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Editorial

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Can epidemiological studies uncover the origin of Behçet's disease?

The origin of Behçet's disease

This Editorial refers to Exploring the variability in Behçet's disease prevalence: a meta-analytical approach by Carla Maldini *et al.* on doi:10.1093/rheumatology/kew486

Whenever prevalence figures of Behçet's disease (BD) are discussed, the geographical roots of this multisystem auto-inflammatory disorder come to mind. It has been hypothesized that BD originated somewhere in the Turkish region, and there are various indications that may support this. One of the most eye-catching is the name-giver, Hulusi Behçet, a Turkish dermatologist who described patients with a trio of symptoms [consisting of aphthous stomatitis, genital ulcers and recurring (hypopyon) uveitis] back in 1937 [1]. However, we believe that reports of patients with symptoms of BD date back to the 5th century BC: in his third book of endemic diseases (from the beginning of the Classical period of the Ancient Greek Empire), Hippocrates described a local epidemic occurrence of such patients [2]. During that century, travelling and ethnic interaction was facilitated by the development of trading routes within the Orient. The building of roads such as the Royal Road of the Persian Empire was followed by the expansion of the Greek Empire of Alexander the Great into Central Asia. BD may have subsequently spread eastwards. We see this possibility supported by various demographic studies indicating the prevalence as being highest in Turkey, then descending in magnitude through the Middle East, and Central and Eastern Asia to Japan [3]. The Silk Road disease theory conceived by Shigeaki Ohno, one of the pioneers of BD research, describes the possible dispersion of BD via these trading routes [4]. In modern times, the epidemiology is reversed towards the West, reflected in a low occurrence in Western countries [3, 5].

Epidemiological studies are frequently cited and used to establish the true rarity of a disease, or to highlight geographical data that might be linked to potential environmental or genetic causes. However, reported prevalence varies not only between countries, but also between study designs. The meta-analytical approach by Maldini *et al.* (published in this issue) endeavours to put an end to the incommensurability of each reported prevalence and calls for standardization of epidemiological study designs. The study reproted by Maldini *et al.* found the highest prevalence of BD to be in the Turkish population (almost 120/100 000, a figure that was not equalled by any of the other cohorts analysed) [6]. However, 120/100 000 is lower than some individual studied, whereas the pooled data reached 10.3/100 000 inhabitants—a figure not often observed in the West or in countries below the equator. The predominance of reports from Middle Eastern countries in the meta-analysis by Maldini in this paper (without corrections for ancestry) might explain the latter.

Corrections were made for clinical and methodological confounding factors via sensitive and robust methods of recognizing the source of the heterogeneity, analysing for sufficient weight and evaluating the degree to which each single study affected the overall figures. The most important aspect was to recognize the risk of undercounting in studies based on, for example, hospital registers (the census method) as compared with studies using a sample survey. The latter method collects cases directly from a community and produces a higher prevalence. Maldini *et al.* indeed demonstrated the highest prevalence numbers (82.5/100 000) in cohorts using sample surveys. It is important to note that this method was restricted to the Middle East and Southeastern cohorts, whereas the Western and Japanese cohorts were studied by sample design and had considerably lower prevalence rates (3.6/100 000). Therefore, the impression that the prevalence of BD is up to 400-fold lower in Middle East and Southeastern countries must be seen in perspective. The only ethnic groups who were studied by both methods were Israeli cohorts, and they demonstrated about 2- to 3-fold higher figures in sample surveys [6]. Interestingly, the prevalence figures among Turkish immigrants (71.2/100 000) acquired in a Western sample survey would equal those of Turkish studies when corrected with this factor [5]. Designed geographical boundaries of countries might conflict in more and potentially higher regional figures, i.e. local epidemiological studies might be more useful in locating the origin of BD. So far, the outcomes of the study by Maldini *et al.* put the prevalence differences between East and West in perspective since the true prevelances remain the highest there, but still support the hypothesis that the Middle Eastern region is where BD might have originated.

Are there any clues other than prevalence figures to support the Silk Road and reverse migration theories? The foremost indication is the parallel occurrence of *HLA-B51* with the Silk Road [3]. *HLA-B51* still has the strongest genetic association with BD as compared to any other known genetic variations [7], elevating the odds of having BD to 5.8 [8], and this might shed light

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on the immunological mechanistic pathways of BD. However, *HLA-B51* cannot be the only explanation for the genesis and immunopathological evolution of BD: certain populations, in the Amazon reservoir or Siberia, for example, have a relatively high occurrence of *HLA-B51* positivity, but do not have a concurrent high prevalence of BD. In addition, not all *HLA-B51*–positive people have BD, and up to 50% of BD patients are *HLA-B51* negative. However, the spread of *HLA-B51* may be informative about the timing of when BD originated, and about the potential interaction of local factors. Other approaches to finding the origin of BD are emerging. Sazzini *et al.* analysed the ancestry of an apparently Western BD population in Italy, by means of innovative detailed molecular analyses. They found that the genetic ancestry of those BD patients of Italian descent was Middle Eastern and Central Asian [9]. Although speculative and biased, clues can also be obtained from the original approach—a bibliometric analysis of the distribution of diseases. Senel *et al.* [10] analysed the number of publications containing indications of the prevalence of BD and found that the highest publication rate appeared in Turkey, which is indirectly indicative of a trend in BD prevalence.

The various presented indications may lead to a hypothetical location of the geographical roots of BD. But can prevalence studies actually unravel the origin of BD? The meta-analysis of such studies by Maldini *et al.* supports the idea that the roots of BD were in the Middle Eastern region, and it guides future studies towards a uniform approach that might lead to an even more precise localization of the highest prevalence of BD. The outcome of upcoming combined novel molecular analyses and epidemiologic studies should improve our understanding about the etiological nature of endemic diseases such as BD.

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