57. Environmental and genetic risk factors for asthma and COPD

395 LATE-BREAKING ABSTRACT

17q21 variants modify the effect of early viral infections on childhood asthma

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Single nucleotide polymorphisms (SNPs) at chromosome 17q21 confer an increased risk of early-onset asthma. We aimed to study whether 17q21 SNPs modify associations between early viral infections and asthma. A case-control analysis was conducted in 499 children (268 with asthma, median age 11y) from the Epidemiologic Study on the Genetics and Environment of Asthma (EGEA). Data from the 12y follow-up were used to assess persistent or remitting asthma in young adulthood. Viral infection before the age of 2 was assessed retrospectively. Odds ratios (ORs) were calculated by generalized estimating equations. For 17q21 variants located in the 17q21 region, the ORs for association between infection and early-onset asthma (age at onset ≤4y) were higher in carriers of risk genotypes (ORs 3.4-6.4) than in non-carriers (ORs 1.8-2.4; p-interaction 0.02-0.04 for 5 SNPs). Risk genotypes also increased the association between infection and childhood asthma in adulthood (ORs 4.8-7.2 in carriers and 1.7-2.2 in non-carriers; p interaction 0.008-0.05 for 10 SNPs). No effect modification by 17q21 variants was found for later-onset asthma (>5y) and asthma that persisted in adulthood (p-interaction =0.15). In children with 17q21 risk genotypes and early-life exposure to environmental tobacco smoke (ETS), ORs for the association between infection and asthma were further increased, up to 1.00 (p=1×10^(-10)), early-onset) and 10.7 (p=3×10^(-7), remittance) for rs8091786 GGT subjects.

This highlights an important role of 17q21 variants in early viral respiratory infection and early exposure to ETS in early-onset asthma and childhood asthma that remits in adulthood.

Funding: Gabriel, PHRC, MSD, ANR-CEBS, EAAC3-GA-LEN.

396 Occupational exposures increase the risk of cough in asthmatic adults in interaction with TRPV1 polymorphisms

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Transient receptor potential vanilloid receptors (TRPV1) are activated by various noxious chemicals and may play an important role in the pathogenesis of irritant-induced cough. The aim was to study the influence of occupational exposures and single nucleotide polymorphisms (SNPs) in TRPV1 and TRPV4 on cough. Cough symptoms and job history were obtained by questionnaire in 211 asthmatic and 497 non-asthmatic adults from the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA). Occupational exposures to vapors, gases, dusts, or fumes (VGDF) were assessed by the ALOHA job-exposure matrix. Twenty-four tagging SNPs in TRPV1 and TRPV4 were tested under a dominant model. OR were calculated by generalized estimating equations. Ever being exposed to VGDF at the workplace was significantly associated with an increased prevalence of cough in asthmatics (nocurnal cough OR 2.52 [95%CI 1.36-4.65], usual cough 2.50 [1.35-4.65], chronic cough 3.10 [1.52-6.30]). In non-asthmatics, effects of occupational exposure and smoking on cough were significantly different for men and women. Further analyses were restricted to asthmatics. For three TRPV1 SNPs in low linkage disequilibrium (r2<0.21), the association between VGDF exposure and nocturnal cough was very strong in carriers of at least one variant allele (OR=4.7, p<0.005) and weaker in wild and type homozygotes (gene-environment interaction p=0.03-0.09). Usual and chronic cough showed similar patterns (interaction p<0.06).

TRPV1 SNPs may enhance susceptibility to cough in asthmatics with a history of workplace exposure to VGDF.

Funded by ANR-SEST, AFSSSET. L Smut is supported by a EACCI-GEN partner fellowship.

397 Genetic influences on the age at onset of asthma: a twin study

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Aim: To study the variation in the age at onset of asthma attributable to genetic and environmental factors.

Methods: Data on the age at onset and predictors of asthma was collected via a multidisciplinary questionnaire study of 34,782 Danish twins, 20-71 years of age. Survival analytic methods were applied to partition variation in the age at onset of asthma into genetic and environmental components.

Results: Sex, hay fever, flurescent eczema, BCG vaccination, smoking, and exposure to passive smoking in childhood significantly predicted age at onset of asthma. The risk of asthma in the co-twin of an affected twin was higher in monogygotic (MZ) than in dizygotic (DZ) twins, hazard ratio=2.59 (1.83-3.68), p<0.001. The risk of asthma in the co-twin decreased with increasing age at onset of asthma in the index twin, hazard ratio (per ten years)0.80, 95% CI (0.76-0.86), p<0.019. The effect was attenuated in DZ twins relative to MZ twins, p=0.005. Genetic factors explained 34% of the variation in the age at onset of asthma.

Conclusions: Natural variation in the age at onset of asthma can be partly ascribed to genetic factors. This result should stimulate research aimed at identifying genes associated with the age at onset of disease and at discovering environmental factors impacting at certain points in life.

398 Genetically elevated C-reactive protein and chronic obstructive pulmonary disease

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Background: It is unclear whether elevated plasma C-reactive protein (CRP) is causally related to chronic obstructive pulmonary disease (COPD). We tested the hypothesis that genetically elevated plasma CRP cause COPD using a Mendelian Randomisation design.

Methods: We measured high-sensitivity CRP in plasma, genotyped for 4 single nucleotide polymorphisms in the CRP gene, and screened for spurious defined COPD and hospitalisation due to COPD in 8,323 individuals from the Copenhagen City Heart Study and in 36,036 individuals from the Copenhagen General Population Study.

Results: Elevated plasma CRP > 3 mg/L compared with < 1 mg/L was associated with a 1.9 and 2.5 fold increased risk for COPD and a 1.8 and 1.7 fold increased risk for hospitalisation due to COPD in the Copenhagen City Heart Study and Copenhagen General Population Study, respectively. Genotype combinations of the four CRP polymorphisms were associated with up to a 6.2% increase in plasma CRP. However, these genotype combinations did not associate with increased risk of COPD or hospitalisation due to COPD in either cohort, or in the two cohorts combined.

Interpretation: Although elevated CRP is related to both a diagnosis of COPD and subsequent hospital admission, genetically elevated plasma CRP is not associated with an increased risk of clinical COPD. This suggests that the association between CRP levels and COPD is not causal.

399 α1 antitrypsin PI MZ heterozygotes have reduced lung function in two large cohorts

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Background: Severe alpha-1 antitrypsin (AAT) deficiency is a known genetic risk factor for chronic obstructive pulmonary disease (COPD). Heterozygous (PI MZ) individuals have moderately reduced AAT serum levels compared to individuals with the normal PI type (PI MM), but whether they have an increased risk of COPD is uncertain.

Methods: We investigated the associations between PI MZ and the COPD-related phenotypes of lung function and quantitative chest CT measurements in two large

Abstract printing supported by Chiesi Farmaceutici SpA. Visit Chiesi Farmaceutici SpA at Stand B.40
populations of current- or ex-smokers: a case-control study from Norway (834 cases and 835 controls) and a multicenter family-based study from Europe and North America (984 probands and 1723 relatives). PI type was determined by isoelectric focusing, and only subjects with PI MM or PI MZ were included. We performed multivariate regression analyses, adjusting for relevant covariates.

**Results:** In the case-control study, 44 cases (5.3%) and 34 controls (4.1%) were PI MZ. In the family-based study, 43 (4.4%) probands and 72 (4.2%) relatives were PI MZ. PI MZ was associated with a 3.5% lower FEV1/FVC ratio in the case-control study (p = 0.04), and a 3.9% lower ratio in the family study (p = 0.009). In the case-control study, PI MZ was also associated with a 3.7% increase in emphysema on quantitative image analysis of chest CT scans (p = 0.003). The emphysema results were not replicated in the family study. PI MZ was not associated with airway wall thickening, other lung function variables or COPD affection status.

**Conclusion:** Compared to PI MM individuals, PI MZ heterozygotes had a lower FEV1/FVC ratio in two independent studies. In the case-control study, PI MZ individuals also had more severe emphysema on chest CT scan.

### 400 Interleukin 6 modulates the risk to develop COPD: a prospective population-based cohort study

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**Introduction:** Cross-sectional studies have linked chronic obstructive pulmonary disease (COPD) to increased levels of interleukin 6 (IL-6) in the systemic circulation and in the airways.

**Objective:** In order to check for causal association, we investigated prospectively the relation between plasma levels of IL-6, variation in the IL-6 gene and the risk of developing COPD.

**Methods:** This study was part of the Rotterdam Study, a prospective population-based cohort study among 7983 subjects aged 55 years or older, including 928 COPD cases, with 15 years of follow-up. At baseline, blood was drawn to measure the -174 G/C IL-6 gene SNP - a SNP located in the promoter region of the IL-6 gene that influences IL-6 transcription - and plasma levels of IL-6.

**Results:** The -174 G/C SNP was genotyped in 6701 subjects. No association was found between the -174 G/C SNP and COPD in the total cohort. When stratified by smoking behaviour, homoyzosity for the C-allele was associated with a 50% protective effect on the development of COPD in never-smokers (95% CI, 0.28-0.98). IL-6 plasma levels were measured in 714 subjects, a randomly selected subset of the total cohort. After adjustment for age, gender, smoking and other potential confounders, high levels of IL-6 (> 2.4 pg/ml, the highest tertile) were associated with a three fold increased risk to develop COPD compared to low levels (95% CI, 1.07-8.24).

**Conclusion:** IL-6 plasma levels are associated with an increased risk to develop COPD. No strong evidence was found for a causal role of the -174 G/C SNP in COPD, although subanalyses suggest that this SNP is associated with a protective effect in never smokers.

**Supported by the FWO and Belgian Thoracic Society.**

### 401 Determinants of the 9-year incidence of COPD in an international cohort of young non-smooth adults. Preliminary results from ECRHS II

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The aim of this study was to investigate factors associated with an increased incidence of COPD in young adults. COPD was defined as FEV1/FVC < 0.70 (GOLD guidelines). We analyzed the data of 4,710 subjects (20-44 years old) with baseline FEV1/FVC < 0.70, who were followed up for 9 years and who did not report lifetime asthma at baseline/last follow-up.

During the follow-up, 121 subjects developed COPD (incidence: 2.88/1000-y, 95%CI 2.41-3.44). The table below shows the incidence rate ratios (IRRs) for the association of some potential determinants measured at baseline with COPD incidence. This preliminary analysis confirms that men, heavy smokers, older and overweight subjects are at increased risk of developing COPD. AHR and family asthma were independent predictors of the occurrence of COPD; further studies are needed to elucidate their role in COPD.

### 402 Emphysema estimated by quantitative HRCT is related to DLCO and KCO

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Limited data is available on the relationship between carbon monoxide diffusivity capacity and emphysema estimated by high resolution computed tomography (HRCT). HRCT scans and pulmonary function tests were obtained from 463 COPD cases (GOLD B-DV) (299 men, 164 women) and 488 healthy controls (260 men, 228 women). All subjects were current or ex-smokers from Norway, aged ≥ 40 years. Regression analyses were done separately for each sex, and DLCO and KCO were used as dependent variables. Age, height, hemoglobin, smoking history, FEV1 and inflation level were included as co-variables in the multivariate analyses. The mean (SD) DLCO (mmol/min/kPa) was 6.1 (1.9) and 4.8 (1.3) in male and female cases, 8.7 (1.7) and 6.3 (1.2) in male and female controls. The mean (SD) KCO (mmol/min/kPa L) was 1.1 (0.3) and 1.2 (0.3) in male and female cases, and 1.3 (0.2) in both male and female controls. Both the univariate and multivariate regression analyses shows a highly significant (p < 0.001) and negative correlation between %LAA and both DLCO and KCO. The adjusted regression coefficients (SE) per 10% increase in %LAA was -0.09 (0.02) (DLCO) and -0.18 (0.02) (KCO) in men, and -0.75 (0.14) and -0.20 (0.03) in women. The significant relation between DLCO and %LAA was also present after adjustments for pulmonary function were made, and this confirms that quantitative HRCT is a valuable tool for characterization of COPD.