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Title: Imputed classical HLA II alleles, occupational allergen exposure and adult-onset asthma

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Body: Background: HLA is a principal candidate gene region for occupational asthma, and HLA-DQ was the only significant locus in the GABRIEL genome-wide association study (GWAS) of late-onset asthma. Aim: To elucidate the role of HLA-II in adult-onset asthma, we imputed classical HLA-II alleles from 7579 single nucleotide polymorphisms. We explored associations between 25 alleles with frequency >5% and adult-onset asthma, and we did separate analyses in subjects exposed to occupational allergens. Methods: We studied 607 subjects with adult-onset asthma and 2104 adults without asthma from three European cohorts (ESE Consortium): ECRHS, SAPALDIA, and EGEA. According to a job exposure matrix, 444 subjects (133 with adult-onset asthma) were exposed to high molecular weight (HMW) agents, with 74% exposed to latex. In addition, we studied 946 HMW-exposed workers (392 with asthma) from Dutch and Danish surveys of bakers and farmers. Results: In the ESE cohorts, DPB1*0301 (OR 0.76, 95%CI 0.60-0.97) and DQA1*0301 (OR 1.22, 95%CI 1.02-1.44) were associated with adult-onset asthma. DQA1*0103 was associated with asthma, but only in HMW-exposed ESE subjects (OR 0.54, 95%CI 0.29-0.98). In the HMW-exposed bakers and farmers, six other HLA-II alleles were associated with asthma

($P < 0.05$). None of the associations in ESE subjects or workers remained statistically significant after correction for multiple testing. Conclusions: Imputation allows a complete evaluation of HLA alleles following GWAS. In a general population and among populations exposed to a variety of occupational allergens, analyses did not reveal a clear association between common classical HLA-II alleles and adult-onset asthma. Funding: ANR-PRSP10 Iago.