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The low-penetrance R92Q mutation of the tumour necrosis factor superfamily 1A gene is neither a major risk factor for Wegener's granulomatosis nor multiple sclerosis

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Inherited autosomal-dominant mutations in the tumour necrosis factor receptor superfamily 1A (*TNFRSF1A*) gene encoding the tumour necrosis factor receptor p55 (TNF-R1) are the cause of an auto-inflammatory syndrome that is characterized by periodic fever attacks, aseptic peritonitis, arthritis, meningitis, conjunctivitis, pleuritis and skin rash (OMIM #142680). The most common TNFR-associated periodic syndrome (TRAPS)-like disease that is associated with a R92Q mutation, however, occurs sporadically, with later onset (median 23 years vs 7 years with other mutations) and a milder and often oligosymptomatic course.^{1,2} Intriguingly, carriers of the R92Q allele bear a slightly increased risk for some other diseases, such as myocardial infarction,³ increased carotid intima-media thickness,³ thrombotic complications in Behcet's disease⁴ and early synovitis.¹

Due to the low uncertain frequency of the R92Q allele in various ethnic populations (0.5-1%), the available data about multiple sclerosis (MS) patients^{5,6} do not exclude a possible risk of R92Q mutations being present. Recent case reports on small-vessel vasculitis in patients with *TNFRSF1A* mutations (R92Q, T50M)⁷ and inflammatory manifestations of *TNFRSF1A* mutations in the central nervous system⁸ prompted us to investigate

a possible mutual relationship between R92Q mutations, MS and Wegener's granulomatosis (WG) in the German population.

A total of 446 MS, 268 WG and 265 control cases (table 1) were analysed for the presence of the R92Q allele by sequencing and *NciI* digestion of a PCR-amplified segment (detailed information on request). Apart from the R92Q heterozygous mutation, we have not found other sequence variations in these patients that affect the extracellular domain of the TNF-R1 receptor. Dinucleotide repeat length analysis performed in 15 R92Q⁺ patients from the MS and WG cohorts confirmed the sharing of an identical repeat length haplotype.⁹

The odds ratios that we obtained (0.64 for MS and 0.91 for WG) do not indicate a significant association of the R92Q allele with these diseases. Although the confidence intervals are relatively large, the data permit us to exclude a more than 2-fold risk of the R92Q allele in cases of WG and a more than 1.3-fold risk for MS cases. As both the frequency and the remaining

Abbreviations: MS, multiple sclerosis; *TNFRSF1A*, tumour necrosis factor receptor superfamily 1A; TRAPS, TNFR-associated periodic syndrome; WG, Wegener's granulomatosis

Table 1 R92Q frequencies in MS and WG patients and in healthy controls

	R92Q ⁺	R92Q ⁻	r(R92Q)*	OR [†]	p [‡]	CI [§]
MS	13	446	2.9	0.64	0.38	0.32-1.26
WG	11	268	4.1	0.91	0.99	0.39-2.09
HC [¶]	12	265	4.5			

*Carrier frequency; [†]OR, odds ratio; [‡]Two-tailed p value using the chi-square test with Yates correction (<http://graphpad.com/quickcalcs/contingency2.cfm>); [§]CI, confidence interval at the 95% level of confidence. OR and CI were determined via the web-based calculator: <http://www.hutchon.net/ConfidORselect.htm>; [¶]Healthy controls (blood donors).

potential risk of the R92Q allele are indeed low, the impact of R92Q mutations on the MS and WG burden in the German population is negligibly small.

Considering the belief that, as yet unknown, susceptibility loci contribute to TRAPS-like manifestations in R92Q carriers, we wondered if those genes that confer susceptibility to WG and MS convert the low-penetrance status of the R92Q allele into a high-penetrance condition. The clinical histories and archival records of those WG and MS patients that carried R92Q, however, did not provide evidence for preceding inflammatory episodes that are typical of TRAPS. Most strikingly, three WG patients suffered from recurrent serositis, which is highly uncommon in WG. Hence, recurrent serositis might be considered to be a manifestation of the R92Q allele on top of an unfolding WG.

With the reasonable assumption that the R92Q allele shows a 1% penetrance rate among the 4% carriers and, in view of the low prevalence of WG (50 per million) in the German population,¹⁰ it is extremely unlikely that both clinical phenotypes developed in a single patient just by coincidence. In the case of MS, such a casual coexistence of both clinical phenotypes is more likely as the prevalence of MS is about 30-fold higher than that of WG.

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Serum serotonin levels are not useful in diagnosing fibromyalgia

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Altered concentrations of circulating serotonin have been implicated in several pathological conditions such as fibromyalgia,^{1–4} rheumatoid arthritis^{2,4,5} and major depression.⁶ In fibromyalgia in particular, several investigators have reported low serum serotonin levels as compared to the general population.^{1,3}

We analysed sera from 20 patients with fibromyalgia, and compared the data with that obtained on analysis of sera from age- and gender-matched controls, including 20 patients with of rheumatoid arthritis, 20 with osteoarthritis, 20 with major depression, and 20 healthy individuals. The patients with fibromyalgia had a mean number of tender points of 16.3 and a mean duration of the disease of 9.65 years. Thirteen patients with rheumatoid arthritis exhibited erosive arthritis. The severity of depression in the patients with major depression

had been determined by the Hamilton rating scale (HDRS)⁷ and the Beck depression inventory (BDI)⁸ with the following results: mean HDRS 25.4 (15–39); mean BDI 29.0 (15–42). Five patients in the depressive group reported pain. All patients were free of anti-depressive treatment. The study was approved by the local institutional ethics committee.

The levels of serotonin in each serum sample was determined three times; twice using a commercially available enzyme immunoassay (ELISA; Serotonin-ELISA Kit, IBL Immuno Biological Laboratories, Hamburg, Germany) and once in a standard reference laboratory using a reversed phase high performance liquid chromatography (HPLC) with electrochemical detection.

Abbreviations: BDI, Beck depression inventory; HDRS, Hamilton rating scale; HPLC, high performance liquid chromatography