Research Article

Global Distribution of Common Variable Immunodeficiency (CVID) in the Light of the UNDP Human Development Index (HDI): A Preliminary Perspective of a Rare Disease

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Common variable immunodeficiency (CVID), although the most common primary immunodeficiency in humans, is a rare disease. We explored the spatial global distribution and country-wise prevalence of CVID, based on published data and those available from databases. As a country’s medical progress is linked to its technological and socio-economic developmental status, we expected that observed CVID prevalence was linked to human wellbeing. To assess this, we examined the correlation of observed CVID prevalence and the UNDP Human Development Index (HDI), which is a key measure of human development. Seventy-four data sets from 47 countries were available (most of them no older than 10 years). Analyses revealed that observed CVID prevalence ranged from 0.001 to 3.374 per 100,000 (mean: 0.676 ± 0.83) and was highest in “high” HDI countries (Spearman’s rho = 0.757). Observed prevalence was particularly high in countries where immunodeficiencies are systematically documented in registers. In “low” and “middle” HDI countries, CVID awareness is extremely poor. Assuming that true CVID prevalence does not differ among countries, this study, though preliminary, provides evidence that the discrepancy between observed and (unknown) true prevalence can be clearly linked to the countries’ developmental status. As a potential alternative explanation, we briefly discuss the possibility that variation in CVID prevalence is related to human genetic lineage.

1. Introduction

Common variable immunodeficiency (CVID), the most frequently occurring form of primary immunodeficiency in humans, is characterized by primary hypogammaglobulinemia caused by several different possible factors [1, 2]. Typically, B and T cell abnormalities occur, often only detected relatively late in the life of patients. This immune problem is termed “variable” because its clinical features comprise a wide array of phenomena. Most often, patients suffer from recurrent airway infections. In addition, more serious health issues such as lymphoproliferative autoinflammatory neoplastic disorders, as well as autoimmune diseases (e.g., autoimmune thrombocytopenia), have been reported [1–3]. First described in 1953 and only named “CVID” 20 years later [4], this immune problem is apparently rare [1, 3, 5]. But exactly how rare is it? Systematic documentation has only started in recent years (e.g., [2, 5]), and awareness of the disease among physicians is still considered to be poor, resulting in an unknown number of undiagnosed or wrongly diagnosed patients [1, 6, 7]. Therefore, little robust information is available on prevalence rates, except perhaps for several “industrialized” countries where systematic documentation in register networks has started in recent years [5, 7]. This documentation gives an idea of CVID prevalence, which is suggested to range from <1 to <4 per 100,000 inhabitants (e.g., [8–11]). Selenius et al. [12] even found a rate of 5.5 per 100,000 in Finland, and proposed that variation...
among countries is the result of slow medical progress. “Emerging” and “developing” countries typically report low prevalence rates at <0.5 per 100,000 inhabitants (e.g., [2, 7, 13–15]). Moreover, for many small “industrialized” countries, no CVID data are available at all (cf. [2, 5, 7]). However, the relationship between development and CVID prevalence remains unclear, as illustrated by the relatively high prevalence rate of Chile (>3 [16]) in contrast with the low rate of the USA (1.5 [7]).

The purpose of this paper is to advance understanding of the spatial global distribution of CVID by country-wise exploring and mapping of CVID. A country’s medical progress is linked to its technological and socio-economic status [17]. Considering this, we hypothesize that observed CVID prevalence is positively linked to key measures of human wellbeing.

2. Methods

We collected country-wise data (number of cases, year) in two ways. First, in June and July 2019, a literature search in Medline, EMBASE, PubMed, DIMDI, Google Scholar, and Web of Science was performed using “primary immunodeficiency”, “immune deficiency”, “Common Variable Immunodeficiency”, “Common Variable Immune deficiency”, and “CVID” (and/or; all years to present). As the intention of authors was not always to report as much as possible about CVID in their country, we only processed publications dealing with cohorts of N ≥ 5 CVID cases as a threshold. Kirkpatrick and Rimington [18] considered data for Australia and New Zealand jointly, which, in accordance with Rimington (17 June 2019, pers. comm.), we provisionally corrected for 95% of all cases to be Australian.

Second, access has been granted to the database of ESID (European Society for Immunodeficiencies; https://esid.org/, accessed 16 June 2019) and LASID (Latin American Society for Immunodeficiencies; https://lasid.org/, accessed 24 June 2019). In addition, the freely accessible database of USIDNET, The United States Immunodeficiency Network, was explored (https://usidnet.org/, accessed 15 June 2019). In the absence of an Africa-wide database, ASID (African Society for Immunodeficiencies) was only able to provide CVID data for South Africa (M. Esser, 3 July 2019, pers. comm.). Other primary immunodeficiency registers could not present data on CVID. With regard to the number of CVID cases in databases, no threshold was set for the inclusion of data.

In most of the sources, the number of CVID cases was given for a time period, e.g., 2008–2014 by Marshall et al. [19]. To simplify analyses, we assumed 100% survival of patients at the year when recording terminated and took the maximum accumulated number of known CVID reports to calculate prevalence (number of patients per 100,000 inhabitants [20]) for that year. For this purpose, we used population density data from the World Bank’s World Development Indicators database (http://datatopics.worldbank.org/world-development-indicators/, accessed 12 June 2019). Accordingly, for each year, the Human Development Index (HDI; http://hdr.undp.org/en/data; accessed 11 June 2019) was adopted from the annual Human Development Report by the United Nations Development Programme [21, 22]. HDI is a measure of average achievement in key dimensions of human development; it summarizes per capita information on life expectancy, education, and gross national income [23]. The HDI is available for 189 countries. The index ranges from 0 to 1, with countries being classified as having “low” (<0.500), “middle” (0.500–0.799), or “high” (≥0.800) HDI.

The measure covers the time period of 1990–2017 or a subset of years within that range. For CVID data from 2018 to 2019, we used the HDI from 2017 because the HDI for 2018 and 2019 had not yet been published.

The correlation between CVID prevalence and HDI was calculated by Spearman’s rank correlation coefficient (rho). Statistical analyses were computed in PAST 3.23 [24] and spatial data were processed in DIVA GIS [25].

3. Results

3.1. Global Distribution and Observed Prevalence of CVID. As shown in Table 1, information from 47 countries from all continents except Antarctica was available for the period 1994–2019. For several countries, information was obtained from different years, so that the total number of data sets was 74. The number of CVID cases spanned an enormous range from 1 in the Dominican Republic (2019) to 4,833 in the US (2019) (median 67). Observed prevalence ranged from 0.001 in India (1994) to 3.374 in Chile (2017) (mean 0.676 ± 0.83). Correcting for the effect of recent attempts to better document primary immunodeficiencies, e.g., by the establishment of national register networks [5], by regarding only the data sets from the last 10 years (N = 64), we found the lowest prevalence to be 0.012 in Egypt (2014).

Data in Table 1 and Figure 1 demonstrate that we generally know the least about CVID in Africa and Asia. In contrast, observed prevalence is relatively high (from West to East) in North America, Europe, and Australia, where in various countries CVID has been increasingly documented (cf. Table 1). The high prevalence in Chile is remarkable given that comparatively few CVID cases have been reported in other South American countries. Likewise, the relatively low prevalence observed in Sweden stands in sharp contrast to prevalence rates observed in other Nordic countries (Figure 1).

3.2. CVID and HDI. Among the 74 data sets, the HDI ranged from 0.452 in India (1994) to 0.944 in Switzerland (2019) (mean 0.838 ± 0.095); 51 data sets (68.9%) had a “high,” while 22 had a “middle” and only one had a “low” HDI (Figure 2, Table 1). When accounting for recent improvements in CVID documentation [5] by including only the data sets for the last ten years, and when including only the largest data set per country (N = 44), the lower range increased to 0.617 in Honduras (2019). The average remained almost unchanged (mean 0.844 ± 0.084), and there was no country with a “low” HDI.

Although this average for 44 countries (2009–2019) was only moderately above that of the HDI for all 189 countries in both 2009 (mean 0.677 ± 0.157) and 2017 (mean 0.709
Table 1: Known CVID cases for 47 countries from various years (74 data sets in total), followed by observed prevalence and HDI. Data sorted in alphabetical order by continent.

| Country    | Continent | CVID cases | Year | Population density | Observed prevalence | HDI | Source for CVID cases |
|------------|-----------|------------|------|--------------------|---------------------|-----|-----------------------|
| Algeria    | Africa    | 29         | 2014 | 39110000           | 0.074               | 0.747 | [30]                 |
| Egypt      | Africa    | 11         | 2014 | 91810000           | 0.012               | 0.683 | [2]                   |
| Morocco    | Africa    | 24         | 2014 | 34320000           | 0.070               | 0.65  | [14]                  |
| South Africa | Africa   | 55         | 2019 | 56720000           | 0.097               | 0.699 | ASID                  |
| India      | Asia      | 14         | 1994 | 942200000          | 0.001               | 0.452 | [31]                 |
| Iran       | Asia      | 98         | 2001 | 76100000           | 0.129               | 0.678 | [32]                 |
| Iran       | Asia      | 208        | 2019 | 82360000           | 0.253               | 0.798 | ESID                  |
| Japan      | Asia      | 136        | 2011 | 127800000          | 0.106               | 0.89  | [33]                 |
| Australia  | Australia | 441        | 2007 | 208300000          | 2.117               | 0.881 | [18]                 |
| New Zealand| Australia | 23         | 2007 | 42240000           | 0.545               | 0.894 | [18]                 |
| Austria    | Europe    | 25         | 2019 | 88600000           | 0.282               | 0.908 | ESID                  |
| Belgium    | Europe    | 19         | 2014 | 11180000           | 0.170               | 0.909 | [2]                   |
| Belgium    | Europe    | 123        | 2019 | 113500000          | 1.084               | 0.916 | ESID                  |
| Czechia    | Europe    | 87         | 2014 | 10510000           | 0.828               | 0.879 | [2]                   |
| Czechia    | Europe    | 111        | 2019 | 105900000          | 1.048               | 0.888 | ESID                  |
| Denmark    | Europe    | 179        | 2017 | 57490000           | 3.114               | 0.929 | [11]                 |
| Estonia    | Europe    | 6          | 2014 | 13160000           | 0.456               | 0.864 | [2]                   |
| Finland    | Europe    | 132        | 2017 | 55030000           | 2.399               | 0.92  | [12]                 |
| France     | Europe    | 532        | 2005 | 64610000           | 0.823               | 0.869 | [9]                   |
| France     | Europe    | 252        | 2008 | 63960000           | 0.394               | 0.878 | [34]                 |
| France     | Europe    | 894        | 2014 | 66130000           | 1.352               | 0.894 | [2]                   |
| France     | Europe    | 1377       | 2019 | 66990000           | 2.056               | 0.901 | ESID                  |
| Germany    | Europe    | 512        | 2013 | 80770000           | 0.634               | 0.928 | [2]                   |
| Germany    | Europe    | 451        | 2014 | 81200000           | 0.555               | 0.93  | [2]                   |
| Germany    | Europe    | 856        | 2019 | 82800000           | 1.034               | 0.936 | ESID                  |
| Greece     | Europe    | 18         | 2014 | 10930000           | 0.165               | 0.864 | [2]                   |
| Greece     | Europe    | 85         | 2019 | 10700000           | 0.794               | 0.87  | ESID                  |
| Iceland    | Europe    | 11         | 2015 | 32910000           | 3.342               | 0.927 | [10]                 |
| Ireland    | Europe    | 28         | 2005 | 41120000           | 0.681               | 0.896 | [35]                 |
| Ireland    | Europe    | 38         | 2014 | 46380000           | 0.819               | 0.921 | [2]                   |
| Ireland    | Europe    | 40         | 2019 | 49000000           | 0.816               | 0.938 | ESID                  |
| Italy      | Europe    | 20         | 2016 | 60670000           | 0.033               | 0.878 | [3]                   |
| Italy      | Europe    | 338        | 2019 | 60480000           | 0.559               | 0.88  | ESID                  |
| Netherlands| Europe    | 190        | 2014 | 16830000           | 1.129               | 0.924 | [2]                   |
| Netherlands| Europe    | 107        | 2019 | 17190000           | 0.622               | 0.931 | ESID                  |
| Norway     | Europe    | 117        | 1999 | 44500000           | 2.629               | 0.911 | [36]                 |
| Poland     | Europe    | 32         | 2014 | 38480000           | 0.083               | 0.842 | [2]                   |
| Portugal   | Europe    | 96         | 2019 | 10290000           | 0.933               | 0.847 | ESID                  |
| Slovakia   | Europe    | 8          | 2014 | 54160000           | 0.148               | 0.845 | [2]                   |
| Slovakia   | Europe    | 60         | 2019 | 54350000           | 1.104               | 0.855 | ESID                  |
| Spain      | Europe    | 213        | 1995 | 39852000           | 0.534               | 0.8   | [8]                   |
| Spain      | Europe    | 139        | 2014 | 46770000           | 0.297               | 0.88  | [2]                   |
| Spain      | Europe    | 69         | 2019 | 46450000           | 0.149               | 0.891 | ESID                  |
| Sweden     | Europe    | 14         | 2014 | 96450000           | 0.145               | 0.933 | [2]                   |
| Switzerland| Europe    | 98         | 2014 | 81400000           | 1.204               | 0.939 | [19]                 |
| Switzerland| Europe    | 152        | 2019 | 85420000           | 1.779               | 0.944 | ESID                  |
| UK         | Europe    | 810        | 2013 | 64110000           | 1.263               | 0.915 | [37]                 |
| UK         | Europe    | 281        | 2014 | 64600000           | 0.435               | 0.919 | [2]                   |
### 4. Discussion

#### 4.1. CVID Distribution and Prevalence with Regard to HDI

Based on our study, CVID is known from only about one-fourth of the world’s countries. This emphasizes that the poor awareness of this disease noted by physicians even in countries where CVID is known (e.g., [1, 7]) is even more drastic at the global scale. While CVID data are mostly recorded in “industrialized” countries, our survey revealed that dramatically little information is available on this disease in Africa and Asia. However, it is noteworthy that there are also highly developed countries for which no information on CVID prevalence is available (to the best of our knowledge), even including some that rank among the “top 25” of highest HDI (e.g., Israel, Singapore [23]).

Among the 47 countries with available CVID records, we hypothesized a positive correlation of observed prevalence and HDI. The latter is a measure of average achievement in key dimensions of human development [23]. We found a strong positive linear relationship supporting this hypothesis. Essentially, 51 of 74 data sets (including multiple years in some countries) originated from “high” HDI countries. In 2017, there were globally 59 “high” HDI countries, suggesting that in general CVID knowledge among those countries is “advanced.” This is a sharp contrast to the 22 data sets from the worldwide 108 “middle” countries and the single data set from one of the 23 “low” HDI countries.

As there is a priori no reason to expect that the true incidence differs among countries [1] (but see discussion of alternative explanations below), our findings suggest that in many of the countries where CVID is known, true prevalence should be much higher than observed. Higher true than observed prevalence has already been suggested in earlier CVID studies at smaller spatial scales; these studies suggest that the discrepancy is due to relatively poor CVID awareness among physicians (e.g., [1, 7, 12]). Taking this a step further,
our results demonstrate that the discrepancy between observed and (unknown) true prevalence can be clearly linked to countries’ technological and socio-economic status. However, given that CVID data were available for fewer than 50 countries, we still regard our results as preliminary, especially as some of the countries with “missing” data also have high HDIs (e.g., Hong Kong, South Korea, Qatar [23]).

4.2. The Value of Databases. Over the last one to two decades, our knowledge on CVID has greatly increased (e.g., [2, 3]), and along with new medical centers dedicated to immunodeficiencies, systematic documentation in national or international registers has started in several countries (e.g., [8–11]). The value of such databases [5] is evident in Table 1. In most countries, the number of CVID cases obtained from databases in our study (N = 30) was considerably higher than the number of cases for the same country taken from publications, with only a few exceptions, i.e., Chile, the Netherlands, Spain, and the USA. This comparison is not entirely valid, however, as the goal of published studies was not always to count all CVID cases in the respective country. Moreover, in the case of Chile, the published data may
overestimate real prevalence, as suggested by Poli et al. [16] themselves, because only ICD-10-coded hospitalizations were used to identify CVID cases.

However, despite these exceptions, our data generally suggest that when CVID data in a country are collected in systematic registers, this gives an “advantage” to those countries with no registers when approaching country-wide prevalence rates. There is a tendency for CVID databases to be predominantly run in “high” HDI countries; two-thirds of all data sets in this study originated from such databases (Table 1). This easily explains why some “high” HDI countries have relatively high observed prevalence rates.

4.3. Alternative Explanations. Along with previous authors, e.g., Yong et al. [1], we assume that true CVID incidence does not differ among countries. However, this assumption remains to be tested. The etiology of this immunodeficiency is not fully understood, despite the fact that CVID obviously has a genetic basis and that in the majority of patients, a polygenic cause is likely [26–27]. Studies so far involve cohorts of some hundred patients from a few countries only (e.g., [26–28]). We do not know whether all people all over the world have equal genotypic preconditions for developing CVID. To date, only Selenius et al. [12] have tentatively discussed whether regionally distinct CVID prevalence rates within Finland could perhaps be explained by influences from genetically distinct founders. Projecting this to the entire world, it cannot be ruled out that distinct genetic lineages (clades) of Homo sapiens vary in their potential to develop CVID. That is, the global distribution of CVID and variation in observed prevalence among countries could perhaps alternatively (or additionally) be explained by “race.” Interestingly, according to The United States Immunodeficiency Network (https://usidnet.org/, accessed 15 June 2019), of 1,776 CVID patients, 1,441 (~81%) were described to be “Caucasian.” However, this could also be the result of unequal access to health care among ethnic groups within the country [29].

Although we suggest considering distinct genetic lineages within our species to explain geographic patterns of CVID prevalence, at the current stage, it is premature to use this information as a basis for any concrete hypothesis.

4.4. Caveats. Some limitations of this study should be pointed out. About half of our data sets originated from published studies. These publications’ aim was not always to provide a country-wide picture of CVID cases. Nevertheless, often these studies were the only available information on CVID cases in a certain country at a certain time. In contrast, as in the Chilean case (see above), data sets may also risk overestimation of prevalence. We are aware that all of these issues create a bias in observed prevalence. However, our goal was to examine the pattern at a large scale rather than make detailed comparisons for particular countries. Moreover, even from certain databases aiming at nation-wide immunodeficiency surveys, the available information can be very limited (cf. Table 1). At the current stage, due to differences in quality of the available data, these problems cannot be solved.

We calculated prevalence using country-wide population data, which is a standard method [20]. This may also lead to bias, as demonstrated by Selenius et al. [12]. These authors calculated CVID prevalence in Finland based on reported cases and population density in districts of hospitals treating CVID; they then used weighted means to extrapolate the prevalence of the entire country. As a result, their country-wide prevalence was higher than that calculated by us.
5. Conclusions

CVID is a rare disease of globally limited awareness, with an immense lack of knowledge especially in “low” and “middle” HDI countries. Among the countries where CVID has been reported, observed prevalence is positively correlated with increasing HDI. When assuming that true CVID prevalence does not differ among countries, the discrepancy between observed and (unknown) true prevalence can be clearly linked to the countries’ developmental status, i.e., HDI. But not all “high” HDI countries have high prevalence rates; rather, these rates were often high in countries where CVID is systematically documented in registers. Also, in future studies, it might be worth considering alternative explanations, such as distinct human lineages and their genotypic preconditions to develop CVID.

Data Availability

Data is available upon request and may be obtained by contacting the corresponding author.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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