Peer reviewed article

COPD and genetics – what's new?

Ladina Joos

Abteilung für Pneumologie, Universitätsspital Basel

Introduction

Chronic obstructive lung disease (COPD) is an enormous cause of global morbidity and mortality. Cigarette smoking is clearly the main risk factor for COPD, however, it is estimated that only 10–20% of chronic heavy smokers will develop symptoms of airway obstruction [1]. This observation demonstrates that other factors are involved and there are epidemiological data to suggest that some of those factors are genetic. The genetic epidemiology was reviewed by Joos et al. [2]. This current review focuses on the two main strategies to identify disease causing genes, linkage analysis and candidate gene approach.

Strategies to identify disease causing genes

Two major strategies have been used to identify genes containing mutations or polymorphisms (common sequence variants) which contribute to the development of COPD. The first strategy is linkage analysis which involves searching the entire human genome for disease-causing genes. The genes are identified solely on the basis of their position in the genome. The second strategy is the candidate gene approach in which individual genes are directly tested for their involvement in a disease process. The genes selected for this approach are those which, because of their function, are plausible candidates for being the disease gene.

Linkage analysis

To perform linkage analysis, phenotypic data and DNA are collected from affected families of at least two generations. Each family member is typed for genetic markers that are scattered throughout the genome, thereby resulting in a complete genome screen. Linkage analysis determines whether any of the markers are inherited with the disease more often than predicted by chance. If so, that disease is said to be 'linked' to that marker on a certain chromosome. An advantage of linkage analysis is that completely novel genes can be identified and implicated in the pathogenesis of a disease. This is because linkage of a disease to a genetic marker depends only on the close proximity of that marker with the disease causing gene and no data concerning the function of the gene are required.

No financial support declared.

Recently, a genome scan exploring genetic linkage to lung function was performed in the Framingham Heart cohort, a longitudinal cohort started in 1948 [3]. This cohort contained numerous extended pedigrees, and provided a unique population for the analysis of genetics of pulmonary function [4]. Joost et al performed a genome scan for FEV_1, FVC, and FEV_1/FVC. The strongest evidence of linkage to FEV_1 occurred on chromosome 6 (LOD = 2.4), and for FVC on chromosome 21 (LOD = 2.6) [3]. In a follow-up study, fine-mapping for the linkage on chromosome 6q and assessment of the association between lung function and specific markers supported the idea that chromosome 6q harboured a gene that was important for lung function [5].

Similarly, a genome-wide scan was performed in the NHLBI family heart study [6]. FEV_1 and FVC were suggestively linked to regions of chromosome 4 and 18.

An additional cohort used for the linkage analysis of lung function was composed of severe early-onset COPD patients without severe AAT deficiency, and control probands matched for age and gender [7]. Both qualitative phenotypes, including airflow obstruction and chronic bronchitis, and quantitative phenotypes, including pulmonary function and bronchodilator responsiveness were evaluated, and several linked genomic regions were identified [8, 9]. Polymorphisms of genes within this region have recently been associated with COPD in the same cohort [10].

Candidate genes for COPD

A large number of candidate genes has been implicated in the pathogenesis of COPD [2]. In this review, we will focus on some of the recent data.

Microsomal epoxide hydrolase

Microsomal epoxide hydrolase (mEH) is a plausible candidate for COPD because of its important role in the lung's ability to metabolize highly reactive epoxide intermediates that may be formed in cigarette smoke. Two common polymorphisms occur in the mEH gene, and these polymorphisms were correlated with the level of mEH enzymatic activity in transfected cell lines [11]. The slow metabolizing form of mEH was

associated with emphysema and COPD [12], and in a smaller Japanese study, the slow metabolizing form of mEH was associated with more severe COPD [13]. A Canadian study found an association of slow metabolizing mEH with an accelerated decline of lung function in smokers [14]. These studies demonstrated that polymorphisms of the mEH gene may be important risk factors in lung disease associated with oxidative stress, consistent with the effects of cigarette smoke components.

Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMP's) are a family of at least 20 proteolytic enzymes that play an essential role in tissue remodeling and repair associated with development and inflammation [15]. Overexpression of metalloproteinases has been associated with several pathological conditions, including the irreversible degradation of tissues in arthritis [16] and the degradation of collagens in tumour invasion and metastasis leading to poorer prognosis in patients with higher expression of MMP's [17]. Several studies in animals and humans have provided evidence that MMP-1 (interstitial collagenase), MMP-12 (human macrophage elastase) and MMP-9 (gelatinase B) are important in airway inflammation and the development of emphysema. Transgenic mice overexpressing human MMP-1 in their lungs were shown to develop morphologic changes strikingly similar to human pulmonary emphysema [18]. On the other hand, MMP-12 knockout mice did not develop emphysema following exposure to cigarette smoke compared to wild type mice [19], suggesting that the presence of MMP-12 is critical in smoke induced lung injury. Smokers with airway obstruction show increased expression of MMP-1 and MMP-9 compared to smokers without COPD and non-smokers [20]. There are several promoter polymorphisms in MMP genes known to alter gene expression [21–24]. A promoter polymorphism in the MMP1 gene (G-1607GG) was associated with rate of decline of lung function in smokers [25]. In the same study, polymorphisms of MMP9 and MMP12 were not individually associated with rate of decline of lung function. However, combination of alleles (i.e. haplotypes) from the MMP1 G-1607GG and MMP12 Asn357Ser polymorphisms revealed an association with rate of decline of lung function ($p = 0.0007$) [25]. In contrast to this study, Minematsu et al. found an association between a MMP9 promoter polymorphism (C-1562T) and the development of emphysema in Japanese smokers [26].

Beta$_2$ receptor polymorphisms

Polymorphisms in the beta$_2$-adrenergic receptor (*ADRB2*) have previously been shown to be associated with several asthma phenotypes [27]. Wang *et al*. showed that the *ADRB2* Arg16 allele was a risk factor for asthma and there was a significant interaction with cigarette smoking [28]. The Arg16→Gly and Gln27→Glu polymorphisms in the *ADRB2* are known to affect agonist-induced receptor downregulation *in vitro* [29] and *in vivo* [30]. In a Chinese population, Ho et al. found that the Arg16 polymorphism was less prevalent in COPD patients than in healthy persons. Additionally, a significant correlation between the Gln27 polymorphism and a low FEV_1 percentage predicted was found [31]. In contrast, a recent study demonstrated the Arg→Gly polymorphism at position 16 was not associated with the rate of decline of lung function, bronchial hyperresponsiveness or bronchodilator response in smokers. However, there was a novel association between heterozygosity at position 27 and decline of lung function, suggesting that this genotype may be protective against an accelerated rate of decline in lung function [32].

Conclusion

Although there is clear evidence of a genetic contribution to COPD, there is still limited evidence about specific genes implicated in its pathogenesis. Inconsistent results in candidate gene and linkage analysis studies due to different COPD phenotypes and different ethnic backgrounds add to the challenge of data interpretation in genetic studies.

Emerging data from linkage studies provide new insights in regions of possible candidate genes. This will increase the efficiency of candidate gene association studies and add to the understanding of the pathogenesis of COPD.

Correspondence:
Dr. med. Ladina Joos
Abteilung für Pneumologie
Universitätsspital Basel
Petersgraben 4
CH- 4031 Basel
E-mail: ljoos@uhbs.ch

References

1 Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J 1977;1:1645–8.
2 Joos L, Pare PD, Sandford AJ. Genetic risk factors of chronic obstructive pulmonary disease. Swiss Med Wkly 2002;132: 27–37.
3 Joost O, Wilk JB, Cupples LA, Harmon M, Shearman AM, Baldwin CT, et al. Genetic loci influencing lung function: a genome-wide scan in the Framingham Study. Am J Respir Crit Care Med 2002;165:795–9.
4 Givelber RJ, Couropmitree NN, Gottlieb DJ, Evans JC, Levy D, Myers RH, et al. Segregation analysis of pulmonary function among families in the Framingham Study. Am J Respir Crit Care Med 1998;157:1445–51.
5 Wilk JB, DeStefano AL, Joost O, Myers RH, Cupples LA, Slater K, et al. Linkage and association with pulmonary function measures on chromosome 6q27 in the Framingham Heart Study. Hum Mol Genet 2003;12:2745–51.
6 Wilk JB, DeStefano AL, Arnett DK, Rich SS, Djousse L, Crapo RO, et al. A genome-wide scan of pulmonary function measures in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Respir Crit Care Med 2003;167:1528–33.
7 Silverman EK, Chapman HA, Drazen JM, Weiss ST, Rosner B, Campbell EJ, et al. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. Am J Respir Crit Care Med 1998;157:1770–8.
8 Silverman EK, Palmer LJ, Mosley JD, Barth M, Senter JM, Brown A, et al. Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. Am J Hum Genet 2002;70:1229–39.
9 Palmer LJ, Celedon JC, Chapman HA, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage analysis of bronchodilator responsiveness and post-bronchodilator spirometric phenotypes in chronic obstructive pulmonary disease. Hum Mol Genet 2003;12:1199–210.
10 Celedon JC, Lange C, Raby BA, Litonjua AA, Palmer LJ, DeMeo DL, et al. The transforming growth factor-{beta}1 (TGFB1) gene is associated with chronic obstructive pulmonary disease (COPD). Hum Mol Genet 2004.
11 Hassett C, Aicher L, Sidhu JS, Omiecinski CJ. Human microsomal epoxide hydrolase: genetic polymorphism and functional expression in vitro of amino acid variants. Hum Mol Genet 1994;3:421–8.
12 Smith CA, Harrison DJ. Association between polymorphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. Lancet 1997;350:630–3.
13. Yoshikawa M, Hiyama K, Ishioka S, Maeda H, Maeda A, Yamakido M. Microsomal epoxide hydrolase genotypes and chronic obstructive pulmonary disease in Japanese. J Mol Med 2000;5:49–53.
14 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;163:469–73.
15 Nagase H, Woessner JF, Jr. Matrix metalloproteinases. J Biol Chem 1999;274:21491–4.
16 Okada Y, Nagase H, Harris ED, Jr. A metalloproteinase from human rheumatoid synovial fibroblasts that digests connective tissue matrix components. Purification and characterization. J Biol Chem 1986;261:14245–55.
17 Kanamori Y, Matsushima M, Minaguchi T, Kobayashi K, Sagae S, Kudo R, et al. Correlation between expression of the matrix metalloproteinase-1 gene in ovarian cancers and an insertion/deletion polymorphism in its promoter region. Cancer Res 1999;59:4225–7.
18 D'Armiento J, Dalal SS, Okada Y, Berg RA, Chada K. Collagenase expression in the lungs of transgenic mice causes pulmonary emphysema. Cell 1992;71:955–61.
19 Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science 1997;277:2002–4.
20 Segura-Valdez L, Pardo A, Gaxiola M, Uhal BD, Becerril C, Selman M. Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD. Chest 2000;117:684–94.
21 Rutter JL, Mitchell TI, Buttice G, Meyers J, Gusella JF, Ozelius LJ, et al. A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an ETS binding site and augments transcription. Cancer Res 1998;58:5321–5.
22 Jormsjo S, Ye S, Moritz J, Walter DH, Dimmeler S, Zeiher AM, et al. Allele-specific regulation of matrix metalloproteinase-12 gene activity is associated with coronary artery luminal dimensions in diabetic patients with manifest coronary artery disease. Circ Res 2000;86:998–1003.
23 Zhang B, Ye S, Herrmann SM, Eriksson P, de Maat M, Evans A, et al. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation 1999;99:1788–94.
24 Shimajiri S, Arima N, Tanimoto A, Murata Y, Hamada T, Wang KY, et al. Shortened microsatellite d(CA)21 sequence downregulates promoter activity of matrix metalloproteinase 9 gene. FEBS Lett 1999;455:70–4.
25 Joos L, He JQ, Shepherdson MB, Connett JE, Anthonisen NR, Pare PD, et al. The role of matrix metalloproteinase polymorphisms in the rate of decline in lung function. Hum Mol Genet 2002;11:569–76.
26 Minematsu N, Nakamura H, Tateno H, Nakajima T, Yamaguchi K. Genetic polymorphism in matrix metalloproteinase-9 and pulmonary emphysema. Biochem Biophys Res Commun 2001;289:116–9.
27 Joos L, Pare PD, Sandford AJ. beta(2)-Adrenergic receptor polymorphisms and asthma. Curr Opin Pulm Med 2001;7: 69–74.
28 Wang Z, Chen C, Niu T, Wu D, Yang J, Wang B, et al. Association of asthma with beta(2)-adrenergic receptor gene polymorphism and cigarette smoking. Am J Respir Crit Care Med 2001;163:1404–9.
29 Green SA, Turki J, Innis M, Liggett SB. Amino-terminal polymorphisms of the human β_2-adrenergic receptor impart distinct agonist-promoted regulatory properties. Biochemistry (Mosc) 1994;33:9414–9.
30 Tan S, Hall IP, Dewar J, Dow E, Lipworth B. Association between beta 2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics. Lancet 1997;350:995–9.
31 Ho LI, Harn HJ, Chen CJ, Tsai NM. Polymorphism of the beta(2)-adrenoceptor in COPD in Chinese subjects. Chest 2001;120:1493–9.
32 Joos L, Weir TD, Connett JE, Anthonisen NR, Woods R, Pare PD, et al. Polymorphisms in the beta2 adrenergic receptor and bronchodilator response, bronchial hyperresponsiveness, and rate of decline in lung function in smokers. Thorax 2003; 58:703–7.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

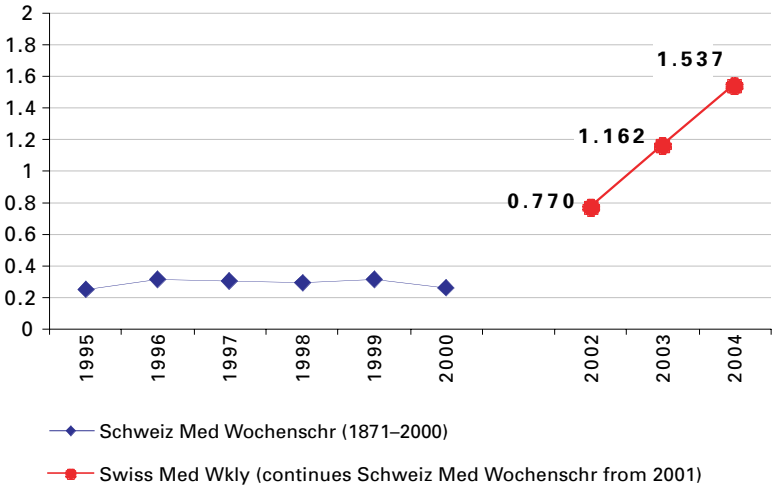
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch