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Title: Association between ADAM33 polymorphisms and asthma control

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Body: Background: A disintegrin and metalloproteinase 33 (ADAM33) has been reported to play an important role in asthma. Objective: To evaluate the potential influence of ADAM33 single nucleotide polymorphisms (SNPs) on asthma control. Methods: In a cohort of 224 Japanese asthmatics (mean age 62.3 years, never- or ex-smokers with 10 pack-years or less; on inhaled corticosteroids for more than 4 years), 4 ADAM33 SNPs (V4, T2, T1 and S2) were analyzed to examine the associations with asthma control test (ACT). We assessed detailed disease history, pulmonary function tests, serum biomarkers and ACT results. Results: T2 AA/AG genotype (n=66) had lower scores of components “impaired daily activity”(p=0.002) and “shortness of breath” (p=0.033) than GG (n=158), and showed higher neutrophil counts (p=0.038). When patients were stratified into two groups according to their serum levels of periostin, a marker of Th2 inflammation, T2 AA/AG (n=28) showed significantly lower scores of component “impaired daily activity” (p=0.0008) and higher neutrophil counts (p=0.023) than GG (n=57) in high periostin group (≥ 95 ng/ml, n=85). In the same group, patients with poorly controlled asthma (ACT ≤ 19) were more frequently observed in T2 AA/GA than in GG (p=0.05). These differences were not observed in low periostin group (<95 ng/ml, n=139). T1 GG/AG (n=57) showed lower scores of component “impaired daily activity” than AA (n=167) (p=0.012). As in T2, the difference was only observed in high periostin group (p=0.003). There were no associations between ACT scores and V4 or S2. Conclusion: Minor allele of ADAM33 T2 may be involved in poor asthma control, potentially causing neutrophilic inflammation in patients with Th2 dominant inflammation.