Interactive Effects of *NOS1* and *NOS3* Genetic Variants and Asthma on FeNO Level in the EGEA Study.

E. Bouzigon, MD, PhD\(^1\), M. Bechet, Msc\(^2\), M. Boussaaha, PhD\(^1\), N. Le Moual, PhD\(^2\), P. Scheinmann, MD\(^3\), J. Bousquet, MD\(^2,4\), I. Pin, MD\(^5\), M. Lathrop, PhD\(^5\), F. Kauffmann, MD\(^6\), F. Demenais, MD\(^1\) and R. Nadif, PhD\(^7\). Email: emanuelle.bouzigon@inserm.fr

\(^1\)Inserm, U794, Paris, France; \(^2\)Inserm, U780, Paris, France; \(^3\)Hôpital Necker-Enfants Malades, Paris, France; \(^4\)CHU Montpellier, France; \(^5\)Inserm, U823, Grenoble, France and \(^6\)CEA-CNG, Evry, France.

Exhaled nitric oxide (FeNO), a marker of airway inflammation in asthma, has been consistently reported to be associated with smoking. NO is produced endogenously by nitric oxide synthases (NOS). The objective is to study associations between FeNO level and 37 single nucleotide polymorphisms (SNPs) in *NOS1* (n=25), *NOS2A* (n=5) and *NOS3* (n=7) genes, and whether these SNPs modify associations between asthma and FeNO in 172 families (532 adults, 38.6 yrs, 53% of males) from the French Epidemiological study on the Genetics and Environment of Asthma. Association analyses between SNPs and log–transformed FeNO at 50 ml/s expiratory flow adjusted for clinical center, sex, height and smoking were conducted using GEE regression–based method. A strong interactive effect between one SNP in *NOS3* gene (rs743507) and asthma was detected on FeNO (P<10\(^{-4}\)). In asthmatics, CC genotype was associated with an increase in FeNO (29.98 vs. 19.03 ppb, P=2.10\(^{-4}\)), whereas this genotype was associated with a decrease in FeNO in non–asthmatics (10.85 vs. 15.61 ppb, P=0.02). We also found significant interactions between asthma and the effect of three SNPs in *NOS1* gene on FeNO (P for interaction <.03). In asthmatics, homozygous for minor allele were associated with a decrease in FeNO (rs816296, rs378221, rs4767535, P values ranging from 0.008 to 0.07) whereas no significant association was detected in non–asthmatics. No interactive effect was observed between SNPs in *NOS2A* gene and asthma on FeNO. In conclusion, associations of *NOS1* and *NOS3* genes with FeNO level differed according to asthma status.

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