De genetische aanleg voor longfibrose bij reuma patiënten

PREDISPOSITION OF *MUC5B* RS35705950 MINOR ALLELE TO RHEUMATOID ARTHRITIS ASSOCIATED INTERSTITIAL PNEUMONITIS

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BACKGROUND

A polymorphism in the *MUC5B* gene (rs35705950) is associated with susceptibility to:

- familial interstitial pneumonia
- idiopathic pulmonary fibrosis
- idiopathic nonspecific interstitial pneumonia

We hypothesised that the *MUC5B* risk allele also predisposes to Rheumatoid Arthritis associated Interstitial Pneumonitis (RA-IP).

METHODS

Demographic and clinical characteristics were collected for RA-IP patients (n=43), all meeting ACR/EULAR criteria 2010 for RA. RA-IP and a healthy subjects cohort (n=249) were genotyped for *MUC5B* rs35705950.

RESULTS

The proportion of male patients (63%) in our RA-IP cohort was high and differed significantly from that in RA (37%) in the Netherlands. Furthermore, a high percentage had a history of smoking, and obtained a diagnosis of IP in the 6th decade of life. The HRCT pattern was predominantly fibrotic: Usual interstitial pneumonia (UIP), possible UIP or fibrotic non-specific pneumonia. Case-control analysis showed a significant allelic association of the *MUC5B* minor allele with RA-IP. The minor allele frequency was 28% in RA-IP and 9% in controls, resulting in a strongly significant difference ($p=5.5x10^{-7}$). The odds ratio for *MUC5B* minor allele carriers was 5.4 (95% CI: 2.7-10.6, $p=2x10^{-7}$). Stratifying by *MUC5B* minor allele, we observed a trend towards significance in mortality, older age and predominantly fibrotic HRCT pattern in *MUC5B* minor allele carriers (table 1). Within IP, high mortality, older age, a history of smoking and male sex are typically found in IPF

Table 1 Demographic and clinical characteristics of 43 rheumatoid arthritis associated interstitial pneumonitis patients stratified according to *MUC5B* rs35705950 genotype.

	controls	all patients	non-carriers MUC5B minor allele	carriers MUC5B minor allele	p-value*
number of subjects	249	43	20	23	
Characteristics					
male, n (%)		27 (63)	11 (55)	16 (70)	0.32
ever-smoker, n (%)		32 (73)	15 (75)	17 (74)	0.94
pack years, mean (SD)		20.8 (12.3)	23.7 (15.3)	18.3 (8.8)	0.29
age at IP diagnosis, mean (SD), y		63.8 (10.4)	61.1 (11.0)	66.1 (9.4)	0.12
age at RA diagnosis, mean (SD), y		56.7 (12.1)	53.7 (11.9)	59.2 (12.0)	0.14
years between RA and IP diagnosis, mean (SD)		6.3 (7.9)	6.8 (8.5)	5.9 (7.4)	0.73
$DLCO_c$% predicted at IP diagnosis, mean (SD)		56.2 (13.2)	56.8 (15.5)	55.7 (11.4)	0.81
FVC% predicted at IP diagnosis, mean (SD)		86.9 (22.6)	89.6 (25.5)	85.0 (20.8)	0.57
ACPA and/or RF positive, n (%)		39 (91)	19 (95)	20 (87)	0.61
lungtransplantation event, n (%)		2 (4.7)	1 (5)	1 (4)	1.00
death, n (%)		11 (26)	3 (15)	8 (35)	0.14
familial history of IP, n (%)		4 (9)	1 (5)	3 (13)	0.61
Chest CT scan pattern					
fibrotic (UIP/possible UIP/fNSIP), n (%)		26 (60)	9 (45)	17 (74)	
inflammation (inconsistent UIP/NSIP/OP), n (%)		17 (40)	11 (55)	6 (26)	0.05
MUC5B genotype					
rs35705950					
GG	205	20			
GT	43	22			
TT	1	1			
Minor Allele frequency	0.09	0.28			$5.5x10^{-7\#}$

*p-value for difference between MUC5B carriers and non-carriers, unless otherwise indicated. #p-value for difference between all RA-IP patients and controls. DLCOc, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; IP, interstitial pneumonitis; RA, rheumatoid arthritis; ACPA,anti-citrullinated peptide antibodies; RF, rheumatoid factor; UIP, Usual interstitial pneumonia; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia

CONCLUSIONS

Rs35705950 minor allele predisposes to RA-IP. Furthermore, the characteristics of the RA-IP cohort do closely resemble those of IPF. This suggests that there could be a 'MUC5B driven' endotype in pulmonary fibrosis, which is characterized by predominantly male patients of older age with a fibrotic HRCT pattern.

De DNA variant rs35705950 in het *MUC5B* gen is geassocieerd met het krijgen van verschillende types longfibrose. We hebben onderzocht of deze DNA variant ook een verhoogde kans geeft op het krijgen van Reumatoïde Artritis geassocieerde longfibrose. Dit blijkt zo te zijn, mensen die deze DNA variant dragen hebben gemiddeld 5x zoveel kans op het krijgen van longfibrose dan mensen die deze variant niet dragen. Verder zien we dat de klinische kenmerken van deze patiënten erg lijken op die van mensen met IPF, een andere vorm van longfibrose. Dit wijst erop dat er een MUC5B gedreven vorm van longfibrose is, die voornamelijk voorkomt bij mannelijke, oudere RA-patiënten met een fibrotisch HRCT patroon.

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