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Comparison of geographic distributions of Irritable Bowel Syndrome with Inflammatory Bowel Disease fail to support common evolutionary roots Irritable Bowel Syndrome and Inflammatory Bowel Diseases are not related by evolution

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ABSTRACT

Irritable Bowel Syndrome (IBS) shares overlapping symptoms and some features of pathogenesis with Inflammatory Bowel Diseases (IBD: Crohn's disease [CD], and Ulcerative Colitis [UC]). Geographic markers such as latitude/sunshine and more recently lactase population distributions are found to be correlated with IBD. As a result of clinical and pathogenic similarities between the 2 conditions, some authorities questioned whether a connection exists between them. We compare IBS directly with IBD, and indirectly with geographic markers associated with IBD, in order to evaluate possible evolutionary links between IBS and IBD. Similar correlations may link IBS as a precursor to IBD and possibly other conditions which are geographically connected with IBD. Data from four systematic reviews on IBD incidence and prevalence, IBS prevalence, and lactase distributions were included. Pearson's correlations were used for comparisons, with IBD values log-transformed because of skewed distribution. The articles provided 18–28 complete set of national data. Direct comparison between IBS and IBD showed no significant correlations ($r = -0.14$, $r = -0.06$ for CD and UC prevalence, $r = -0.10$ for CD incidence). Indirect comparisons also failed to show correlations of IBS with lactase distributions ($r = -0.17$), sunshine ($r = -0.2$) or latitude ($r = 0.097$); however, there was significant correlation between lactase distributions and CD incidence ($r = -0.84$), prevalence ($r = -0.55$) and UC prevalence ($r = -0.59$). Both sunshine ($r = -0.53$) and latitude ($r = 0.58$) are also significantly related to CD incidence. It is concluded that IBS and IBD do not follow similar global geographic patterns. This suggests a lack of an evolutionary genetic background coincident with emergence of lactase persistence. As well, vitamin D has no obvious impact on development of IBS. Similarities with IBD may result from sub groups (not yet identified) within the current Rome criteria of IBS. Alternatively limited intestinal gut–brain responses to host microbial interactions may result in similar overlap features in both.

Introduction

In the last 4 or 5 decades, relationships between fixed geographic markers and many "western" lifestyle linked diseases in highly industrialized nations have been reported. In this paradigm, higher disease rates at higher latitudes and lower rates toward the equator with low latitudes have been described. The converse of these observations is the inverse relationship between sunshine, ultraviolet B light (UVB, 280–350 nm of visible light) and these "western" diseases. However it was also hypothesized that patterns of such diseases are also related to less fixed lactase phenotypic distributions (ie. Lactase persistence/lactase non persistence (LP/LNP) [1]. For reasons which are outlined previously [2], the Inflammatory Bowel Diseases (IBD; Crohn's disease [CD] and Ulcerative colitis [UC]) represent good models to use to evaluate possible ecological and perhaps evolutionary root links between diseases. IBD rates show similar directional patterns with latitude/UVB and LP/LNP.

These observations raise the possibility that both geographic disease modifiers (latitude/UVB) as well as the slower shifting distributions of LP/LNP populations over the last several millennia to several centuries had impact on determining patterns for some modern day diseases.

The role of latitudinal geographic patterns in causality or contribution to "western" diseases seems to favor newly found functions for vitamin D [3,4]. This is supported by both observational [5,6] and some

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interventional studies related to IBD [7] and some cancers [8–11]. A possible similar modifying role for LP/LNP distributions is not yet forthcoming. However, since there are several genetic associations with evolution of LP status, such variables are contenders for possible disease modification [12–18]. In addition cultural, economic and temperature related environmental differences exist between LP and LNP populations. All of which could impact on disease expression.

In the last few years, Irritable Bowel Syndrome defined by the Rome criteria (IBS: which up to recent findings was not associated with any specific pathology or pathogenic features) was reported to have several subtle features related which resemble somewhat those associated with IBD (but without tissue destruction) [19–24,25]. As well IBS–like symptoms in quiescent IBD raise a question whether these two conditions are related [19,26–29].

In this report, we compare global distribution of IBS with fixed geographic variables (i.e., UVB, latitude), and with slowly shifting geographic variable LP/LNP which showed previously related to IBD. We also compare global distributions of IBS directly with those of IBD. This exercise is made possible by the availability of more robust data on global distributions of IBD [30], IBS [31] and LP/LNP distributions [32] as well as latitude and sunshine.

The hypothesis

IBD has consistently been shown to be geographically correlated with a number of other "western" lifestyle diseases up to the turn of this century (2000). This relationship was initially reported to vary directly with increasing latitudes and inversely with increasing sunshine exposure. However initial observations showed that IBD rates were higher in Australia and New Zealand which are relatively high sunshine exposed countries. Also it has been observed that IBD rates are slower to materialize in a geopolitical west to east directions (North America, Western Europe and Asia). It has been hypothesized that IBD and other western diseases also correlate with LP/LNP distributions. While latitude/sunshine could possibly be related to increasing protective effects of vitamin D, the direct relationship with LP/LNP is less clear. It is postulated that evolutionary signatures of genes which accompanied emergence of LP in the modern world, may predispose to changing environment and lifestyles in inducing such "western" type of diseases.

IBS is a collection of symptoms (related to abdominal discomfort and altered bowel habits) putatively caused by several different etiological agents is much more common and wide spread. Nevertheless, in the last decade similarities in pathophysiology and some pathology tended to overlap with IBD. These similarities prompted a query whether the two conditions are related. If IBS is pathogenically related to IBD we might expect that distribution of IBD and IBS would tend to parallel each other since IBD shares geography (and some genetic predisposition) with other western diseases. The current hypothesis is that similar global distributions of IBS to that of IBD would provide evidence for common evolutionary root sources. Such an observation would raise a plausible explanation for recently reported similarities in pathogenesis between IBD and IBS. As such IBS could predispose to IBD. Different global correlations would support a different common disorder which represents gut microbial and nervous systemic interactions coexisting and overlapping with IBD.

Methods

Literature search

Data utilized were abstracted from 4 systematic reviews. Previously used search strategies are outlined for each systematic review in the result section. In this report the data from Lovell et al. [31] were used as independent variables (based on Table 4 and Supplemental Table 1 of the report). This systematic review included a strategy search up to October 2011. Modifications of individual local data (cities or regions from different countries) for IBD and LP/LNP distributions were carried out to allow national rate comparisons for the variables and are described here. The data of Lovell et al. were already listed as national percentages of the population.

First, the incidence rate and prevalence of IBD were obtained as follows: The incidence rate for CD was calculated as previously published (2, 30). Incidence data on ulcerative colitis was omitted from this analysis because it was previously published and is related closely with incidence of CD (2). The prevalence of CD and UC were obtained based on Molodecky et al. [30]. Nationwide values were generally preferred for comparison purpose because for other variables, such as LP/LNP and IBS, values were generally reported on national levels. However when national values were not available, prevalence was estimated from regions within those countries, using population weighted data and calculated using the following formula, also previously published [2].

Estimation of national disease rates (D) based on regional data where X_i = number of patients with new or ongoing disease (CD or UC) in region or city "i", A_i = population of region/city and P is the total population is the following: $D = \frac{\sum_{i=1}^{n} X_i}{P}$, where $P = \sum_{i=1}^{n} A_i$ and n is the number of cities and/or regions.

Secondly, LNP prevalence, were based on published data from Itan et al. [32] and other sources [2]. Lactase status proportions were based on intestinal biopsies or indirect tests of lactose tolerance and lactose breath hydrogen tests. In all three cases, tests were validated against genetic results [33,34]. In order to estimate some national rates (e.g. USA) the above formula was used to obtain population weighted estimates [2].

Thirdly IBS data were derived from Lovell et al. who reported national prevalence rates expressed as percentages [31].

Fourthly, national yearly Ultraviolet B (280–315 nm) exposures were deduced from the data of Lee-Taylor and Madronich [35] and were previously described [2]. Briefly monthly surface level radiation based on a radiative transfer model driven by satellite – measured variables was used. Annual averages from the sum of monthly averages for the period 1990–2000 were computed. To obtain a single representative value for each of the countries, population-weighted averages were calculated of the UVB surface radiation for the locations of the largest population centers in each country. A single population-weighted latitude is calculated for each country using the same population weighting as applied to the calculation of the population-weighted UVB.

Calculation of national annual average UVB exposure $\overline{UVB} = \frac{\sum_{i=1}^{N} P_i UVB_i}{P}$, $P = \sum_{i=1}^{N} P_i$, where P_i are the populations of the N population centers considered and UVB_i is the annual UVB exposure at population center i. The number of population centers (N) included in the calculation of a national average varied from 1 for small countries to typically 10 or more for the larger countries with many large population centers.

Lastly, for latitudes, that are presented in terms of single values for each country, a population-weighted latitude is calculated for the country using the same population weighting as applied to the calculation of the population-weighted UVB. So $\overline{LAT} = \frac{\sum_{i=1}^{N} P_i \, LAT_i}{P}$, where LAT_i is the latitude of population center i and $P = \sum_{i=1}^{N} P_i$.

Data analysis

Pearson's correlations were used to assess relationships among IBS, IBD, LNP, UVB and latitude. Then, negative Binomial Regressions (assuming IBD as the dependent variables) were used to assess associations between IBD and IBS while adjusting for the potential effects of LNP, UVB and latitude. Both IBD incidence and prevalence were log-transformed because of skewness of data. Negative binomial regression is used instead of Poisson regression because of over-dispersed