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Variation outside of the range of the TRPM8 receptor affects multiple sclerosis prevalence rates

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Abstract

Introduction: TRPM8 is an immune system regulator with a peak activity at 8°C–10°C. Multiple sclerosis (MS) is a condition that is noted for an increasing prevalence with latitude. Prevalence rates have, however, been noted to drop in northern regions with averages yearly temperatures below 8°C.

Aim: To determine whether MS prevalence rates are associated with the peak of TRPM8 activity of 8°C–10°C both by average yearly temperature and by variation towards that temperature.

Material and methods: Multivariate analysis was used to determine the significance of association between MS prevalence, average yearly temperature, and with variation towards a particular temperature. This method was repeated for eight independent regions, all regions combined, and all regions except Russia and Scandinavia.

Results and discussion: Results showed an average yearly temperature for peak MS prevalence between 6.00°C and 10.80°C depending on region. The average temperature for peak effects of variation was between 7.80°C and 8.70°C depending on region, with the UK and Scandinavia non-significant. The average temperature of association with MS for all regions was 9.21° by temperature ($P < 0.05$) and by variation 8.67°C ($P < 0.005$). Without Russia and Scandinavia the average temperature was 10.55°C ($P < 0.05$) and variation was not significant.

Conclusions: Removing northern regions from the model causes variation to become non-significant by removing areas where, on average, variation towards warmer temperatures increase MS rates instead of variation towards lower ones. This provides evidence that average yearly temperature and variation from that temperature are responsible for significant variations in MS prevalence rates worldwide.

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1. INTRODUCTION

A previous study[1] showed that multiple sclerosis peaked in prevalence at around 8°C where TRPM8 receptor activity peaks[2] when trends in multiple sclerosis (MS) rates were analyzed. In addition, the areas with the highest reported prevalences[3] of MS were shown to have very narrow variation from their average temperature, which was at or near 8°C,[4] while all others declined in prevalence in either direction from this peak TRPM8 receptor reactivity (Figure 1). How variation towards a particular temperature affected MS rates, however, was not examined. Presumably if variation crosses the point of peak incidence – where the TRPM8 receptor ceases to function shortly after reaching the point of its greatest activity – then the result would be a sharp and definable change in MS prevalence rates. The most distinctive way that this variation would occur is if a particular area has a significant portion of the year which was on one side of that temperature. In order to determine if this is the case a sweeping analysis of a very large (n = 101) number of MS prevalence locations was tested to determine if this was the case.

2. AIM

The goal of this study is to determine if variation towards a particular temperature has significant effects on MS prevalence rates.

3. MATERIAL AND METHODS

Seven separate regions – two of which have average yearly temperatures below 8°C and five above that temperature – were examined independently and collectively. The purpose of doing so is to determine if such variation has an impact if it crosses from below that temperature into the TRPM8 reactive range and if it crosses from inside the TRPM8 reactive range to outside of it. Differences of 'average temperature from a particular temperature' were calculated

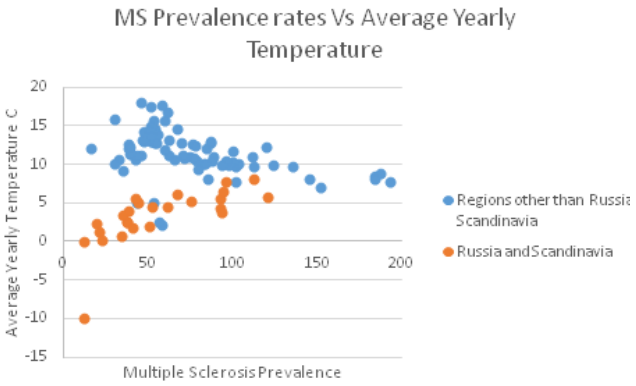

Figure 1. Scatterplot of MS prevalence rates used in this study.

for significance as the dependent variable in a multivariate analysis in which MS rates and 'average yearly variation in temperature' were calculated as independent variables. This was done with by analyzing the average yearly temperature's[4] difference from a specific temperature using the Norwegian Meteorological Institute. This was tested all along the known temperature range until a temperature of the highest significance was identified. This was then done for the variation, as well, in order to determine where the highest significance of 'temperature variation to a particular temperature' was located. Due to the fact that not all regions would reflect a complete range of average yearly temperatures, curves could be expected to result by which the significance of a result would increase in a gradual, linear fashion after a particular point. In the case of such 'gradient curves' the significant point would be the point at which the curve was at the point of an acceptable confidence interval. For 'average temperature from a particular temperature' this will be a 95% confidence interval ($P < 0.05$) and for 'temperature variation to a particular temperature' the standard will be one half of one percent ($P < 0.005$). This will be tested in seven regions, as a whole world result, and the whole world results without Russia and Scandinavia.

Table 1. The average yearly temperature at which each region achieved the highest significance (or significance by gradient curve) and the degree of that significance. Average variation at which the temperature achieved the highest significance and the degree of that significance. The number of data points is also listed.

Measure	Russia	Scandinavia	New Zealand	France	Italy	United Kingdom	Balkans	Average	Whole World	Whole World without Russia, Scandinavia
Average yearly, °C	6	7.2	9.5	10.8	10.11	8.75	9.2	8.79	9.21	10.55
Variation, °C	8.6	n.s.	7.8	7.925	8.6	n.s.	8.7	8.325	8.67	n.s.
Average yearly, °C P value	0.0001	0.000702	3.7^-151	0.04978	0.0005	0.000447	7.47649E-05	NA	0.05	0.05
Variation, °C P value	2.2741^-05	n.S.	1.9^-159	0.004968	0.005	n.s.	5.82689E-15	NA	0.005	ns
Data points (n)	13	11	13	22	14	14	14	NA	103	78

4. RESULTS

4.1. Russia

Average yearly temperature peaked at 6°C for Russia,[5] with a peak variation of 8.6°C. The significance for these two points was $P < 0.0001$ and $P < 2.2741 \times 10^{-5}$, respectively. Russia is below the activity range for the TRPM8 receptor but has wide variation, meaning that much of Russia's year is above 8°C. The two lowest average yearly temperatures (Yakutsk –9.96C, and Irkutsk 0.05C) are located here and both had the lowest rates of MS of all locations (both 12 cases per 100 000 populations) (Figure 1).

4.2. Scandinavia

Average yearly temperature[6–13] peaked at 7.2°C and was significant ($P < 0.0007$). Variation did not peak and was not significant at any temperature. Scandinavia is below the TRPM8 receptor range but the variation is lower than Russia, meaning that much of the year is not above 8°C and variation into that range is not significant.

4.3. New Zealand

New Zealand's results[14] were significant to the point of being definitive: average yearly temperature peaked at 9.5°C ($P < 3.7 \times 10^{-151}$) and variation peaked at 7.8°C ($P < 1.9 \times 10^{-159}$). These exceptionally significant results mark New Zealand's results as being potentially definitive in the diagnostic of MS rates according to temperature.

4.4. France

France[15] has a peak average yearly temperature of 10.8°C ($P > 0.04978$), combined with a peak variation of 7.925°C ($P < 0.004968$). Variation in France is extremely low, and as a result both are gradient curves – each has a point at which they are of the significance necessary to demonstrate their significance by the standards of this test.

4.5. Italy

Italy[16–39] has a peak average yearly temperature of 10.11°C ($P < 0.0005$) and a peak variation of 8.6°C ($P < 0.005$) which is a gradient curve. It is worth noting that the only locations which were located south of Russia and Scandanavia which were below an average yearly temperature of 8°C were located in northern Italy[36–39] (Figure 1).

4.6. United Kingdom

The United Kingdom[40–57] demonstrated a peak average yearly temperature of 8.75°C ($P < 0.0005$) and peak variation was not significant. It should be noted that the UK has average yearly temperatures at the peak of the TRPM8 range, meaning that all parts of this range would demonstrate high effects on the TRPM8 receptor and few would show a reduction of its activity. In addition, variation outside of that range is not continuous enough to produce significant results for variation. The four highest MS prevalence rates in the world[54–57] were located in the northern United Kingdom and their rates relative to the rest of the tested locations is distinctive (Figure 1).

4.7. Balkans

The Balkans[58-69] had a peak average yearly temperature of 9.2°C ($P < 7.48 \times 10^{-5}$) and a peak variation towards 8.7°C ($P < 5.83 \times 10^{-15}$). This highly significant result is comparable in importance to New Zealand.

4.8. Whole world variation

When all relevant tested locations[5–69] ($n = 103$) were averaged together, the result was 9.21°C for a peak average yearly temperature with variation ($P < 0.05$) and 8.67°C for a peak variation temperature ($P < 0.005$). When Russia and Scandinavia were removed due to their being below the TRPM8 range by average then the peak average yearly temperature jumps to 10.55°C ($P < 0.05$) with a gradient curve and the variation is non-significant all along the range.

5. DISCUSSION

Differences from one region to another in both results can be explained by differences in the samples that were examined: without a complete range of temperatures to test than only so much accuracy in the result can be expected. A gradient curve can be expected if there are not samples on both sides of peak TRPM8 receptor activity (8°C) that also demonstrate variation that crosses that point to a significant degree (that is, enough to produce a significant result). Additionally, variation in this case is measuring where the TRPM8 receptor functions, meaning that if too much of the range is outside of the TRPM8 range then the results will not be significant. Commensurately, if too little of the range is outside of the TRPM8 receptor's functional range, then the result can also be expected to be non-signficant-such as the UK. This is why whole world variation showed a significant result when Russia and Scandinavia were considered, but not when they were removed. It also explains why the point of significance (10.55°C) is also the point of least significance ($P < 0.98$) for variation. The point at which variation has become significant at or around 8°C is – regardless of what region is considered – the point at which the TRPM8 receptor's activity ceases.

6. CONCLUSIONS

Variation across the point of a cessation or activation of the TRPM8 receptor has highly significant effects in all regions of the world.

Conflict of interest

Author declare to have no conflict of interest.

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