al. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. *J Allergy Clin Immunol.* 2009;123(6):1376–1383.

13. Taille C, Guenegou A, Almokli A, et al. ETB receptor polymorphism is associated with airway obstruction. *BMC Pulm Med.* 2007;7:5.

14. Sunyer J, Pistelli R, Plana E, et al. Systemic inflammation, genetic susceptibility and lung function. *Eur Respir J.* 2008;32(1):92–97.

15. Yanbaeva DG, Dentener MA, Spruit MA, et al. IL6 and CRP haplotypes are associated with COPD risk and systemic inflammation: a case-control study. *BMC Med Genet.* 2009;10:23.

16. Cho MH, Klanderman BJ, Litonjua AA, Sparrow D, Silverman EK, Raby BA. Foliculin mutations are not associated with severe COPD. *BMC Med Genet.* 2008;9:120.

17. Yamamoto T, Yoh K, Kobayashi A, et al. Identification of polymorphisms in the promoter region of the human NRF2 gene. *Biochem Biophys Res Commun.* 2004;321(1):72–79.

18. Korytina GF, Akhmadishina LZ, Tselousova OS, Zagidullin Sh Z, Viktorova TV. Polymorphism of the genes for antioxidant defense enzymes and their association with the development of chronic obstructive pulmonary disease in the population of Bashkortostan. *Genetika.* 1999;35(7):967–976. Russian.

19. Yang IA, Holz O, Jorres RA, et al. Association of tumor necrosis factor-alpha polymorphisms and ozone-induced change in lung function. *Am J Respir Crit Care Med.* 2005;171(2):171–176.

20. Shukla RK, Kant S, Bhattacharya S, Mittal B. Association of genetic polymorphism of GSTT1, GSTM1 and GSTM3 in COPD patients in a north Indian population. *COPD.* 2011;8(3):167–172.

21. Xie J, Xu Y, Zhang Z, Ni W, Chen S. Heat shock protein 70 gene polymorphisms in Han nationality of China with chronic obstructive pulmonary diseases. *J Huazhong Univ Sci Technolog Med Sci.* 2004;24(1):28–31.

22. Beghe H, Hall IP, Parker SG, et al. Polymorphisms in IL13 pathway genes in asthma and chronic obstructive pulmonary disease. *Allergy.* 2010;65(4):474–481.

23. Li LJ, Gao LB, Lv ML, et al. Association between SNPs in pre-miRNA and risk of chronic obstructive pulmonary disease. *Clin Biochem.* 2011;44(10–11):813–816.

24. Zhu G, Warren L, Aponte J, et al. The SERPINE2 gene is associated with chronic obstructive pulmonary disease in two large populations. *Am J Respir Crit Care Med.* 2007;176(2):167−173.

25. Galanter J, Choudhry S, Eng C, et al. ORMLD3 gene is associated with asthma in three ethnically diverse populations. *Am J Respir Crit Care Med.* 2008;177(11):1194–1200.

26. Liu S, Li B, Zhou Y, Zhong N, Ran P. Genetic analysis of CC16, OGG1 and GPCR29 polymorphisms and susceptibility to COPD. *Respirology.* 2007;12(1):29–33.

27. Young RP, Hopkins R, Black PN, et al. Functional variants of antioxidant genes in smokers with COPD and in those with normal lung function. *Thorax.* 2008;63(5):394–399.

28. Raby BA, Hwang ES, Van Steen K, et al. T-bet polymorphisms are associated with asthma and airway hyperresponsiveness. *Am J Respir Crit Care Med.* 2006;173(1):64–70.

29. Pabst S, Venice V, Lennarz M, et al. Toll-like receptor 2 gene polymorphisms Arg677Trp and Arg753Gln in chronic obstructive pulmonary disease. *Lung.* 2009;187(3):173–178.

30. Spelaets M, Menentiti V, Kostikas K, et al. Association ofTLR4-T399I polymorphism with chronic obstructive pulmonary disease in smokers. *Clin Dev Immunol.* 2009;2009:260286.

31. Hoffjan S, Stemmler S, Parwez Q, et al. Evaluation of the toll-like receptor 6 Ser249Pro polymorphism in patients with asthma, atopic dermatitis and chronic obstructive pulmonary disease. *BMC Med Genet.* 2006;5:34.

32. Ferrarotti I, Zorzetto M, Beccaria M, et al. Tumour necrosis factor-alpha polymorphisms in a phenotype of COPD associated with emphysema. *Eur Respir J.* Mar 2003;21(3):444–449.