with FEV_1 in a GWAS study (Wilk 2007). We recently found a *GSTO1* SNP associated with lower FEV_1 in heavy smokers only (≥12.5 py; unpublished) suggesting a gene by smoking interaction. Since the GST-family deals with oxidative stress, we hypothesize that *GSTO2* SNPs may also interact with ETS exposure and affect lung function.

Methods: Genotyped individuals (n=8128) from the LifeLines study, a general Dutch population cohort, were included. We selected 4 *GSTO2* tagging SNPs (MAF=0.10, R^2<0.8) (table 1). Associations between daily hours of ETS exposure (<1/≥1hr), ETS exposure at work (no/yes), history of active smoking (not, < and ≥10.5 py), SNPs (recessive model) and FEV_1 were assessed by linear regression models, adjusted for sex, age, height, weight, and smoking habits.

Results: Daily ETS exposure (≥1hr b=-37ml; p=0.011) and history of active smoking (≥10.5 py b= -121ml; p<0.001) were associated with FEV_1. ETS exposure at work and the SNPs were not significantly associated with FEV_1. However, *GSTO2* SNPs clearly interacted with ETS exposure and history of active smoking (table 1).

Table 1. GSTO2 by exposure interactions and FEV1 (ml (95% CI))

SNPs	ETS (≥1 hr/day)	ETS at work (y)	≥10.5 py
rs157077	–108 (–200; –15)	–194 (–334; –54)	–109 (–200; –18)
rs156697	–59 (–137; 19)	–170 (–295; –46)	–63 (–141; 15)
rs987247	–105 (–199; –11)	–179 (–321; –37)	–115 (–208; –22)
rs156699	–94 (–178; –10)	–218 (–349; –87)	–74 (–158; 10)

Conclusion: We show that ETS exposure has deleterious effects on FEV_1 in subjects homozygous for the minor allele of *GSTO2* SNPs.

220. Genes, environment and obstruction

1729

Late-breaking abstract: GST omega gene polymorphisms, environmental tobacco smoke (ETS) and lung function in a general Dutch population cohort

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Background: Both ETS exposure and SNPs in Gluthatione S-tranferase (GST) genes are associated with FEV_1 level. A *GSTO2* SNP (rs156697) was associated with FEV_1 in a GWAS study (Wilk 2007). We recently found a *GSTO1* SNP associated with lower FEV_1 in heavy smokers only (≥12.5 py; unpublished) suggesting a gene by smoking interaction. Since the GST-family deals with oxidative stress, we hypothesize that *GSTO2* SNPs may also interact with ETS exposure and affect lung function.

Methods: Genotyped individuals (n=8128) from the LifeLines study, a general Dutch population cohort, were included. We selected 4 *GSTO2* tagging SNPs (MAF=0.10, R^2<0.8) (table 1). Associations between daily hours of ETS exposure (<1/≥1hr), ETS exposure at work (no/yes), history of active smoking (not, < and ≥10.5 py), SNPs (recessive model) and FEV_1 were assessed by linear regression models, adjusted for sex, age, height, weight, and smoking habits.

Results: Daily ETS exposure (≥1hr b=-37ml; p=0.011) and history of active smoking (≥10.5 py b= -121ml; p<0.001) were associated with FEV_1. ETS exposure at work and the SNPs were not significantly associated with FEV_1. However, *GSTO2* SNPs clearly interacted with ETS exposure and history of active smoking (table 1).

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Conclusion: We show that ETS exposure has deleterious effects on FEV_1 in subjects homozygous for the minor allele of *GSTO2* SNPs.

1730

Genetic overlap of airway obstruction and emphysema

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Airway obstruction and emphysema are two features of chronic obstructive pulmonary disease (COPD). COPD patients can display one phenotype or both at one time. We used the Nelson cohort comprising ~3000 individuals with lung function measurements and CT-scans to determine genes that contribute to both features. We performed genome-wide association studies on both sub-phenotypes. Airway obstruction was investigated in a case-control design (1030 cases with FEV1/FVC<0.7, 953 controls with FEV1/FVC>0.7 and FEV1 >90%pred, both groups being heavy-smokers with >20 pack-years, and 846 blood bank controls). Emphysema was investigated as a quantitative trait. To account for center-derived differences in these measurements we used 15th percentile (p15) of density distribution adjusted for air density in the trachea. p15 was analyzed using linear regression adjusting for age and pack-years smoking in 3047 subjects. To find overlap between these two sub-phenotypes we selected all SNPs with p<0.001 in each analysis, yielding a total of nine SNPs corresponding to four genes. When these genes were investigated in GeneMania they were enriched with an additional 9 genes directly interacting or co-expressed/co-localized with query genes and two of them point to a drug resistance pathway (GATHER p<0.0001, Bayes factor 6).

This is an interesting approach that can help identifying a shared etiology of two distinct sub-phenotypes of a single complex disease.

1731

Susceptibility to chronic mucus hypersecretion: A genome-wide association study

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Background: Patients with COPD with chronic mucus hypersecretion (CMH) have a significantly increased FEV_1 decline and a higher risk of hospitalization

than those without CMH. Moreover, although individuals with CMH are more likely to be ex- or current smokers, so far it is unclear why some smokers develop CMH and others do not. A plausible explanation for this phenomenon would be a genetic predisposition.
Methods: We performed a genome wide association study (GWAs) using the Nelson study (a population-based lung cancer screening study from Groningen and Utrecht, the Netherlands) including 717 subjects with and 1,795 without CMH, all ex or current heavy smokers (>20 pack years). Lung function results and information about sputum expectoration during the previous year were collected at the start of the study. To enhance power we added 590 blood bank controls. Genotyping data were analyzed using PLINK with adjustment for center (Groningen/Utrecht). We aimed to replicate the results by evaluating the top single nucleotide polymorphisms (SNPs) in 7 European cohorts contributing 487 cases and 1,118 controls.
Results: We identified 77 SNPs associated with CMH with a p-value $<10^{-4}$, of which 5 SNPs had a p-value $<10^{-5}$. Meta-analysis of selected top SNPs in the initial and replication cohorts identified 3 SNPs with a p-value $<10^{-6}$ and 3 with a p-value $<10^{-5}$. Some genes close to these SNPs have been reported to be associated with epithelial changes.
Conclusion: This study suggests that susceptibility to CMH is associated with genetic predisposition. To confirm these data replication will be extended to 3 additional cohorts.

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Common variant of gasdermin-like gene, fetal and early life smoke exposure and the risk of asthma-like symptoms in preschool children

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Rationale: Single nucleotide polymorphisms in the region of gasdermin-like (GSDML) gene on chromosome 17q12-21 are associated with increased risks of childhood-onset asthma. These risks seem to be modified by environmental tobacco smoke.
Objectives: To assess whether the associations of GSDML with asthma-like symptoms are modified by smoke exposure, both during fetal and in early life.
Methods: This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onwards in the Netherlands. We genotyped GSDML (rs2305480) and assessed maternal smoking repeatedly during pregnancy and smoke exposure in early life at the age of 2 years by questionnaires. Asthma-like symptoms were reported by parents at the ages of 1, 2, 3 and 4 years. The analyses were based on 2,025 Caucasian children with complete data.
Results: GSDML was associated with asthma-like symptoms at the ages of 2, 3 and 4 years (overall Odds Ratio 1.15 (1.06, 1.26)). The GSDML effect on asthma-like symptoms was stronger among children who were exposed to smoke during fetal life (p interaction=0.030). Smoke exposure in early life also tended to increase the effect of GSDML on asthma-like symptoms, but the test for interaction was not significant (p interaction=0.240). The modifying effects by fetal and smoke exposure in early life were independent. The strongest effects were present in children aged 3 and 4 years with both the risk-allele and smoke exposure during fetal and early life.
Conclusion: GSDML is associated with asthma-like symptoms in preschool children, and this association seems to be modified by fetal and smoke exposure in early life.

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Interactions between current tobacco smoke exposure and GSTP1 on lung health outcomes at 6, 12 and 18 years

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Introduction: Inhaled pollutants are a cause of oxidative stress. During childhood and adolescence exposure to second-hand tobacco smoke is common. This is a period of rapid lung development and exposure may have severe implications for lung function growth. Glutathione S-transferase P1 (GSTP1) is expressed in the lungs and is important in detoxifying inhaled exogenous toxins.
Aims: To investigate the effects of current tobacco smoke exposure and the interaction between two polymorphisms in *GSTP1* (Ile105Val and Ala114Val) on FEV_1, FVC and airway responsiveness (AR) at 6, 12 and 18 years in a longitudinal birth cohort.
Methods: Genotyping was performed using a PCR method. Genotyping for *GSTP1* 105 was completed in 117, 171 and 123 individuals at 6, 12 and 18 years, respectively and for *GSTP1* 114 in 115, 168 and 121 individuals at each follow-up. The frequency of current tobacco smoke exposure at each follow-up was 39%, 35% and 67%, respectively.
Results: *GSTP1* 105 Ile/Ile was associated with lower AR at 6 years (p=0.007). At 6 years children with *GSTP1* 105 Ile/Ile who were exposed to parental tobacco smoke had lower AR (p=0.019). At 12 years children with *GSTP1* 105 Ile/Ile had higher FEV_1 if they were not exposed to parental tobacco smoke (p=0.028). At 18 years individuals with *GSTP1* 114 Ala/Val had higher FVC in those non-exposed (passive/active) (p=0.014).
Conclusions: These data suggest that *GSTP1* may not always modulate the adverse effects of tobacco smoke exposure on lung function outcomes. Other GSTs or detoxification pathways may play a more important role in modulating the effects of tobacco smoke (passive/active) at 12 and 18 years in this study cohort.
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Association between SNPs in *NR3C1* and *NR3C2* gene and asthma

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Background: Stress is a risk factor for asthma. Single nucleotide polymorphisms (SNPs) in the glucocorticoid receptor (*NR3C1*) and in the mineralocorticoid receptor (*NR3C2*) have been associated with cortisol responses to stress. We hypothesized therefore that these SNPs are associated with individual susceptibility to asthma development.
Methods: We studied the role of a history of asthma at age 16 years and SNPs in *NR3C1* (rs6196, rs10482642, rs4912903, rs6198, rs258813, rs33388, rs17100236, rs2963155, rs41423247, rs9324924, rs4244032, rs4607376) and *NR3C2* (rs5522, rs2070951) in the TRAILS study (n=2,230, 49% males). History of asthma at age 16 years was defined as doctor diagnosis asthma ever assessed at age 11 years and/or symptoms of asthma and/or using asthma treatment in the past 12 months assessed at age 11, 14 and 16 years. Logistic regression analyses were performed to study the association between SNPs and asthma using initially a general model (explored further in case of $p<0.10$).We used an FDR cut off of $p<0.05$.
Results: Ten percent (n=209) of all adolescents had a history of asthma at age 16. Individuals with homozygote variants for rs2070951 had a higher risk to develop asthma than individuals with heterozygote variants and wild types (GG vs CG/CC OR 1.58 (1.08-2.32), p=0.02). However, after correction for multiple testing this association was no longer significant. All other SNPs were not significantly associated with asthma.
Conclusion: We showed no association between SNPs in *NR3C1* or *NR3C2* and asthma.

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Detection of specific mitochondrial RNA gene mutations in asthma patients: Contribution of haplogroup U

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Background: Maternal history of asthma is among the most consistently reported risk factors for asthma in children. Furthermore, a number of studies suggest that mitochondrial dysfunction plays a role in the pathogenesis of asthma. Until now, it was never investigated whether an implication of mitochondrial tRNA gene mutations exists in the genetics of bronchial asthma.
Methods: To shed more light on the role of the mitochondrial genome in the etiology of asthma we analyzed the mitochondrial tRNA genes, and part of their flanking regions, in 26 unrelated patients with asthma and we compared the findings with a set of 60 healthy controls.
Results: We found a total of 10 mutations in 19 out of 26 asthmatic patients. Four of the mutations (595insC in $tRNA^{Phe}$, A8343G in $tRNA^{Lys}$, T10448C in $tRNA^{Arg}$ and G709A in 12S rRNA) were not found in the control group. Five mutations were observed in controls but in a significantly lower rate: 3.3%, vs. 27% (A12308G in $tRNA^{Leu(CUN)}$), 5% vs. 7.7% (G15928A in $tRNA^{Thr}$), 10% vs. 57.7% (A750G in 12S rRNA), 1.67% vs. 3.87% (T3197C in 16S rRNA and A15954C in MT-NC10). In the control group we did not observe any of the 9 combinations of mutations detected in asthma patients. We observed that 27% of the asthma patients (vs. 3% of the controls) belonged to the haplogroup U (characterized by the presence of A12308G and T7028C mutations), for which several studies already reported an association with atopic phenotypes.
Conclusions: Mitochondrial tRNA and rRNA mutations are more frequent in asthma patients than controls. However, it is certain that further studies in larger cohorts are needed to confirm these observations.

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Common functional variants of MMP-1, MMP-3, ACE-1 and 5-HTT genes are associated with distinct symptoms in COPD

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Background: Pathogenesis of chronic obstructive lung disease (COPD) includes primary inflammatory events, activation of cytokines, and collagenolysis, thus causing increased remodeling of bronchial tissues and vascular walls. The
Aims: Aims of present study were to test possible associations between some common functional gene variants and prevalence of typical clinical symptoms in COPD.
Patients and methods: The study involved seventy-three patients with COPD (44 to 86 years old, a mean of 61 years). Clinical diagnostics was performed by common criteria, including evaluation of bronchial and endothelial dysfunction. Genotyping of matrix metalloproteinase genes, i.e., *MMP-1* (1G/2G^{-1607}), *MMP-3* (5A/6A^{-600}); SERT gene (*5-HTT* HTTLPR, S/L variants), and ACE-I I/D gene polymorphisms was performed by standard PCR.
Results: Allelic distribution of the studied genes among COPD patients did not differ from general population. Respiratory insufficiency grade was associated with hyperactive L allele of serotonin transporter gene (5-HTT). Pulmonary hypertension (≥40 mm) correlated with 1G/1G genotype of matrix metalloproteinase-1 (MMP-1) gene, but not with S genotype of 5-HTT gene. Among patients with bronchial dyskinesia, higher frequency of MMP-3 5A/5A genotype was revealed. Endothelial dysfunction showed a highly significantly correlation with "high-producer" D allele of ACE-I gene.
Conclusions: Preliminary findings suggest a significance of common gene variants modulating collagenolysis, vascular responses/hemostasis, and endothelial functions, in COPD.