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

Figure 1 Measurement of the concentration of serotonin in the serum using a scrambled ELISA panel (A) and using reverse-phase HPLC (B). Dots show individual patients. The scattered lines show the minimum/maximum of the fibromyalgia group. 0, control group; 1, patients with fibromyalgia; 2, patients with rheumatoid arthritis; 3, patients with osteoarthritis; 4, patients with major depression.

The Serotonin-ELISA kit has a detection limit of 4.1 ng/ml. The results of this assay indicated a significantly lower concentration of serotonin in the sera of patients with fibromyalgia (minimum 10 ng/ml, maximum 115 ng/ml) compared to the control group ($p = 0.001$; minimum 131 ng/ml, maximum 322 ng/ml), the rheumatoid arthritis group ($p = 0.012$; minimum 20 ng/ml, maximum 245 ng/ml), and the major depression group ($p = 0.028$; minimum 16 ng/ml, maximum 299 ng/ml). The levels of serotonin in the sera of patients with major depression were significantly lower ($p = 0.03$) than those in the sera of the control group (data not shown). The question remained as to whether this

statistically significant difference was robust enough to be informative clinically. We therefore repeated the ELISA using a scrambled panel of sera (fig 1A). The results of the ELISA using a scrambled panel, confirmed a significant difference between the fibromyalgia group and the control group ($p = 0.01$) as well as the rheumatoid arthritis group ($p = 0.02$). Analysis of the sera at the reference laboratory using reversed phase HPLC (fig 1B) failed to indicate a significant difference in the levels of serotonin in the patients with fibromyalgia and any of the other groups.

Thus, although the levels of serotonin in the sera of patients with fibromyalgia appears to exhibit a tendency to be lower than in patients with rheumatoid arthritis and healthy controls, at least when measured by ELISA, the variation of serotonin levels within the disease groups is too broad to differentiate fibromyalgia from other conditions, and most especially clinical depression. We therefore conclude that measurement of the concentration of serotonin in the serum is not a useful tool for the diagnosis of fibromyalgia.

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