

GENE ASPECTS ON COPD PHENOTYPES

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Chronic obstructive pulmonary disease (COPD), one of the leading causes of death world-wide, is a heterogeneous syndrome. Understanding the heterogeneity of COPD and subdividing it into its unique subtypes is necessary to both define its pathogenesis and enable development of new subtype-specific therapies. Longitudinal data to elucidate the genetic, clinical, and radiographic determinants of disease expression and progression are needed. The COPDGene project is attempting to: a) identify new genetic loci that influence the development of COPD and COPD-related phenotypes; and b) classify COPD into subtypes that can ultimately be used to develop effective subtype-specific therapies. COPDGene is a cohort of 10,000 smokers who either have or are at risk for developing COPD. This cohort was assembled at 21 medical centers across the United States. All subjects have undergone inspiratory and expiratory Chest CT scans which are being quantitatively analyzed and used in combination with clinical characteristics to subdivide the cohort into coherent clinical/image based subtypes. A Genome-Wide Association Analysis has been done and whole exome sequencing is underway. Genetic analysis of case/control status has confirmed risk for COPD to be associated with a number of genes including HHIP, FAM-13 and nicotine addiction loci. Unique genetic associations with specific subtypes of COPD are also being identified including associations with risk for mild upper-lobe predominant COPD and risk for more severe, progressive centrilobular emphysema. Lower-lobe predominant panlobular emphysema has been long identified as associated with alpha-1 antitrypsin deficiency. Image based subtyping of COPD has identified a large number of subjects (both current and former smokers) who have gas trapping, emphysema, airway inflammation and decreased quality of life, but who do not have physiologic obstruction. These subjects would not be classified as having COPD by traditional spirometry based criteria. A new classification system based on pathophysiologic subtypes of COPD is needed and can be accomplished by integrating genetic, clinical, physiologic, and CT-based phenotypes.

LUNG FUNCTION AND COPD PHENOTYPES

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If one aim for COPD research is to lead to improvements in symptoms and outcomes for COPD patients then the chances of success will be maximised by ensuring the best definition of what is COPD and clarifying if phenotypes exist with differing potential for intervention. Airflow obstruction is an essential requirement for COPD and using FEV₁/FVC as a fixed ratio leads to higher prevalence rates and sex bias compared to using lower limits of normal (LLN). The airflow obstruction should then be persistent but how best to assess this is not well defined. The presence of continuing airflow obstruction post bronchodilator (BD) can be seen in asthma as well as COPD. Using post BD change as a percent of predicted (PP) avoids sex bias when defining reversibility and <9PP makes asthma less likely. A COPD

phenotype of airflow obstruction plus a low FEV₁ identifies more severe disease. Mortality better relates to FEV₁ when expressed in relation to 'the bottom line' such as FEV₁/ht³ rather than relating it to a predicted value. Phenotypes defined by a low gas transfer are better related to mortality than those defined by a low Kco. This is because Kco can fall with worsening disease, as in pure emphysema, or paradoxically increase if progressive airway closure reduces effective alveolar volume. These points will be illustrated with results using long term follow up data from over 500 patients with alpha-1 antitrypsin deficiency, 1500 patients with COPD and from over 4000 patients with other lung diseases. In conclusion, the interests of COPD patients will be best served by careful attention to detail in defining the disease and its phenotypes to reduce misclassification. Only then will studies have the best chance of identifying successful interventions.

NEW GOLD GUIDELINES – HOW DO WE USE THEM?

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The 2011 revision of the GOLD document (1, 2) has in some areas been changed substantially compared to previous versions. The new document strongly suggests that assessment of any COPD patient should involve the following 4 components: 1) assessment of symptoms, 2) assessment of airflow limitation, 3) assessment of exacerbation history, and 4) assessment of comorbidities. Instead of just evaluating stages as defined by FEV₁, GOLD now suggests a combined assessment of symptoms and risk of exacerbations. Symptoms can be assessed by the mMRC breathlessness scale, the COPD Assessment Test (CAT) or the Clinical COPD Questionnaire (CCQ). Patients can be characterised as having few symptoms or many symptoms based on either of these questionnaires. Exacerbation risk can be assessed using exacerbation history and spirometry (FEV₁), and patients are characterised as having either low risk or high risk of exacerbations. Patients with less than 2 exacerbations last year, no admissions because of exacerbations and an FEV₁ of 50+ % of predicted have a low risk of exacerbations. Patients with 2+ exacerbations last year, one or more admissions or an FEV₁ < 50 % of predicted have a high risk of exacerbations.

This combined assessment can subsequently be used for determining treatment, both non-pharmacological and pharmacological treatment. The document emphasises the importance of smoking cessation and the strong evidence base for pulmonary rehabilitation and advocates physical exercise in all COPD patients. The document maintains that bronchodilators are the main drugs for COPD with inhaled corticosteroids and PDE4-inhibitors being reserved for patients at high risk of exacerbations only.

The new GOLD document also includes new chapters on management of exacerbations and on managing COPD with comorbidities.

References

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2. Vestbo J, Hurd SS, Rodriguez-Roisin R. The 2011 revision of the Global Strategy for the Diagnosis, Management, and Prevention of COPD (GOLD) -why and what? *Clin Respir J* 2012, doi: 10.1111/crj.12002.