Title: MUC1 gene polymorphisms are associated with serum KL-6 levels and pulmonary dysfunction in pulmonary alveolar proteinosis

Dr. Shinichiro 18720 Ohshimo ohshimos@hiroshima-u.ac.jp MD ¹, Dr. Nobuhisa 18774 Ishikawa nobuhi@hiroshima-u.ac.jp MD ², Dr. Yasushi 18775 Horimasu yasushi17@hiroshima-u.ac.jp MD ², Dr. Kazunori 18776 Fujitaka fujikazu@hiroshima-u.ac.jp MD ², Dr. Yoshinori 18777 Haruta yharuta@hiroshima-u.ac.jp MD ², Dr. Hiroshi 18778 Murai hmurai@hiroshima-u.ac.jp MD ², Dr. Nobuyuki 18779 Hirohashi hirohasi@hiroshima-u.ac.jp MD ¹, Dr. Koichi 18780 Hattori nhattori@hiroshima-u.ac.jp MD ², Prof. Dr. Yoshiharu 18781 Tanigawa tanigawa@hiroshima-u.ac.jp MD ¹, Prof. Dr. Nobuo 18782 Kohno kokohno@hiroshima-u.ac.jp MD ², Dr. Francesco 18783 Bonella Francesco.Bonella@ruhrlandklinik.uk-essen.de MD ³, Prof. Dr. Josune 18784 Guzman Josune.Guzman@ruhr-uni-bochum.de MD ⁴ and Prof. Dr Ulrich 18785 Costabel ulrich.costabel@ruhrlandklinik.uk-essen.de MD ³.
¹ Department of Emergency and Critical Care Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; ² Department of Molecular and Internal Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; ³ Department of Pneumology and Allergology, Ruhrlandklinik, University Hospital, University Duisburg-Essen, Essen, Germany and ⁴ General and Experimental Pathology, Ruhr University, Bochum, Germany.

Body: BACKGROUDS: KL-6, a human MUC1 mucin, is a sensitive biomarker for interstitial lung diseases including pulmonary alveolar proteinosis (PAP). Recent studies have demonstrated a correlation between MUC1 gene single nucleotide polymorphisms (SNPs) and serum KL-6 levels. AIMS: To investigate the correlations between serum KL-6 levels, pulmonary dysfunction and MUC1 SNPs in PAP. METHODS: 24 Caucasian patients with PAP and 30 healthy Caucasian were prospectively collected. Serum KL-6 levels were analyzed using ELISA and MUC1 rs4072037 SNPs were genotyped using polymerase chain reaction. The correlation between serum KL-6 levels, pulmonary dysfunction and MUC1 SNPs were evaluated. RESULTS: The frequency of MUC1 rs4072037 SNPs was significantly different between PAP patients and healthy volunteers (PAP, A/A 46%, A/G 54%, G/G 0%; healthy, A/A 30%, A/G 40%, G/G 30%; p=0.013). Serum KL-6 levels in PAP patients were significantly higher than in healthy volunteers (p<0.0001); in addition, serum KL-6 levels in PAP patients with A/A genotype were significantly higher than in PAP patients with A/G genotype (p=0.01). Serum KL-6 levels were significantly correlated with serum LDH levels, inversely correlated with PaO₂ at rest, total lung capacity, diffusing capacity for carbon monoxide (D LCO) and time to next whole lung lavage (p=0.002, p=0.036, p=0.038, p=0.028 and p=0.018, respectively). MUC1 A/G genotype was associated with decreased alveolar-arterial oxygen difference (A-aDO₂) and increased D LCO.
compared with A/A genotype (p=0.022, p=0.044, respectively). CONCLUSIONS: MUC1 rs4072037 SNPs were correlated with serum KL-6 levels and the severity of pulmonary dysfunction in PAP.