Trade-offs in aging lung diseases: a review on shared but opposite genetic risk variants in idiopathic pulmonary fibrosis, lung cancer and chronic obstructive pulmonary disease

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Purpose of review
The process of aging involves biological changes that increases susceptibility for disease. In the aging lung disease IPF, GWAS studies identified genes associated with risk for disease. Recently, several of these genes were also found to be involved in risk for COPD or lung cancer. This review describes GWAS-derived risk genes for IPF that overlap with risk genes for lung cancer or COPD.

Recent findings
Risk genes that overlap between aging lung diseases, include FAM13A, DSP and TERT. Most interestingly, disease predisposing alleles for IPF are opposite to those for COPD or lung cancer. Studies show that the alleles are associated with differential gene expression and with physiological traits in the general population. The opposite allelic effect sizes suggest the presence of trade-offs in the aging lung. For TERT, the trade-off involves cellular senescence versus proliferation and repair. For FAM13A and DSP, trade-offs may involve protection from noxious gases or tissue integrity.

Summary
The overlap in risk genes in aging lung diseases provides evidence that processes associated with FAM13A, DSP and TERT are important for healthy aging. The opposite effect size of the disease risk alleles may represent trade-offs, for which a model involving an apicobasal gene expression gradient is presented.

Keywords
aging, chronic obstructive pulmonary disease, genome-wide association studies, idiopathic pulmonary fibrosis, lung cancer, trade-off

INTRODUCTION
It is well accepted that the influence of genetic variation on disease development is large. In the last decades, tremendous progress was made in identifying spurious deleterious alleles of high penetrance that strongly contribute to disease development. This has provided unique opportunities, not only for disease diagnostics, but also for development of therapies that aim to biologically compensate or nullify the mutational effect. However, most diseases are not caused by deleterious alleles but are associated with common polymorphisms in our DNA. These polymorphisms have a minor effect on gene function and in ideal circumstances have neutral impact on sustaining healthy life. However, under changing circumstances and in certain combinations, their impact may be altered and particular alleles may contribute to disease development.

The results of over a decade’s worth of genome-wide association studies (GWAS) have taught us a lot. On the down-side, the effect size of common polymorphisms is most often extremely low, which precludes translation to the clinic. However, on
the up-side, patterns between diseases are starting to arise [1]. Disease-associated genes overlap among many diseases, and these patterns indicate that similar pathobiological processes underlie widely varying clinical entities [2–6,7]. Recent GWAS results provide evidence that one such group of diseases with overlapping genes consists of pulmonary aging diseases: idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) and lung cancer [7,8]. With increasing age, the lung changes to the extent that alleles that initially had neutral impact, may increase risk for disease development in aged tissue. Most interestingly though is that the implicated genes in aging pulmonary diseases do overlap, but the alleles do not: opposing alleles at the same locus confer risk for very different clinical entities. This review focuses on overlapping genes and opposite risk alleles in the aging lung diseases IPF, COPD and lung cancer.

AGING AND LUNG DISEASE
As we get older, the chance of developing a lung disease increases. Older persons, aged at least 65 years, report high rates of respiratory symptoms, which commonly associate with COPD, IPF and lung cancer [9]. Overall, there is an almost five-fold increase in incidence of IPF and COPD related solely to age [10], and two-thirds of new lung cancer cases are diagnosed in patients over the age of 65 [11].

COPD is prevalent and a significant cause of mortality in the elderly population. The key element in the diagnosis of COPD is the presence of a persistently reduced ratio of forced expiratory volume in one second/forced vital capacity (FEV₁/FVC), which is also a characteristic of a naturally aged lung [12]. Increase in alveolar size with emphysematous changes in the upper lobes of the lungs are commonly present in more severe COPD. An increase in alveolar size is also a feature of a naturally aging lung [13], however, in COPD the process is associated with inflammation and alveolar wall destruction [12].

IPF is a rare fibrotic lung disease and typically characterized by symmetric bibasilar peripheral fibrogenesis of the lung [14]. IPF survival is 2–3 years and worsens with increasing age [14]. Progressive decline in lung function parameters such as diffusing capacity of the lungs for carbon monoxide (DLCO) is characteristic for IPF. However, in contrast to the decrease in DLCO that is seen in the naturally aging lung, the decrease in IPF is associated with ongoing interstitial fibrogenesis. Naturally aging lung may also contain increased thickening of alveolar septa, without inflammation or fibrosis [13]. A characteristic of IPF lung biopsy is spatial heterogeneity, showing normal lung areas interspersed among areas of fibrosis [15]. Interestingly, these normal areas commonly show thickening of alveolar septa, which may be a sign of aging.

Malignant transformation of cells in lung cancer is caused by accumulated DNA damage. Usually, smoking is the main source of the damage, however, natural biological processes do also contribute. Several forms of lung cancer exist and all are positively associated with age [16]. Median survival in lung cancer is extremely low, and depends on cancer type and stage. Age is a major risk factor with 72% of deaths in lung cancer occurring in patients over 65 years of age [11].

AGING LUNG DISEASES MAY OVERLAP
COPD is an independent risk factor for lung cancer. Several epidemiologic studies and lung cancer screening trials have shown a two- to four-fold increase in lung cancer risk in patients with COPD in comparison with non-COPD smokers [12]. This risk is highest when airflow obstruction and emphysema coexist in a patient [17]. Squamous cell carcinoma in particular is more commonly seen in patients with COPD, and tumor localization strongly associates with areas with the highest degree of emphysema [17]. The risk of developing lung cancer in patients with IPF is approximately seven times higher than that of the general population [18]. IPF patients with
lungs. Patients with co-occurring lung cancer and IPF have worse survival than with only lung cancer or only IPF [19,20].

IPF and COPD features may coexist, a condition known as combined pulmonary fibrosis and emphysema (CPFE). CPFE is characterized by both upper-lobe emphysema and lower-lobe fibrosis [21]. Patients with CPFE are at increased risk of developing lung cancer than with IPF only, and tumors are commonly localized in fibrotic areas [22**].

**GENETIC DISEASE**

Although aging is a risk factor for IPF, COPD and lung cancer, the majority of the aging population does not develop any of these diseases. This is also true for smokers, and indicates that genes play an important role in disease development.

Germline mutations associated with COPD account for approximately 5% of cases, almost all smokers. The most frequent cause is the presence of autosomal recessive mutations in SERPINA1 [23] which associates with lower lobe emphysema. However, a few cases with dominant mutations in TERT and upper lobe emphysema have also been described [24,25].

The most common consequence of TERT mutations, however, is IPF [26]. In IPF, approximately 20% of patients have a familial form of the disease. Familial IPF is most often caused by mutations in telomere related genes [27–29] or by mutations in surfactant processing genes. A remarkable overlap between aging lung diseases and mutations in surfactant processing genes exists. Carriers of autosomal recessive [30] or dominant surfactant processing mutations [31], can have coexisting emphysematous or large cystic changes [32–34] or may develop lung cancer [35–37], all depending on which gene harbors the mutation.

In lung cancer, somatic mutations are the mainstay and these mutations are also found in tumors of patients with preexisting COPD [38] or IPF [39,40]. Twin siblings of affected persons had a 7-fold increased risk for lung cancer, with no difference in risk between monozygous and dizygous twins, underlining the importance of the environment in development of lung cancer [41].

**GENOME-WIDE ASSOCIATION STUDIES**

The majority of elderly lung patients do not carry highly penetrant mutations. In these patients, small constitutional genetic differences, may become of consequence during aging and a history of noxious exposure.

Observations that GWAS risk loci for COPD and lung cancer overlap have been numerous [42–44]. However, recently it was found that several risk genes for COPD or lung cancer were also involved in IPF. A recent GWAS showed that the genes FAM13A and DSP that associate with COPD overlap with IPF although with opposite risk alleles [7**]. Furthermore, meta-analysis of cancerous diseases showed that the gene TERT confers risk for lung cancer [8**], and for IPF [45,46] although again, opposite risk alleles are involved [3].

Although the risk alleles in FAM13A, DSP and TERT are intronic, genetic and physiological consequences of allele carriershhip have been described. Figure 1 and Table 1 summarize shared risk genes, alleles, associated phenotypes and expression.

**FAMILY WITH SEQUENCE SIMILARITY 13 MEMBER A**

Alleles localized at chromosome 4q22, in the gene Family with sequence similarity 13 member A (FAM13A) are among the strongest risk factors for aging lung diseases. The same risk allele is independently associated with COPD [42,57] and lung cancer [43]. Moreover, variants in the gene are independently associated with lung function in the general population [42,48,58,59]. In COPD, the allele is not only associated with risk for disease, but also with phenotypes of disease, such as reduced FEV₁/FVC ratio and presence of chronic bronchitis [50,60–62]. In IPF the same allele also associates with worse lung function (low DLCO) and with worse survival [47*]. However, surprisingly, the risk for IPF disease development is conferred by the opposite allele [46].

For several FAM13A polymorphisms a quantitative effect on gene expression has been demonstrated [59,63]. Risk alleles for COPD, and lung cancer associate with increased gene expression of FAM13A [49,59,64,65]. The risk allele for IPF is the opposite and associates with decreased gene expression.

So far FAM13A was only shown to contribute to development of disease in the elderly, however its contribution to changes in lung function was also found in pediatric cohorts [66]. In human fetal lung, expression of FAM13A is influenced by polymorphisms, and expression levels increase with fetal lung age [67] but an essential role in lung development seems unlikely because Fam13a-deficient mice showed no gross defects in major organs and had normal lung function [68**].
### Table 1. Characteristics of shared disease loci in idiopathic pulmonary fibrosis, lung cancer and chronic obstructive pulmonary disease

| Gene      | Locus      | Ancestral allele | Variant allele | Global MAF | Risk allele | Expression |
|-----------|------------|------------------|----------------|------------|-------------|------------|
|           |            |                  |                | COPD       | Lung cancer | IPF        | General population | Risk allele | Expression |
| FAM13A    | rs2609255  | T                | G              | 0.35       | G (7, 46, 47) | T (48)    | Lower FEV1/FVC | T (48)      | G (49)      |
|           | rs2771167  | T                | C              | 0.48       | T (42, 43)   | T (43)    | Lower FEV1/FVC | C (51)      | G (52)      |
| DSP       | rs2076295  | G                | T              | 0.43       | [7]         | [7]       | [51]         | G (51)      | [52]        |
| TERT      | rs2736100  | A                | C              | 0.48       | A (45, 46, 54)| A (55)  | Short leukocyte telomere length | C (55) | A (56)      |

**Changes associated with aging**: Decrease in **DSP** expression, Decrease in FEV1/FVC, Decrease in telomere length. **Associated gene**: **DSP** high, **FAM13A** high, **TERT** low.

**FIGURE 1.** Genes associated with development of aging lung diseases idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease and lung cancer. Disease-predisposing genes overlap but alleles have opposite effect size. Aging and a history of noxious exposure changes genetic requirements for maintenance of a healthy lung. In the aged lung, subtle differences in gene expression conferred by risk alleles in **DSP**, **FAM13A** and **TERT**, can influence biological processes and increase risk for specific aging-associated lung diseases. Presence of disease contributes to tissue aging and increase the risk for secondary lung cancer. **GENENAME** high, allele associated with increased gene expression; **GENENAME** low, allele associated with decreased gene expression.

*The minor allele differed per study population, therefore, the ancestral allele and MAF were derived from https://www.ncbi.nlm.nih.gov/projects/SNP.

**Joint analysis United States Patent Application 20160060701 at http://www.freepatentsonline.com/y2016/0060701.html.**

**Cases and controls.**

*The referenced study presents results for rs2609264; however, there is complete/significant linkage disequilibrium (r²) between rs2609255 and rs2609264: r² = 0.97 in Asian and r² = 1 in European population computed at http://archive.broadinstitute.org/mpg/snap/idsearchpw.php.
The mechanisms by which \textit{FAM13A} contributes to disease is not understood. \textit{FAM13A} has a diverse role in signal transduction that seems to be highly dependent on context [68**,69–71]. In lung cancer, \textit{FAM13A} was identified as a key regulator of tumor growth and progression [69]. In human lungs, \textit{FAM13A} is expressed in airway epithelial and mucosal cells, club cells, alveolar type II epithelial cells and macrophages [68**,70] and can be induced by hypoxia [72]. In COPD and IPF lung tissue, \textit{FAM13A} expression was not influenced by allele carriage and was not significantly different from controls [46,49]. However, increased protein levels of \textit{FAM13A} were detected in very severe COPD lungs whenever compared with healthy ex-smokers [68**]. Furthermore, only Fam13a wild type mice can develop emphysema, whereas Fam13a-deficient mice are protected from emphysema development, even after 6 months of exposure to cigarette smoke [68**]. This suggests that \textit{FAM13A} expression may be essential for emphysema development, in line with the finding that higher expressing alleles associate with development of COPD.

\textbf{DESMOPLAKIN}

The desmoplakin (\textit{DSP}) gene at 6p24 harbors one of the top risk alleles in IPF GWAS [46,73], and the opposite allele was recently found to confer risk for COPD [7**].

In both control and IPF lung samples, the \textit{DSP} risk locus associated with differential expression of \textit{DSP}. Lower expression levels associated with the risk allele for IPF [52*], higher expression levels associated with the opposite allele. Interestingly, the expression of \textit{DSP} decreased with age in control lung samples [52*]. However, in case of disease, the expression of \textit{DSP} increases and levels in IPF lung samples are higher than in controls [52*].

Desmoplakin is a critical component of desmosomes that are important for cell–cell adhesion. Desmosomes have also been shown to influence cell proliferation, differentiation, migration and apoptosis [74]. Staining of fibrotic and normal human lung tissue localized DSP to airway epithelia and epithelial cells lining cystic areas of the fibrotic lung [52*]. Staining in normal alveolar tissue was not detected, but one must keep in mind that DSP may be present at the intersections of alveolar type I cells, which may not be visible by immunohistochemistry.

\textit{DSP} is essential for development, mutations in \textit{DSP} cause Mendelian disorders primarily affecting the skin and heart. Dsp-deficient mice are not viable [75], and mice heterozygous for cardiac-restricted deficiency of DSP have reduced survival and develop arrhythmogenic right ventricular cardiomyopathy, including fibrosis in the myocardium [76].

Desmosomes are found in tissue that experience intense mechanical stress or shear stress, hence the association with cardiomyopathy [77]. Induction of loss of desmoplakin in cardiomyocytes causes upregulation of profibrotic genes [78]. A possible cause of IPF was suggested to involve increased tractional stress, because IPF is typically characterized by fibrogenesis at bibasilar peripheral lung regions wherever mechanical stress is the highest [79]. This process was further suggested to be accelerated by dysfunctional surfactant fluid through admixture with MUC5B protein [80]. The IPF predisposing allele in DSP associates with decreased expression of desmoplakin, which may decrease structural integrity at sites of highest tractional stress and subsequently trigger fibrogenesis.

Interestingly, loss of DSP is also considered an early step in carcinogenesis. Reduction of DSP can be caused by an epigenetic mechanism and reduced levels are present in primary lung tumors independent of tumor grade, tumor stage and lymph node status [81]. Further cancer cell experiments showed that overexpression of \textit{DSP} led to significant reduction of lung cancer cell proliferation and anchorage-independent growth [81].

\textbf{TELOMERASE REVERSE TRANSCRIPTASE}

Telomerase reverse transcriptase (\textit{TERT}) at 5p15 encodes an enzyme essential for telomere length maintenance. The \textit{TERT} allele that increases risk for IPF [45,46,54] is the opposite of the risk allele for lung cancer [3,8**,53]. The risk allele for IPF associates with lower expression of the gene [56*] and with shorter leukocyte telomere length in the general population [55]. The allele for lung cancer is the opposite and associated with higher expression and longer telomeres. Moreover, longer leukocyte telomere length associates with an increased risk of developing lung cancer [82].

Germline mutations in \textit{TERT} that cause IPF or (rarely) emphysema lead to haploinsufficiency of telomerase and accelerated shortening of telomeres upon cell division [83]. Critically short telomeres signal senescence or apoptosis [84]. Mouse models deficient for normal telomere function develop pulmonary emphysema when exposed to cigarette smoke [24], or pulmonary fibrosis when exposed to bleomycin [85].

Telomere shortening or dysfunction in alveolar type II cells seems critical for fibrogenesis. Telomere shortening was observed in alveolar epithelial cells from patients with COPD [86] and IPF [87**]. Recently, shortest telomeres were found in alveolar...
type II cells in fibrotic areas of IPF lung in comparison with nonfibrotic areas [87**]. Furthermore, selective shortening of telomeres in alveolar type II cells in mice resulted in age-dependent lung remodeling and fibrosis [88**].

Progressive telomere shortening from cell division, also known as replicative aging, provides a barrier for tumor progression [89]. However, in lung tumors, somatic mutations in the promoter region of TERT contribute to increased transcription and cellular immortality [90]. Tumorigenesis is dependent on sequential accumulation of mutations, which are crucial for malignant transformation of the cell [91]. Carriage of the allele for longer telomeres may allow for more cell divisions and increase the chance of accumulating critical oncogenic mutations. Furthermore, longer telomere length associates with higher intrinsic epigenetic age acceleration [92]. Telomerase is thought to regulate the balance between ageing and cancer. Indeed, Tert overexpression in mice increased tumor development, but in a model of tumor-resistant mice, Tert overexpression showed to be beneficial and increased longevity [89].

Reduction in leukocyte telomere length was proposed as a biomarker of aging [93]. Patients with COPD have accelerated shortening of leukocyte telomere length, but this is not related to clinical parameters [94]. Patients with IPF, however, not only have very short telomeres, the decrease in blood and lung is also associated with worse survival [87**]. Furthermore, the leukocyte telomere length in IPF is significantly shorter than in other lung diseases with comparable disease burden [96]. It can, therefore, be concluded that only in IPF – and not in COPD or lung cancer – the genetic constitution of the patient is the cause of the short telomeres.

**TRADE-OFFS IN THE AGING LUNG**

The identification of genetic correlations between diseases can provide useful pathological insights [1]. In the aging lung, polymorphisms in FAM13A, DSP and TERT connect three lung diseases: IPF, COPD and lung cancer. Clinically, these three diseases are also connected by shared risk factors: noxious particles and gases (i.e. from smoking), and aging.

Aging involves changes in cellular levels of gene transcript and proteins that are partly regulated by the presence of genetic variants. The risk alleles in FAM13A, DSP and TERT for IPF were opposite to those for COPD or lung cancer. Furthermore, the polymorphisms were shown to influence gene expression levels: risk alleles for IPF associate with low expression and risk alleles for COPD and lung cancer associate with high expression.

The opposing alleles in TERT, FAM13A and DSP probably represent trade-offs in an aging organism. A trade-off exists whenever a benefit in one context entails a cost in another [97]. A textbook example of trade-off is the sickle cell causing mutation HbS, which also protects against malaria. The trade-off associated with the TERT variant is easiest to understand: high expression of TERT is associated with the capacity of rejuvenation and repair but confers an increased risk of developing cancer. Trade-offs for FAM13A and DSP may involve protection from noxious gases or tissue integrity.

Trade-offs associated with optimal expression levels may be caused by involvement of different cell types or different lung areas. Hypothetically, low FAM13A levels in airway cells may be optimal to decrease risk for COPD but may be too low in alveolar cells to prevent IPF. In the context of lung localization, a gradient of optimal expression levels may exist. In IPF, fibrogenesis follows an apicobasal gradient with basal and peripheral predominance of fibrosis [14]. The cause of this gradient is unknown, but may be associated with regional differences in lung mechanical stress or perfusion. Its presence, however, suggests that a trade-off between the upper and lower parts of the lung may exist. The low-expressing alleles – associated with IPF – may be too low at basal lung areas. Moreover, the high expressing alleles – associated with COPD – may be too high for the apical lung regions (Fig. 2). Further research is required to understand which trade-offs are present in the aging lung.

Given the presence of opposite risk alleles and the additive effect of each allele on expression, it appears that in the aging lung, heterozygotes are at an advantage. In fact, in humans a significant association between increased genome-wide heterozygosity and survival is present [98]. Lung diseases contribute significantly to mortality; thus it is possible that individuals heterozygous for the studied polymorphisms in TERT, DSP and FAM13A are at an advance whenever becoming of age. Allele frequencies are driven by evolutionary processes, maintaining the alleles best fitted for survival in the context of reproduction. Alleles are, therefore, not optimized for aging. The alleles in TERT, DSP and FAM13A that influence susceptibility for aging lung diseases IPF, lung cancer and COPD are well tolerated in early life, they influence phenotypic traits but do not associate with disease. It is conceivable that alleles influencing expression of these genes to a higher degree may not be well tolerated and will affect health at a prereproductive age. Some experimental studies on over-expression and under-
expression of the genes showed deleterious consequences, supporting this hypothesis. This has to be kept in mind whenever trying to translate findings on risk alleles into therapies that interfere with expression levels of genes associated with aging lung diseases.

CONCLUSION

In conclusion, IPF risk genes, FAM13A, DSP and TERT are shared with COPD or lung cancer. This underlines the importance of these genes in the development of lung disease in the aging population. Risk alleles were shown to have opposite effect size and opposite influence on expression levels (Fig. 1 and Table 1). A trade-off model is presented (Fig. 2) demonstrating how opposing alleles may influence disease risk. Further studies are required to understand how these genes contribute to health and disease in the aging lung.

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Conflicts of interest

There are no conflicts of interest.

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