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Title: Interaction between the Arg16 homozygous genotype, inhaled corticosteroids and long acting beta agonists for asthma exacerbations in children? Leukotriene receptor antagonists to the rescue?

Dr. Steve 5939 Turner s.w.turner@abdn.ac.uk MD [1], Dr. Kaninika 5940 Basu K.Basu@bsms.ac.uk [2], Ms. Lauren 5941 Bignell L.Bignell1@uni.bsms.ac.uk [2], Prof. Jon 5942 Ayres j.g.ayres@bham.ac.uk [3], Dr. Roger 5943 Tavendale r.tavendale@dundee.ac.uk [4], Prof. Brian 5944 Lipworth brianlipworth@gmail.com [4], Dr. Anil 5945 Mehta a.mehta@dundee.ac.uk [4], Prof. Somnath 5946 Mukhopadhyay S.Mukhopadhyay@bsms.ac.uk [2] and Prof. Colin 5952 Palmer c.n.a.palmer@dundee.ac.uk [4]. [1] Child Health, University of Aberdeen, Aberdeen, United Kingdom ; [2] Academic Department of Paediatrics, University of Brighton, Brighton, United Kingdom ; [3] Institute of Occupational and Environmental Medicine, University of Birmingham, Birmingham, United Kingdom and [4] Population Pharmacogenetics Group, University of Dundee, Dundee, United Kingdom .

Body: Introduction. Here we test the hypothesis that when compared to children with at least one Gly16 allele, children homozygous for the Arg16 SNP of the B2AR gene are at increased risk for asthma exacerbation if treated with long acting beta agonists (LABA) and that this risk is countered by leukotriene receptor antagonist (LTRA) treatment. Methods. Children with asthma were recruited in two cohorts using a common methodology. Details of exacerbations and asthma treatment were determined from questionnaire. DNA was extracted, Arg16Gly genotype was determined and analyses adjusted for confounders. Results. Questionnaire and DNA were available in 2036 children, mean age 9.5 years (SD 3.8), 59% male. There were 1098 children treated with inhaled corticosteroid (ICS) monotherapy, 364 with ICS+ LABA, 164 with ICS+LTRA and 325 with ICS+LABA+LTRA. Compared to children with at least one Gly16 allele, children homozygous for Arg16 were at increased risk for exacerbations in the group with ICS monotherapy (OR 1.53 [95% CI 1.06, 2.23] p=0.025) and ICS+LABA (OR 1.96 [95% CI 1.02, 3.77] p=0.045). Arg16 homozygous genotype was not associated with increased risk for exacerbation in children treated with ICS+ LTRA± LABA. There was no evidence of an Arg16 gene dose effect. Conclusions. There is a modest increase in asthma exacerbations among those homozygous for Arg16, compared to others, if treated with ICS±LABA. This increased risk seems to be countered by treatment with LTRA. On a whole population basis, these observations could explain many potentially avoidable exacerbations in children with asthma.