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The digital epidemiology of dysencephalia splanchnocystica, AKA meckel–gruber syndrome: Retrospective analysis and geographic mapping via google trends

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ABSTRACT

Background: Genetic diseases are diverse and many of which have debilitating consequences affecting the individual, the society, and the economy. Trends databases, including *Google Trends* database, can be used to estimate the digital epidemiology of these diseases. Digital Epidemiology is valuable when it comes to conditions of low prevalence as in the case of ciliopathies including that of Meckel–Gruber Syndrome. **Aims and Objectives:** To assess the digital epidemiology and the geographic mapping of Meckel- Gruber syndrome via a trends database of the surface web. **Materials and Methods:** Google Trends database will be usedfor geographic mapping and retrospective analysis of interest of users of the Surface Web. The aim is to infer and predict the digital epidemiology of Meckel–Gruber Syndrome. A retrospective analysis is conducted as far as the trends database permits (2004-2017). The trends database was explored using the thematic expression of keywords specific to Meckel–Gruber Syndrome including its synonyms. Subsequently, descriptive and inferential statistics were carried out to estimate the digital epidemiology as well as the geographic mapping. The aim was to conclude the existence of any significant change in web users' interest and the variation of that interest versus geography (country) and chronology (time). **Results:** Concerning geographic mapping, signals of web users were found to be originating from the United States (68.49%) and Finland (31.51%). Globally, the average value of the relative interest of surface web users in Meckel–Gruber Syndrome was 34.10 (+/- 14.59). There was an overall decline in web users' attention towards the condition for the period 2004 – 2010 versus 2011 – 2017 (20.06 vs 4.88, *p-value* < 0.001) and for period 2004-2006 versus 2007-2009 (29.14 vs 14.19, p = 0.001). **Conclusion:** Digital epidemiological analysis has been proven feasible with good accuracy via Googles Trends. In the case of Dysencephalia Splanchnocystica, the geographic mapping of the surface web has been limited to the developed world. Prospectively, Google Trends can be integrated into a predictive early warning system to anticipate any change in the interest of the users of the Indexed Web in a particular disease including genetic ones.

Key words: Ciliopathies, Meckel-gruber syndrome, Dysencephalia splanchnocystica, Digital epidemiology, Retrospective studies

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INTRODUCTION

Genetic diseases are diverse and some of which are fatal. For instance, *Ciliopathies* including *Meckel-Gruber syndrome* (MGS) impose serious consequences affecting the society, economy, and physical-mental health. Johann Friedrich Meckel was the first to report cases of this *Syndromic Ciliopathy* during the early 19th century. Nearly one century later, Gruber also published similar observations, and he coined the syndrome with the term *Dysencephalia Splanchnocystica* (DS) because the condition affects a plethora of visceral organs, including the liver and kidneys, leading to

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the formation of pathologic encystations.[1-3] Meckel-Gruber syndrome is a rare fatal autosomal recessive condition that exists more frequently in populations where high consanguinity occurs, and it is mapped to at least twelve different loci in different chromosomes.[1-6] Hence, MGS represents a genetic heterogeneity.[1-6] The triad of enlarged polycystic kidneys, occipital Encephalocele, and postaxial polydactyly are characteristic for the syndrome.[1-3] However, other associated abnormalities may coexist including orofacial clefts, CNS malformation, genital anomalies, and cystic changes in other viscera including the liver.[1] Failure of the mesodermal induction cascades is incriminated for the pathophysiology of MGS. Mesodermal induction cascades the early morphogenesis via multiple homeobox genes and growth factors, in addition to the regulation of Hedgehog signalling, ciliary protein localisation, ciliary motility, and ciliogenesis.[1, 7, 8]Hence, *Meckel Syndrome*is categorised under *Syndromic Ciliopathies*.

Trends databases can be used for an accurate geographic mapping (geo-mapping) and estimation of the digital epidemiology of a varied array of diseases, including rare genetic disordersas in the case of MGS.[9-11] This study will explore the digital epidemiology of MGS via retrospective analysis of data retrieved from *Google Trends* database.[12-14] This study was instigated by the first reported case of MGS from Iraq. Concomitantly, a collateral study is being conducted to conclude the molecular genetics of the saidcase via *Next-Generation Sequencing* (NGS) and *Whole Exome Sequencing* (WES).[15-21] Sequencing will be carried out following DNA extraction from the parents of an aborted affected fetus with MGS.[22]

MGS is a rare condition and its exact prevalence in the region of the Middle East, specifically in Iraq, is not adequately estimated.[1,6,7] Further, the disease is more populated in specific ethnicities in correspondence with the molecular genetics and pathogenesis of the syndrome.[1-6] Prospectively, it is anticipated that the digital exploration of trends database, including *Google Trends*, via automated *Machine Learning* and *Deep-Thinking* algorithms will make a massive impact on epidemiologic studies, including retrospective inspection, real-time examination of trends, and predictive analytics.[23-28]

MATERIALS AND METHODS

Several databases, including trends databases, exist on the surface web. These can be exploited to describe or infer the *Digital Epidemiology* of a specific phenomenon including diseases and genetic diseases. Accordingly, Google Trends database was used to assess the interest (attentiveness) of surface web users in MGS via thematic keywords that are synonymous for MGS. The analysis is retrospective (2004−). The keywords were four in total including "Meckel-Gruber syndrome", "Meckel Syndrome", "Gruber Syndrome", and "Dysencephalia Splanchnocystica". Inferential statistics and hypothesis testing were applied to conclude the existence of any significant variations in web users' interest based on their location (mapped geography) and year-to-year variations (chronology). This innovative method, when combined with *Machine Learning* technologies, can be applied for real-time apprehension and predictive analytics of the epidemiological trends.

The analysis of Google Trends database reflects an extrapolation of data generated from millions of users of the *Visible Internet* (*Visible Web*). Accordingly, this manuscript is considered a hybrid study of an i*nternet snapshot* of a trends database and a retrospective analysis (level-2a) in compliance with the hierarchy of evidence-based studies imposed by the *Oxford Centre for Evidence-based Medicine* (CEBM).[9,30]A literature review was systematically conducted on NCBI-PubMed/Medline, EMBASE, the Cochrane Library, Scopus, EBSCO – CINAHL, Web of Science, and Google Scholar. The grey literature was also consulted. Concerningthe literature review, the epidemiology of MGS was based on up-to-date data retrieved from recently published papers in the past five years (2013-2017). Statistical analyses were carried out using *Microsoft Excel 2016* and the *Statistical Package for Social Sciences* (SPSS 20). The level-of-evidence of bibliographic materials has also been assessedincompliancewiththe Oxford CEBM via tools of *critical appraisal* of the literature.[31,32]

RESULTS

The geo-mapping of MGS was found to be strictly originating from two countries of the developed world, the United States (68.49%) and Finland (31.51%). Data signals were neither arising from the Middle East (including Iraq) nor any of the developing countries (including India and China) (Figure 1). Based on keywords search, Google Trends displayed the *relative interest index* (RII) towards Meckel syndrome on a scale of 0-100. The RII for two keywords ("Gruber Syndrome" and "Dysencephalia Splanchnocystica") conveyed no data signals which indicates the lack of interest (attention) or knowledge of the surface web users towards those synonyms of MGS. Web users commonly searched for the other two keywords "Meckel Syndrome" and "Meckel-Gruber Syndrome". Those keywords averaged an RII of 34.10 for "Meckel Syndrome" and 12.56 for "Meckel-Gruber Syndrome" (Figures 2 and 3).

Concerning the RII, statistical outliers weredetected starting from January-2004 and ending in July-2007 which

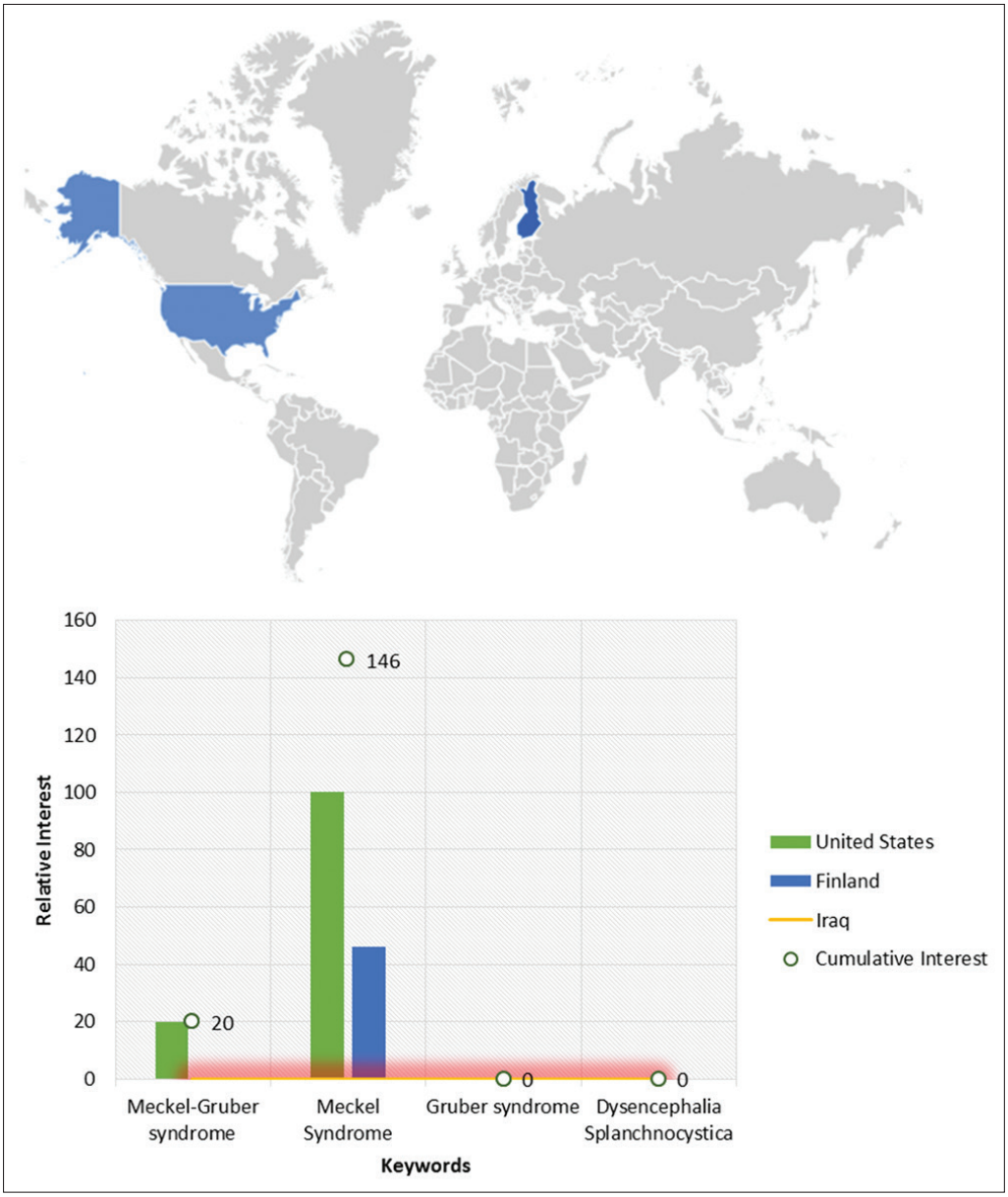

Figure 1: The Correlation of Keywords versus Geographic Location

indicates some considerable rise in web users' attention (RII) by seeking online data in connection with Meckel Syndrome (Figure 3). These were explicitly observed sporadically in 2004 (January, February, April, June, November, and December), 2005 (January, February, April, and November), 2006 (February and August), and 2007 (only in July). Perhaps, It is a mere coincidence that most of those outliers are chronologically existing during the harsh winter specifically in Finland and the northern regions of the US. However, a hypothesis should be designed and tested in future studies for this purpose. Related queries by web users, as conveyed by *Google Trends* included "meckel diverticulum", "diverticule de Meckel", "joubert syndrome", "meckel cartilage", "meckel scan", and "bardetbiedlsyndrome".All those queries are oriented towards diagnostic tests, embryonic structures, and some related medical conditions. Some of these medical conditions are also related to *Syndromic Ciliopathies* and *Ciliary Motility Disorders* including *Ciliary Dyskinesia.*

For the period from the beginning of 2004 until the end of 2017, there was a statistically significant difference in between the two keywords "Meckel Syndrome" and "Meckel-Gruber Syndrome" (*p-value*<0.001). The majority of surface web users were most familiar with the keyword "Meckel Syndrome". Further, year-to-year variation in between the two commonly used keywords was statistically significant for each year (2004-

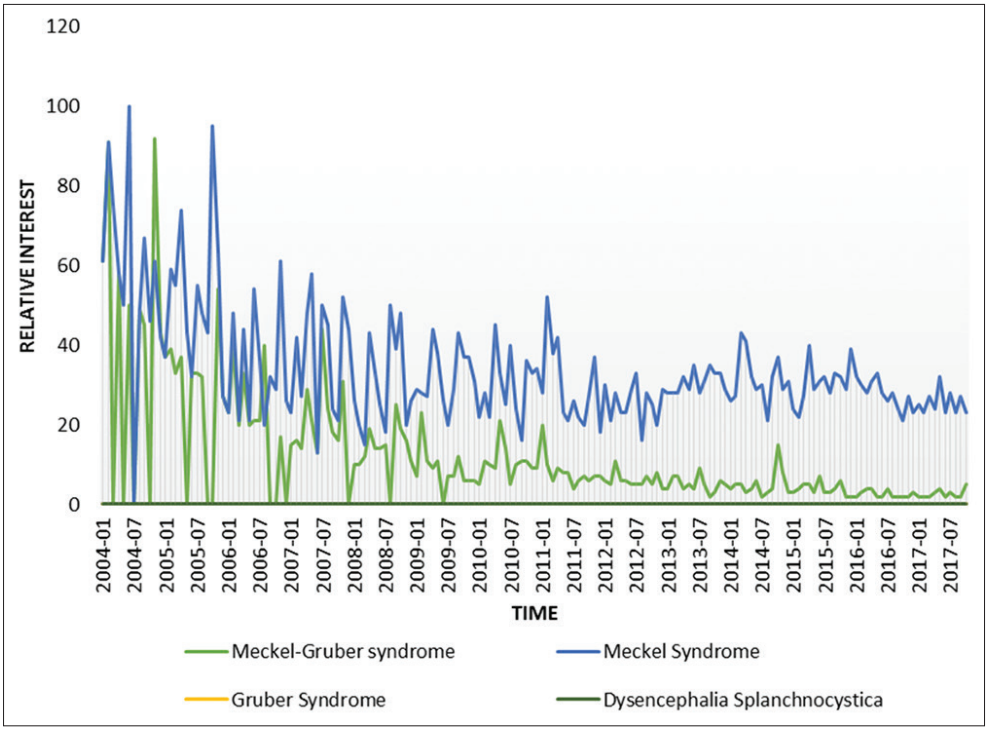

Figure 2: The Interest of Users of the Surface Web towards Meckel-Gruber Syndrome

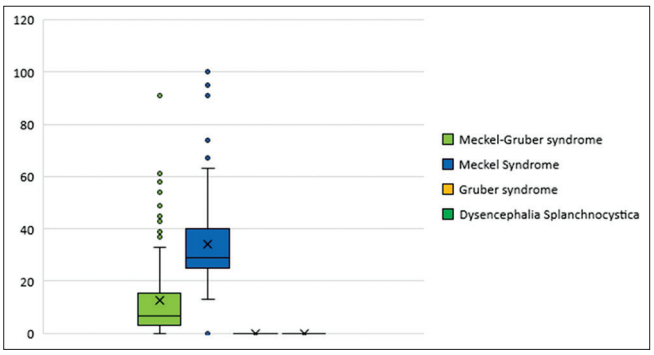

Figure 3: Boxplot Presentation of the Interest of Surface Web Users towards Meckel-Gruber Syndrome

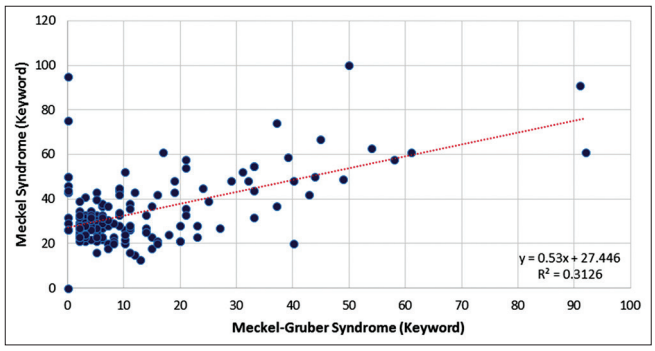

Figure 4: The Correlation of Two Keywords for Meckel–Gruber Syndrome

2017) with an exception for the year 2014 (p=0.074). Accordingly, it can be apprehended that web users were seeking a considerable amount of data on the syndrome using the keyword "Meckel-Gruber syndrome" as well as "Meckel Syndrome" in 2004. For the subsequent years, the web users preferably chose to search for data on the web based on the keyword "Meckel Syndrome". Linear regression analysis confirmed the existence of a positive relationship (R^2 score=0.3126) between the two keywords (Figure 4). Over the years, there was an overall decline in web users' attention towards the disease. A significant decrease in RII was inferred for the period 2004−2010 versus 2011−2017 (20.06 vs 4.88, *p-value*<0.001), in addition to a considerable decline for the period 2004-2006 versus 2007-2009 (29.14 vs 14.19, p=0.001).

DISCUSSION

Digital epidemiological analysis has proven useful via *Google Trends*. In the case of Dysencephalia Splanchnocystica (MGS), digital mapping of the surface web has been limited to two countries from the developed world. To recapitulate, Google Trends can be integrated into a predictive early warning system to anticipate any change in the interest of surface web users (RII) in a rare genetic disease. Real-time analytics can also be potentially used, via trends databases, when combined with tools of *Machine Learning and Data Crunching*.

The combinatory prevalence of cystic renal diseases and associated ciliopathies is approximately 1:2000.[33] The global incidence of Meckel-Gruber syndrome is around 1:140,000

live births while being higher in the Finnish ethnicities (1:9000), although the frequency is also high among Belgians and Bedouins Kuwaitis while being highest among Gujarati Indians (1:1,300).[34,35] The syndrome affects individuals from all ethnic backgrounds with an almost equal male-to-female ratio which is consistent with the autosomal recessive inheritance.[36] Data from our study is compatible with the existing body of literature concerning the Finish ethnicities and the population in the US. However, data concerning other ethnicities, including those from the Middle Eastern (Kuwait and Qatar) and Indian, are lacking from our digital epidemiological analysis. Faulty data could be due to the limitations of the database itself (Google Trends) or the use of *Virtual Private Networks* (VPN) and *Internet Protocol Masking* (IP Masking) in the developed regions of the world. These technical methods are frequently used as hack methods by web users to access government-censored (or restricted) websites including social communication media, pornography sites, and the deep web.[37-40]

MGS does also exist in Arabs inhabiting the north-east of Israeli occupied territories in Palestine, while the incidence among Israeli Jews is even higher than the worldwide average (1:50,000).[34, 35, 41] Further, genomic analysis of MGS in Arabs revealed marked genetic heterogeneity and displayed novel candidate genes, while in the state of Qatar, the incidence (2:1000) live births in the local population is analogous to reports from communities where consanguinity is remarkably high (above 40%).[36] Barisic and colleagues, via analysis of data accessed via the *European Surveillance of Congenital Anomalies* (EUROCAT) network, inferred that the prevalence of the syndrome was stable over time (2.6:100,000 live births) although regional differences within Europe were still observed.[1]

CONCLUSION

The digital epidemiological analysis is feasible to be applied via trends databases including the well-established *Google Trends* database. In the case of *Dysencephalia Splanchnocystica*, the geographic mapping was highly restricted to the developed world. The attention of web users towards *Meckel Syndrome* is significantly in decline over the past decade. The analysis of trends databases is precious and can be capitalised on for real-time and prospective analytics particularly when integrated into a predictive *machine learning* algorithms of an early warning system to anticipate any change in the trends. Hence, real-time and predictive analytics can significantly enhance epidemiological studies and their societal-economic benefits.

This study may have some limitations due to the sole use of *Google Trends* as a representative for the trends databases of the *Visible Web*. Further, the analysis was retrospectively specific for a restricted period (2004-2017). Additionally, data collected from *Google Trends* might be occasionally faulty or misleading as some users surfing the *Surface Web* can be deploying the use of *Virtual Private Networks* and *Internet Protocol Masking*. Subsequent studies should incorporate more than one database. Additionally, ventures into the *Deep Web* and its *Darknet* should be attempted to recover any relevant data including geographic mapping whenever feasible.

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Authors Contribution:
AAI - Study design, review of the literature, statistical analysis, and preparation of the manuscript.

Work attributed to: The study was conducted in the College of Medicine at the University of Baghdad in Iraq.

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