Letter

$5HT_{2A}$ polymorphism His452Tyr in a German Caucasian systemic sclerosis population

Holger Kirsten[1,2,3*], Jana Burkhardt[1*], Helene Hantmann[2], Nico Hunzelmann[4], Peter Vaith[5], Peter Ahnert[1,6] and Inga Melchers[7]

[1]Institute of Clinical Immunology and Transfusion Medicine, Center for Biotechnology and Biomedicine (BBZ), University of Leipzig, Johannisallee, 04103 Leipzig, Germany
[2]Fraunhofer Institute for Cell Therapy and Immunology, Perlickstr., 04103 Leipzig, Germany
[3]Translational Center for Regenerative Medicine, University of Leipzig, Phillip-Rosenthal-Str., 04103 Leipzig, Germany
[4]Department of Dermatology, University of Cologne, Kerpener Straße, 50924 Cologne, Germany
[5]Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Hugstetter Str., 79106 Freiburg, Germany
[6]Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Haertelstr. 16-18, 04107 Leipzig, Germany
[7]Clinical Research Unit for Rheumatology, University Medical Center, Breisacher Str., 79106 Freiburg, Germany
*These authors contributed equally to this work.

Corresponding author: Inga Melchers, inga.melchers@uniklinik-freiburg.de

Published: 26 March 2009
Arthritis Research & Therapy 2009, **11**:403 (doi:10.1186/ar2606)
This article is online at http://arthritis-research.com/content/11/2/403

See related research by Beretta *et al*., http://arthritis-research.com/content/10/5/R103 and related letter by Beretta and Scorza, http://arthritis-research.com/content/11/2/404

Recently, Beretta and colleagues [1] reported a protective association of the serotonin 5-HT_{2A} receptor gene polymorphism His452Tyr (C+1354T, rs6314) with systemic sclerosis (SSc) in an Italian population. $5HT_{2A}$ accounts for most vasoconstrictive and platelet aggregation due to serotonin activity [2]. Beretta and colleagues also demonstrated that plasma from healthy heterozygous carriers of His452Tyr showed decreased platelet aggregation after serotonin stimulus compared to plasma from healthy individuals homozygous for His452. In consequence, they suggested a functional role of His452Tyr in reducing susceptibility to SSc.

We performed a population-based replication study in an independent and larger German Caucasian SSc cohort, approved by local ethics committees. DNA was purified from blood samples after obtaining written informed consent. Patients were included according to the German Network for Systemic Scleroderma guidelines [3]. The patient cohort was characterised as follows [4]: all fulfilled minimal requirements of LeRoy and colleagues [5] and 81% fulfilled ACR criteria [6]; 80% were females, 50% presented with the limited cutaneous form (lSSc [3]), 33% with the diffuse cutaneous form (dSSc [3]), 89% carried antinuclear antibodies (ANA-positive), 43% anticentromere antibodies (ACA-positive), 39% antitopoisomerase I antibodies (ATA-positive), and they had a mean age of disease onset of 49.5 ± 13.8 years. Mass spectrometry-based genotyping was applied as described, with minor modifications [4]. Power was >96% to replicate the allelic association and >99% to replicate a decreased minor allele frequency within cases [7], as reported for the Italian population.

HapMap data reveal considerable variation of Tyr452 frequency among populations. It is especially high within Africans, emphasizing the importance of appropriate case-control matching. The frequency in our controls was very similar to that in the Caucasian HapMap cohort (0.065 versus 0.063, respectively). It was higher in the Italian population (0.124).

We did not find a protective association of His452Tyr with SSc. In contrast, the frequency of Tyr452 was not decreased, but even increased in all SSc patients (Table 1). Also, no association was found when SSc subgroups stratified for the fulfilment of ACR-criteria, clinical classification (lSSc, dSSc), autoantibody status (ANA-, ACA-, ATA-positive) or sex were compared to healthy donors. However, Tyr452-positive SSc patients were less frequently dSSc positive than His452 homozygous SSc patients ($P = 0.048$, 9% versus 20%, respectively). This might indicate that the $5HT_{2A}$ polymorphism may influence the severity of SSc.

In summary, we could not replicate an association of the $5HT_{2A}$ His452Tyr polymorphism with SSc in a larger German

SSc = systemic sclerosis.

Table 1

Distribution of C+1354T within German systemic sclerosis patients and controls

	Genotype					C versus T	
	CC	CT	TT	Total	MAF	OR (95%CI)	P^a
Patients	176	31	2	209	0.084	1.32 (0.8-2.2)	0.28
Controls	203	28	1	232	0.065		

[a]*P*-values were calculated with Fisher's exact test. Genotypes in cases and controls were consistent with Hardy-Weinberg equilibrium. Frequencies of genotypes were also not significantly different between patients and controls ($P = 0.52$, exact Fisher Freeman Halton test). CI, confidence interval; MAF, minor allele frequency; OR, odds ratio.

Caucasian cohort. However, an influence of this single nucleotide polymorphism on severity of SSc may exist.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Support originated from the BMBF ('German Network for Systemic Scleroderma' to IM and NH; 'Hochschul-Wissenschafts-Programm'to PA), the SAB (7692/1187) and EFRE (EFRE4212/04-04) to PA.

References

1. Beretta L, Cossu M, Marchini M, Cappiello F, Artoni A, Motta G, Scorza R: **A polymorphism in the human serotonin 5-HT_{2A} receptor gene may protect against systemic sclerosis by reducing platelet aggregation.** *Arthritis Res Ther* 2008, **10:** R103.
2. Welsh DJ, Harnett M, MacLean M, Peacock AJ: **Proliferation and signaling in fibroblasts: role of 5-hydroxytryptamine2A receptor and transporter.** *Am J Respir Crit Care Med* 2004, **170:**252-259.
3. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, Moinzadeh P, Müller-Ladner U, Pfeiffer C, Riemekasten G, Schulze-Lohoff E, Sunderkoetter C, Weber M, Worm M, Klaus P, Rubbert A, Steinbrink K, Grundt B, Hein R, Scharffetter-Kochanek K, Hinrichs R, Walker K, Szeimies RM, Karrer S, Müller A, Seitz C, Schmidt E, Lehmann P, Foeldvári I, Reichenberger F, *et al.*: **The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement.** *Rheumatology* 2008, **47:**1185-1192.
4. Kirsten H, Blume M, Emmrich F, Hunzelmann N, Mierau R, Rzepka R, Vaith P, Witte T, Melchers I, Ahnert P: **No association between systemic sclerosis and C77G polymorphism in the human PTPRC (CD45) gene.** *J Rheumatol* 2008, **35:**1817-1819.
5. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell N, Wollheim F: **Scleroderma (systemic sclerosis): classification, subsets and pathogenesis.** *J Rheumatol* 1988, **15:**202-205.
6. Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee: **Preliminary criteria for the classification of systemic sclerosis (scleroderma).** *Arthritis Rheum* 1980, **23:**581-590.
7. Garnier S, Dieude P, Michou L, Barbet S, Tan A, Lasbleiz S, Bardin T, Prum B, Cornelis F: **IRF5 rs2004640-T allele, the new genetic factor for systemic lupus erythematosus, is not associated with rheumatoid arthritis.** *Ann Rheum Dis* 2007, **66:**828-831.