**A Disintegrin and Metalloprotease 33 Polymorphisms and Lung Function Decline in the General Population**

**Abstract**

* Are SNPs in ADAM33 associated with accelerated lung function loss in a general population?
* SNPs studied:
	+ F+1, Q-1, S\_1, S\_2, T\_1, T\_2, V\_4, and ST+5

**Introduction**

* ADAM33 associated with asthma in various isolated populations
	+ Dutch, American, German, Korean populations
	+ Want to demonstrate not only that is ADAM33 a susceptibility gene but also that ADAM 33 plays a role in asthma progression
	+ Asthma progression markers:
		- FEV1 (Forced Expiratory Flow) decline
		- COPD (chronic obstructive pulmonary disease)
			* Polymorphisms in ADAM33 may be associated with FEV1 decline and therefore put subject at risk for COPD

**Methods**

* **Subjects**
	+ 2,467 subjects
	+ Exclusively white and of Dutch decent
	+ Surveys of respiratory symptoms, smoking status, age, sex taken every 3 years
* **Genotyping**
* 8 SNPs were genotyped
* genotyped individuals with more than 1500 ng of isolated DNA available from blood test
* **Statistics**
	+ Subjects have COPD:
		- FEV/VC < 70 % of predicted value
		- FEV1 < 80% of predicted value
		- Differences in allele prevalence (either + or – for COPD) evaluated using chi-squared test
		- Relative risk for COPD in SNPs calculated
		- Linear mixed effect models used to determine effect of polymorphisms in ADAM33 on annual decline of FEV1

**Results**

* Frequencies for minor alleles
	+ F+1 .35
	+ Q-1 .125
	+ S\_1 .084
	+ S\_2 .28
	+ ST+5 .58
	+ T\_1 .21
	+ T\_2 .17
	+ V\_4 .26
* Males FEV1 declined at 6ml/year less than females
	+ Could be attributed to height difference
* Rare alleles O-2 or S\_2 had significant excessive decline in FEV1 of 9.6 ml/year (O\_2) and 4.9 ml/year (S\_2) vs. the wildtype
* S\_1 heterozygous = excessive decline of 3.6 ml/year (significant in p test)
* S\_1 homozygous = 6.4 ml/year (non-significant in p test)
* No association between level of baseline FEV1 with any of the SNPs
	+ Suggests SNPs effect FEV1 decline instead of maximum lung function
* Performed a permutation tests to assess whether results were due to chance
	+ 3000 purmutations per SNP
	+ Results were not due to chance
* Subjects with minor alleles for SNPs for F+1, S\_1, S\_2, and T\_2 had COPD more than did the remaining SNPs (all statistically significant)

**Discussion**

* Polymorphisms in ADAM33 are associated with excessive lung function decline in the general population
	+ Low lung function is associated with COPD and cardiovascular disease
	+ 1st and 5th leading causes of death according to WHO
* ADAM33 plays a role in development of COPD and lung function loss
* ADAM33 expressed in airway smooth muscle cells and fibroblasts
	+ Fibroblasts contribute to the “remodeling process” present in asthma
* ADAM33 is a member of ADAM family proteins
	+ Cell adhesion
	+ Cell fusion
	+ Cell signaling
	+ Proteolysis
* S\_1, S\_2 =associated with FEV1 decline an COPD
* F+1, T\_2 = associated with COPD but not FEV1 decline
* Q-1= associated with FEV1decline but not COPD
	+ Strongest FEV1 decline
	+ Located in intro before exons Q, P, R
		- Comprise EGF (epidermal growth factor)
		- Mice lacking EGF receptor demonstrated abnormal branching and poor aveolization
		- EGFR signaling regulates matrix metalloproteases
			* Regulate epithelial-mesenchymal interactions during morphogenesis
* While no study has shown ADAM 33 binding to EGF or EGFR ligands some ADAM proteins are involved in shedding of EGFR ligands in mouse embryonic cells
* SNP Q-1 may influence the splicing of ADAM33 to produce a variant (β-ADAM33)