72. Genetics of airway diseases and treatment

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LSC 2011 Abstract: Association of IL-9 and IL-4R genes and their
phenotypes among Sudanese with asthma
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Background: Asthma is a "complex" heritable disorder, candidate genes that may
be involved in the pathogenesis of asthma including: interleukin 4 (IL-4), IL-5,
IL-9, and IL-13 (Postma et al. 1995). Asthma prevalence in Sudan was found to be 12.5% in children aged 13-14 year in the Capital Khartoum (Mohamed et al. 1999).
Objectives: To detect polymorphisms of IL-9 in chromosome 5 and IL-4R in chromosome16 contributing to asthma and to estimate the environmental com-
ponents: Total immunoglobulin E levels, skin prick test, and eosinophil count in Sudanese population.
Methods: Seventy, nuclear and extended families were sampled in the initial phase of the study. Ventilatory function, skin, prick test blood sample for DNA analysis, immunoglobulin E, eosinophil count were carried out in the whole sample. Geno-
typing for IL-9, IL-4R and IL-13, polymorphisms using PCR were also carried out for a subset of the sample.
Results: Phenotypic analyses of the pedigrees suggest a likely genetic cause for asthma, as shown in one extended family. Level of total immunoglobulin E was found to be 71% in asthmatic, and 24% in non asthmatic. Eosinophil count was found to be 58% in asthmatic, while found to be 17.4% in non asthmatic. Hypersensitivity symptoms to six allergens showed positive skin test. (p = 0.00). Genotyping for IL-9, IL-4R suggest the presence of association for both IL-9 and IL-4R (P=0.008&0.007).
Conclusions: Asthma runs in families showing strong linkage to genes. There seems to be sufficient phenotypic and genotypic indicators to suggest a genetic predisposition component to asthma among Sudanese, and warrant some further investigation.

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Polymorphisms in toll-like receptor 4 are associated with severity but not susceptibility for asthma in a Chinese Han population
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Background: Asthma is a genetically heterogeneous disease. Polymorphisms of genes encoding components of the vitamin D pathway have been reported to be associated with the risk of asthma. Previously, we demonstrated that the vitamin D status in serum was associated with lung function in Chinese asthma patients. In this study, we tested whether polymorphisms of vitamin D receptors (VDR), vitamin D 25-hydroxylase (CYP2R1) and vitamin D binding protein (GC) were associated with asthma in a Han Chinese Population.
Methods: We sequenced 8 exons of VDR and all 5 exons of CYP2R1 and identified only two mutations on the coding regions in a Han Chinese case-control cohort of asthma. These two polymorphism markers were rs2228570 on exon 4 of VDR and rs12794714 on exon 1 of CYP2R1. We then genotyped the two markers in the cohort that consisted of 467 asthma patients and 288 unrelated healthy. We also genotyped two common polymorphism marker rs4588 and rs7041 in vitamin D binding protein (group-specific component, GC) gene by a PCR-restriction frag-
ment length polymorphism (RFLP) method. We analyzed the association between these polymorphisms and asthma susceptibility and asthma relevant traits.
Results: Polymorphism markers in VDR and CYP2R1 were not associated with asthma in the Han Chinese cohort. The variants of vitamin D binding proteins were associated with asthma susceptibility. Compared with GC1, GC2 was strongly associated with the risk of asthma (OR=3.59, 95% CI 1.01-11.78 p=0.006).
Conclusions: The results provide supporting evidence for association between GC variants and asthma susceptibility in the Chinese Han population.

P434
Vitamin D binding protein variants associate asthma susceptibility in a Chinese Han population
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Background: Asthma is a genetically heterogeneous disease. Polymorphisms of genes encoding components of the vitamin D pathway have been reported to be associated with the risk of asthma. Previously, we demonstrated that the vitamin D status in serum was associated with lung function in Chinese asthma patients. In this study, we tested whether polymorphisms of vitamin D receptors (VDR), vitamin D 25-hydroxylase (CYP2R1) and vitamin D binding protein (GC) were associated with asthma in a Han Chinese Population.
Methods: We sequenced 8 exons of VDR and all 5 exons of CYP2R1 and identified only two mutations on the coding regions in a Han Chinese case-control cohort of asthma. These two polymorphism markers were rs2228570 on exon 4 of VDR and rs12794714 on exon 1 of CYP2R1. We then genotyped the two markers in the cohort that consisted of 467 asthma patients and 288 unrelated healthy. We also genotyped two common polymorphism marker rs4588 and rs7041 in vitamin D binding protein (group-specific component, GC) gene by a PCR-restriction frag-
ment length polymorphism (RFLP) method. We analyzed the association between these polymorphisms and asthma susceptibility and asthma relevant traits.
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Conclusions: The results provide supporting evidence for association between GC variants and asthma susceptibility in the Chinese Han population.
**P437**

**Use of partition tree to identify genetic marker combination predicting bronchodilator response by inhaled short-acting beta 2 agonist**

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**Objective:** To identify genetic marker to predict bronchodilator response by inhaled short-acting beta 2 agonist after methacholine-induced bronchoconstriction.

**Methods:** A total of 480 patients were enrolled, who showed ≥ 20% decrease of FEV1 in methacholine bronchial provocation test and subsequently inhaled 2 puffs of salbutamol (200 mcg), then FEV1 was re-measured 10 minutes later. Twenty SNPs (3 in 10 genes related with airway inflammation, structural changes, or smooth muscle function) was scored by high throughput technique. They were TNFα (308G>A), IL1β (117C>T), IL10 (-1082A>G), IL4RA (-1745G>A), VEGFR1 (-2021G>A), VEGFR2 (2012G>A, -592C>T, 320T>A), VEGFR2 (889G>A, 1416A>T), TGFβR3 (447C>T), 2753G>A, 2753G>A, FGFR1 (284G>A, -1162G>A, 538A>G), CSF2 (536C>T), IL13 (-1111C>T), IL4 (-111G>A) and ADRβ2 (792C>G). The partition tree was used to investigate SNP combinations. The first partition was done by the SNP discriminating the patient group from the control group and the inference was repeated in the dominant model of minor frequency allele. Then subsequent partition was performed by the other SNPs until statistical significance disappeared.

**Results:** The SNP, -2012G>A in VEGFR1, was the most significant and used in the first partition (27.5±19.8% vs. 20.0±13.8% increase, p<0.001). The best responders with AA or AG of -2012G>A and CC of -1111C>T were discovered after second partition (30.3±16.7% increase). The poorest responders with GG of -20121G>A, GG of 2753G>A, and GG of 1162G>A were discovered after third partition (17.2±15.4% increase).

**Conclusions:** The combination of genetic markers related to the airway inflammation or structural changes can be useful in predicting bronchodilator response by short-acting β2 agonist.

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**Association between beta2 adrenergic receptor (ADRB2) haplotype pair and severe asthma in an Australian Caucasian population.**

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**Background:** Studies in mild asthmatics showed adverse outcomes with chronic use of short or long acting beta agonists in individuals with asthma susceptibility in Russian patients. Also the frequency of allele rs4707A was increased in adult asthma Russians ethnicity compared to controls (p=0.02, OR=1.3). Allele rs220891G was found to be overrepresented in Bashkirs with asthma (p=0.04, OR=2.51). There were no significant differences in the allele frequencies in SNPs rs2787095, rs2485700, rs2280091 was more common in the control group than in the case group (p=1×10⁻¹⁴) and offered a protective effect against asthma in Russians. In summary, our results suggest an association between the ADAM33 gene polymorphisms and asthma in Russians and Bashkirs.

**Objectives:** To identify genetic marker to predict bronchodilator response by inhaled short-acting beta 2 agonist after methacholine-induced bronchoconstriction.

**Methods:** A total of 480 patients were enrolled, who showed ≥ 20% decrease of FEV1 in methacholine bronchial provocation test and subsequently inhaled 2 puffs of salbutamol (200 mcg), then FEV1 was re-measured 10 minutes later. Twenty SNPs (3 in 10 genes related with airway inflammation, structural changes, or smooth muscle function) was scored by high throughput technique. They were TNFα (308G>A), IL1β (117C>T), IL10 (-1082A>G), IL4RA (-1745G>A), VEGFR1 (-2021G>A), VEGFR2 (2012G>A, -592C>T, 320T>A), VEGFR2 (889G>A, 1416A>T), TGFβR3 (447C>T), 2753G>A, 2753G>A, FGFR1 (284G>A, -1162G>A, 538A>G), CSF2 (536C>T), IL13 (-1111C>T), IL4 (-111G>A) and ADRβ2 (792C>G). The partition tree was used to investigate SNP combinations. The first partition was done by the SNP discriminating the patient group from the control group and the inference was repeated in the dominant model of minor frequency allele. Then subsequent partition was performed by the other SNPs until statistical significance disappeared.

**Results:** The SNP, -2012G>A in VEGFR1, was the most significant and used in the first partition (27.5±19.8% vs. 20.0±13.8% increase, p<0.001). The best responders with AA or AG of -2012G>A and CC of -1111C>T were discovered after second partition (30.3±16.7% increase). The poorest responders with GG of -20121G>A, GG of 2753G>A, and GG of 1162G>A were discovered after third partition (17.2±15.4% increase).

**Conclusions:** The combination of genetic markers related to the airway inflammation or structural changes can be useful in predicting bronchodilator response by short-acting β2 agonist.

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**Pharmacogenetic control of bronchial obstruction in steroid depend asthma (SDBA) patients.**

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Multidrug resistance gene (MDR1) encodes P-glycoprotein 170 (Pgp170), which realize efflux of glucocorticosteroids (GCS) from the cell. C3435T of gene MDR1 in SDBA patients is supposed to be associated with dose of GCS, their anti-inflammatory activity, degree of bronchial obstruction. Methods: Blood samples were taken from 40 SDBA patients and 103 controls. Genotypes were analyzed using PCR-RFLP method.

**Results:** Homozygous 3435C in SDBA patients were observed more frequently, than in controls: 35% (n=14) vs 8% (n=9) (p=0.001; OR=6.6; C65% 3.2-9.8). Mean daily dose of oral GCS (GCS) was higher in patients with CC genotype if compared with genotype 3435T: 2.86 mg/day vs 1.86 mg/day (p=0.041).

In patients with allele C bronchial obstruction was less severe. However, if compared with TT genotype, post-bronicholtic increase of velocity characteristics and Sgaw was not so marked. In patients with allele C require higher oGCS doses, probably, due to enhanced activity of Pgp170 and accelerated GCS efflux. In patients with TT genotype significant obstruction may be due to inadequate oGCS dose, while reversibility of distal obstruction may be due to intact function of bronchial smooth muscles and their sensitivity to GCS.

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**Effect of ADRβ2 polymorphism on the airway response to cold air in asthmatics.**

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**Background:** Previously we’ve found out that the decline in β2-adrenoceptors (β2-AR) function affects airway response to cold air.

**Objective:** The aim of our study was to reveal the contribution of Arg16Gly SNP (rs1042723) in the development of cold air hyperresponsiveness (CAH) in asthmatics.

**Methods:** The study included examination of 60 mild to moderate asthmatics of Caucasian race, mostly non-smokers (mean age 36±1.39). All the patients underwent spirometry before and after the challenge with 3-minute isocapnic (5% HEL) cold air (ICAH) or severe cold air (ICAIH). More than 10% drop in FEV1 was interpreted as a positive result. Intracellular cyclic adenosine monophosphate (cAMP) concentration in lymphocytes was measured before and 30 min after ICAH under in vitro stimulation with 10⁻M ephrinep. PCR-RFLP analysis was used for genotyping.

**Results:** Arg16Gly genotype dominated in the group with CAH (x²=7.47, p=0.002). Mean FEV1 drop differed between homozygous patients (16.0±3.2 L) in Arg16 vs. 8.6±1.12 L in Gly16, (p=0.005). cAMP concentration didn’t depend on genotype before the challenge, but 30 min after there was a significant fall in cells ability to produce cAMP in subjects with Arg16Gly genotype (p=0.03). Moreover, Arg16 homozygotes had lower cAMP level as compared Gly16 (48.3±8.61 and 78.59±8.13 pmol/10⁶ cells, respectively, p=0.004).

**Conclusions:** ADRβ2 haplotype pair 2/4 is associated with severe asthma. Known haplotype difference in receptor expression and acute bronchodilator response in mild compared to severe asthmatics suggests a role for ADRβ2 haplotypes in the development and/or treatment response in severe asthmatics.
Conclusions: These data suggest a definite proof for contribution of primary β2-AR dysfunction into the development of CAHR in our population sample. CAHR was strongly associated with Arg16Gln genotype. Blunted cAMP response in Arg16Gln subjects indicates inherited predisposition of their β2-AR to acute desensitization during the ICAH.

P441 Role of -511C>T and +3953C>T SNPs of IL1B gene as risk factors of COPD and bronchial asthma in Bulgarian patients: a case-control study

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A common characteristic of COPD and bronchial asthma is the chronic inflammatory process in the lungs. In the current case-control study we investigated -511C>T polymorphism in IL1B promoter and +3953C>T silent polymorphism of IL1B and their haplotypes as candidate risk factors of COPD and Bronchial asthma. We genotyped 163 patients with COPD, 47 with Bronchial asthma and 174 control individuals using Taqman genotyping assay for IL1B -511C>T and PCR-RFLP-based method for +3953C>T. We did not observe any significant differences in genotype frequencies of studied SNPs between controls and patients both with COPD and asthma, however the minor T allele of IL1B -511C>T was less frequently found in controls (0.305) than the patients with COPD (0.377, p=0.046) and especially with asthma (0.415, p=0.012). In carriers of IL1B -511T allele (TT and TC genotypes) had 1.56-fold higher risk for development of COPD (p=0.045) and 2.25-fold higher risk of Bronchial asthma (p=0.019). The performed estimations of IL1B haplotypes showed that T_C haplotype (alleles found to determine enhanced expression of IL-1β, appeared to be associated with higher risk of COPD (OR=1.25, p=0.231) and asthma (OR=1.78, p=0.035) compared to the most common C_C haplotype and with 1.70-fold higher risk of COPD (p=0.018) and 1.37-fold higher risk of asthma (p=0.313) compared to the C_T haplotype, associated with lower IL1B expression. We suggest that the -511C>T promoter SNP and +3953C>T silent polymorphism of IL1B may influence the genetic predisposition of COPD and Bronchial asthma: the carriers of alleles and haplotypes supposed to define higher IL-1β levels are more susceptible for these diseases.

P442 Association of IL-1β (-511C>T) and IL1RN 86-bp VNTR polymorphism in susceptibility to chronic obstructive pulmonary disease between male and female patients in northern Indian population

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Background: Chronic obstructive pulmonary disease (COPD) is characterized by chronic obstruction of air flow affecting peripheral airways, associated with chronic bronchitis (mucus hyperscretion) and emphysema (destruction of airway parenchyma), together with fibrosis, tissue damage and inflammation of the small airways. Interleukin 1 (IL-1) and other cytokines play a central role in inflammation in the airways and development of extensive tissue remodeling. Particularly, 2G allele of -1607insG polymorphism of MMP1 had, although not significantly, lower values of the spirometric index FEV1% pr. (49.8±3.14%) compared to the patients with other genotypes (52.3±7.16, p=0.375). In particular, this difference was higher, reaching a statistical significance, in the subset of patients with smoking history (44.18±13 vs. 50.91±14, p=0.034).

Our data suggest that -1607 2G allele of IL1B gene and -1171 6A allele of MMP3 gene do not represent risk factors for development of COPD, however the homozygous 2G/2G genotype of MMP1 seems to affect the lung function, especially of smokers, possibly by enhancing MMP1 gene expression.

P443 VEGF gene polymorphisms are associated with post-natal lung function development

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Background: Vascular endothelial growth factor (VEGF) is involved in angiogenesis and suggested to be involved in airway remodeling and asthma susceptibility. Objective: To study single nucleotide polymorphisms (SNP) in the VEGF gene in relation to lung function and hyperresponsiveness at birth and at six years of age, and development of asthma at six years of age. Methods: We analyzed 13 SNPs in the VEGF gene in 411 children born to asthmatic mothers from the Copenhagen Prospective Study on Asthma in Childhood birth cohort. Lung function measurements were performed at school age but not at birth, and independent of asthma. This suggests a role of VEGF variants in the small airways. Interleukin 1 (IL-1) and other cytokines play a central role in inflammation in the airways and development of extensive tissue remodeling during the pre- and post-natal period.

We analyzed the SNPs and outcomes using an additive genetic model in a linear regression analysis adjusting for multiple testing using the Bonferroni threshold as level of significance.

Results: Three SNPs, from the same linkage disequilibrium block, were associated with FEV1 at age 6: rs699947 (P = 2.03E-05), rs833069 (P = 0.00149) and rs3025010 (P = 0.00177). Stratifying for asthma did not alter the individual effects.

We found no association between SNPs and lung function or hyperresponsiveness at birth, or hyperresponsiveness or asthma at age 6.

Conclusion: VEGF gene variants were associated with lung function at school age but not at birth, and independent of asthma. This suggests a role of VEGF and VEGF gene variants for postnatal lung function development. Possible interaction between VEGF gene variants and postnatal environmental risk factors should be targeted in future studies.

P445 Predictive role of MMP-2 genetic variants on severe hematologic toxicity of NSCLC patients treated with first-line, platinum-based chemotherapy

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Purpose: MMP-2 plays an important role in hematopoietic recovery after chemotherapy-induced myelosuppression. In this study, we investigated the association between MMP-2 SNPs and the incidence of adverse hematologic events in advanced NSCLC patients treated with platinum-based chemotherapy. Methods: A retrospective pharmacogenetic association study was performed in 1004 Chinese patients with advanced NSCLC receiving platinum-based regimens (including NP, GF, TC, TP). Information about grade 3 or 4 hematologic toxicity neutropenia, anemia, and thrombocytopenia) was available. 16 tag SNPs of MMP-2 were assessed.

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P446 EGFR, HER2 and KRAS mutational status according to adenocarcinoma
patterns/sub-types
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Lung adenocarcinomas represents about 42% and 28% of NSCLC diagnosed in women and men. Several subtypes are recognized by WHO. EGFR, HER2 and KRAS gene mutations have been described. Authors intends to identify differences between adenocarcinomas subtypes/patterns concerning EGFR, HER2 and KRAS mutations, gene copy number and protein expression.

45 lung adenocarcinomas were evaluated for EGFR, HER2 and KRAS mutational status by PCR, fragment analysis and direct sequencing. EGFR and HER2 gene copy number by fluorescence in situ hybridization (FISH). EGFR and c-erbB-2 protein expression was evaluated by immunohistochemistry (IHC). 8 cases showed EGFR exon 21 mutation (37.5%). In two cases the mutation was present in only one pattern of the tumour. 10 cases showed EGFR exon 19 deletions (32%). The mutation was present in only one of the patterns in 4 cases showed synchronous exon 19 deletions and exon 21 point mutations. Of the 14 cases with EGFR mutations 10 cases were FISH positive (71%). KRAS mutations were identified in 5 cases (16%), one coexisting with EGFR exon 21 point mutation. All cases were HER2 wild-type. 8 cases with EGFR mutations demonstrated EGFR protein expression and 6 cases were negative. EGFR mutational status and FISH results showed a moderate agreement/concordance. Concordance between EGFR FISH results and mutational status with EGFR IHC expression was fair. Frequently, when a mutation is identified it is present in all the patterns of 1 adenocarcinoma. Mutations of HER2 do not seem to be important in lung adenocarcinomas pathology. KRAS and EGFR mutations are in general mutually exclusive, but in rare cases they may coexist.

P447 Genetic analysis of two novel mucin-like genes in the disease-susceptibility locus for diffuse panbronchiolitis
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Diffuse panbronchiolitis (DPB), which is characterized by chronic inflammatory disease of the respiratory bronchioles and sinobronchial infection, is a complex genetic disease affecting East Asians. DBP is strongly associated with HLA-B54 in Japanese and HLA-A11 in Koreans. We hypothesized that a major susceptibility gene for DBP might be located between the HLA-A and HLA-B loci and recently cloned two novel mucin-like genes designated panbronchiolitis related mucin-like 1 and 2 (PBMUCL1 and PBMUCL2) in the candidate region. We found disease-associated genetic polymorphisms in the new genes. The aim of the study is to compare genetic polymorphisms of the genes between Japanese and European descent, because genetic predisposition to DBP has been assumed only in Asians. Methods: We genotyped polymorphisms in 50 DNA samples of European descent and compared their frequency and haplotype structure with 108 Japanese DBP patients and 98 Japanese controls. Expression of PBMUCL1 transcript was investigated in primary-cultured human bronchial epithelial (HBE) cells. Results: The haplotypes were different between European descent and Japanese. The mRNA expression pattern of the HBE cells with Asian-specific haplotype was analyzed. Conclusions: Further analysis of newly identified mucin-like genes may provide insights into the pathogenesis of the disease.

P448 Genetic epidemiology of hereditary hemorrhagic telangiectasia complicated with pulmonary arteriovenous malformation
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Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal domi-
nor disorder characterized by aberrant vascular development such as arteriovenous malformation (AVM). We report here a genetic epidemiologic study in a county, A, in the Akita prefecture (population 1.1 million) located in northern Japan. Method and subjects: A total of 137 pedigrees were members of which were traced of which 81 were alive and 37 were affected by HHT. Complications associated with pulmonary arteriovenous malformations (PVM) were proven in six out of seven families. Results: Linkage analysis in two large families complicated with PVM revealed a linkage to the HHT1 locus (encoding endothlin; ENG). Three novel mutations were found in four families, all of which led to a frame shift: a G to C transversion at the splicing donor site of intron 3 (Intron+1 G→C) in one family, one base pair insertion (A) at nucleotide 828 (exon 7) of the endothelin cDNA in two large families (a 828/829 ins A), and a four base pair deletion (AAAG) beginning with nucleotide 1120 (exon 8) of the endothelin cDNA (c.1120-1123 del/AAG) in one family. The insertion of A in exon11 (c.1470-1471 insA) mutation was found in one family. Summary and conclusion: The population prevalence of HHT in the county was estimated to be 1.8000–1.5000, roughly comparable with those reported in European and U.S. populations, which is contradictory to the traditional view that HHT is rare among Asians. We recommend that families with HHT be screened for gene mutations in order that high-risk individuals complicated with PVM receive early diagnosis and treatment initiation that will substantially alter their clinical course and prognosis.

P449 Genetic polymorphisms in TNF genes and tuberculosis in cystic fibrosis patients
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The genes for tumor necrosis factor-{alpha} (TNF-{alpha} and TNF-beta) and lymphotaxis (LT-{alpha}; LTA) are arranged in tandem within MHC III region of chromosome 6 in the same transcriptional orientation. This formation is conserved, even in marpsuials, suggesting that there may be some functional advantage to this arrangement. The TNF is highly conserved between species and there is no evidence for any association between TNF polymorphisms and CF lung disease progression. In the same time the carriers of -308A allele more frequently had asthma and other atopic disorders as compared to patients homozygous for -308G allele (14.9 vs. 5.3%, p<0.05). There was no case of tuberculosis among patients with 252G allele. In the same time 7.9% of 252A /A carriers tuberculosis infection was documented (p<0.03). Besides, the subjects with genotype 252A/A demonstrated a significant elevation of plasma TGF-beta in comparison with carriers of 252G allele (72.6 vs 32.4 pg/ml; p<0.05). Our data confirm the critical importance of -308A TNF allele for asthma development and provide robust evidence that LTA gene variants are involved in tuberculosis etiology.