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WORLDWIDE BARRIERS TO GENETIC TESTING FOR MOVEMENT DISORDERS

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ABSTRACT

Background: Despite enormous advances in identifying genetic variants responsible for many neurological diseases, access to genetic testing access to genetic testing may be limited in clinical practice.

Objectives: To assess worldwide access to genetic tests for movement disorders and factors impacting their utilization.

Methods: The Rare Movement Disorders Study Group of the International Parkinson and Movement Disorder Society designed an online survey electronically mailed to all 7815 members.

Results: Survey data completed by 1269 participants from 109 countries were analyzed. Limited access to geneticists and genetic counsellors was reported in many world regions compared to Europe and North America. Availability of genetic testing was limited, with rates of access lower than 50%. Genetic testing for chorea was the most commonly available. For parkinsonism, dystonia, ataxia, hereditary spastic paraplegias, and metabolic disorders, there was limited access to genetic testing in all countries compared to Europe and North America, with significant differences found for Africa, Central/South America, Asia. In many regions, genetic testing was supported either by private or public funding. Genetic testing was free of charge in Europe according to 63.5% of respondents. In North America, Africa, Central/South America, Asia and Middle East access to free of charge genetic testing was by far significantly lower compared to Europe.

Conclusions: This survey highlights difficulties in accessing genetic testing and individuals with expertise in genetics at the worldwide level. In addition, we highlighted major disparities in genetic testing among world regions, likely due to a variety of factors including financial barriers.

INTRODUCTION

During the past two decades, there have been remarkable developments in identifying genetic variants responsible for many neurological diseases, and parallel advances in clinical diagnostic testing for these diseases, especially in the movement disorders field [1]. Clinical diagnostic testing, initially focusing on one or a few genes at a time, have been replaced by much broader testing strategies, such as disease-specific gene panels [2, 3] and whole exome sequencing (WES). Multiple reviews regarding the optimal use of different genetic tests have been published, and professional societies have devoted enormous efforts to education regarding the use of modern genetic testing [4-6].

Although these advances are valuable, access to genetic testing may be limited in clinical practice [7]. There is little knowledge regarding which factors influence access to genetic testing in neurological disorders and specifically in the movement disorders field. It is likely that lack of access might occur not only in resource-poor areas but also in those countries where gene panels or WES are available, but not covered by public funding or private insurances. It is crucial to clarify these issues in order to improve the diagnosis of rare neurological disorders and improve access to treatments and potential specific disease-modifying strategies.

Based on these premises, the Rare Movement Disorders Study Group of the International Parkinson and Movement Disorder Society (RMDSG) developed a survey, which was sent to all Society members, in order to assess accessibility to genetic testing by movement disorders clinicians from the five continents.

METHODS

Survey Design

The RMDSG developed a 21-question online survey (Supplementary Material), which was e-mailed to all 7815 members affiliated with the International Parkinson Disease and Movement Disorder Society (IPMDS). Responses were anonymous. The survey was launched with an introductory rationale and instructions. Data collection occurred over a 3-month period from May 9th 2018 to July 10th 2018, with two reminder emails [8].

The survey included questions addressing the ease of access to general practitoners, general neurologists, movement disorders neurologists, paediatric neurologists, geneticists and genetic counsellors. It was inquired whether genetic testing for various types diseases manifesting with movement disorders (dystonias, parkinsonian disorders, choreas, cerebellar ataxias, hereditary spastic paraplegias (HSP), metabolic disorders and other genetic disorders) was offered. In addition to access to disease-specific tests, the availability of WES was evaluated. Finally, a set of answers explored access to geneticist consultation to interpret ambiguous genetic test results, the availability of a genetic national network, and the means of funding for genetic testing.

To assess geographic variability, 7 regions were defined: North America, Central (including Caribbean) and South America, Europe, Middle East, Africa, Asia and Oceania. This study did not require approval of an ethics committee nor informed consent, as no human subjects or human biological material was used, and only the anonymous responses to the survey were analyzed [9].

Statistical analysis

We used descriptive statistics to summarize demographics, means, and standard deviations for continuous variables, as well as frequencies and proportions for categorical variables. Differences between groups of quantitative data were assessed by Student's t-test and ANOVA as required. Differences between proportions were explored through the use of the Chi-squared test (Yates corrected). Conditional on significant p-values, post-hoc chi-square tests were applied to compare frequencies distribution between each region respectively with Europe and North America, which were also compared between each other (total of 11 comparisons for each variable); accordingly, Bonferroni's correction was applied, and significance level was set at $p \leq 0.004$. Access to and availability of different resources (e.g. access to practitioners; availability of genetic testing, etc.) were expressed in terms of rate ratios. Accessibility to general practitioners (GPs) and access to chorea testing were taken as the references in the calculation of the rate ratios mentioned above. The Katz logarithmic method was applied to calculate the 95% confidence interval corresponding to each of these rate ratios. Statistical significance was set at $p \leq 0.05$ level.

DATA SHARING

The data of this study are available from the corresponding author upon reasonable request.

RESULTS

Demographics

1269 surveys were received from 109 countries from all continents, resulting in an overall response rate of 16%. Most of respondents practiced in Europe, Asia, and North America (North America = 228; Central-South America = 167; Europe = 382; Africa = 72; Asia = 237; Oceania = 28; Middle East 45). The country of practice was not indicated by 110 respondents and their surveys were not included in the analysis comparing world regions. 75% of respondents answered all questions. The majority of respondents identified themselves as movement disorders specialists (n=877; 76%) (Supplementary Table 1). Movement disorders specialists represented >50% of participants in each region, with Europe having the highest percentage (> 85%). More than 50% of respondents spent their practice seeing patients with movement disorders. 39% practiced in a university setting, 26% in a combined (private practice/university setting), 21% in a government setting, 10% in private practice, and 4% in another setting.

Access to health care professionals and genetic testing

Access to a geneticist or genetic counsellor was often challenging or absent. Rate ratio analysis, taking general practitioners (GPs) as reference, showed that genetic specialists were 25-33-fold less accessible than GP (Supplementary Table 2).

When analyzing different regions (easy vs challenging/no access) (figure 1A), challenging/absent access to general neurologists was more frequently reported by respondents from Africa, Asia, Central/South America and Oceania compared to Europe and North America. Access to movement disorders and pediatric neurologists (figure 1A) as well as to geneticists and genetic counsellors (figure 1B) was more frequently reported to be challenging/absent in Africa, Asia, Central/South America and Middle East compared to Europe and North America. Overall, Africa and North America represented the two extremes for access to movement disorders and pediatric neurologists.

Genetic testing was offered in the institution of 46% of respondents. For 68% genetic testing was available in their city and for 87% it was available in their country.

Overall, availability of genetic testing was low, with rate of access lower than 50%. Genetic testing for chorea was the most commonly available (408/943, 43%), followed by ataxias (373/931, 40%), dystonias (310/894, 35%), parkinsonian disorders (320/939, 34%), metabolic disorders (296/887, 33%), HSP (244/900, 27%) and other movement disorders (193/867, 22%). There was significantly lower access for all other tests relative to chorea ($p<0.0001$) (Table).

Genetic testing was more accessible in Europe and North America, with a significant imbalance in the availability with respect to the other regions, except for chorea testing (Figure 2). The lowest values for access were reported in Africa for dystonia testing (1%) and the highest for parkinsonisms testing in North America (53%). For parkinsonisms, dystonias, ataxias, HSP and metabolic disorders, there was significantly limited access to genetic testing in Africa, Asia, Central-South America compared to Europe and North America ($p<0.004$ for all comparisons). Genetic testing for dystonias ($p=0.002$) and metabolic disorders ($p<0.0001$) was more frequently available in Europe compared to North America (Figure 2). For any other genetic testing (as per question 10 of the survey), respondents from Europe reported more frequently access compared to all regions including North America ($p<0.004$ for all comparisons). Fewer than 5% of respondents from Oceania and the Middle East could access testing for chorea, dystonia, ataxia, HSP and metabolic disorders. However, due to the small sample size of these groups, differences with Europe and North America were not statistically significant.

Access to WES was reported by only 23% (208/885) of respondents and was significantly more accessible in Europe and North America compared to Africa, Asia, Central/South America and Middle East ($p\leq0.004$) (Figure 3).

Only 30% of respondents reported that they had easy access to expert genetic interpretation of ambiguous results, with significant variations across regions ($p<0.0001$). All regions, except Oceania, had more challenging access to genetic consultation compared to Europe and North America (Figure 4A). Moreover, 37% of respondents reported that there was a

national network for genetic testing in their country, and 44.2% of these were from Europe (Figure 4B).

Financial barriers to genetic testing

Testing was reported to be available for free for individuals who could not afford it, only by 31% of the respondents. In most cases (58%), genetic testing was covered by either private or public funding (due to overlapping payment mechanisms), followed by research funding (16%), private funding (14%), public funding (9%). The source of funding was unknown for 4% of respondents.

With respect to the source of funding for genetic testing, there were no significant differences between Europe and North America and each one of the other regions (Figure 5A). Often, in each region, genetic testing was supported by a mixture of private and public funding. Yet, in Europe, genetic testing was free of charge according to 63% of respondents. In North America, Africa, Central/South America, Asia and Middle East access to free of charge genetic testing was by far significantly lower compared to Europe (Figure 5B).

DISCUSSION

Over the last decade, major advances in gene identification have led to the delineation of hundreds of variants linked to many diseases manifesting with movement disorders [10]. Genetic diagnosis can be relevant for symptomatic treatment [11], for prognosis and for family counselling, as in Huntington's disease (HD). Moreover, although being far from genotype-specific treatment options [12], experimental trials targeting the products of gene abnormalities are currently ongoing in HD [13] and Parkinson's disease associated with glucocerebrosidase [14] or LRRK2 variants [15]. However, despite the increasing availability of modern genetic tests which allow simultaneous testing of many gene variants at a lower cost compared to traditional individual gene tests, there is minimal access to genetic testing in clinical practice at the worldwide level for the majority of movement disorders.

This survey, designed by the RMDSG, identified major challenges in accessing genetic testing in clinical practice. Main challenges were related to the availability of testing and access to specialist health professionals with expertise in interpreting a specific test result. Yet, funding modality was also a significant limiting factor.

Despite growing numbers of gene variants reported to be associated with childhood and adulthood onset movement disorders [16], access to geneticists and genetic counselling was limited in all regions compared to Europe and North America. However, even in these relatively resource-rich areas, more than 50% of respondents experienced such challenges. When considering genetic testing for specific movement disorders, inequality of access was striking, except for chorea testing, for which access was more uniform across regions, albeit at low values. The broad availability of testing for HD explains this result, given the rarity of the other genetic choreas and also considering the HD gene was the first gene discovered in people with movement disorders [17]. Specifically, responses from Africa, Asia and Central/South America reflected the lack of access to genetic testing for all other movement disorders, compared to Europe and North America. The level of access to genetic testing did not necessarily mirror the response rate in each region, as the number of respondents from Asia and Central/South America was comparable to North America. Lack of access to genetic testing for different movement disorders was also reported in Oceania and the Middle East, but comparisons did not reach statistical significance. Data from these regions should be interpreted cautiously, given the small number of respondents that did not allow meaningful comparisons.

A similar result, highlighting differences between Europe and North America and the rest of the world, was obtained when inquiring about WES. This technology involves sequencing of the protein coding regions of the whole human genome, which requires a high level of expertise and bioinformatic resources for deidentified data processing and storage. More importantly, interpretation of genetic data and correlation with the clinical phenotype demands a mutual exchange of clinical and genetic information [18]. The interaction between the neurologist and the neurogeneticist is crucial for the interpretation of WES results, specifically in case of variants of unknown significance, secondary or unexpected findings. Also, WES might fail in detecting copy-number variants and repeat expansions [19] and negative results require careful discussion with expert professional figures. However, despite technological developments, we demonstrated poor access not only to geneticists or genetic counselors, but also to movement disorders specialists and pediatric neurologists in

most of world regions compared to Europe and North America. More importantly, in case of ambiguous results from genetic testing, access to geneticists was reported challenging or not available in Africa, Asia, Central/South America and Middle East compared to North America and Europe.

Over the past years, scientific societies have promoted a series of initiatives to assist clinicians when dealing with genetic disorders such the Movement Disorder Society Genetic mutation database (MDSGene) [16, 20]. This instrument includes data on more than 1651 different mutations from 6628 movement disorder patients extracted from 1250 publications [13] and is constantly being updated. Such databases provide aids to clinical diagnosis, especially when genetic consultation is not available to discuss results. There are many other resources which could be developed to improve access to genetic testing, including development of national or international genetic networks which might produce a guide on how to approach genetic diagnosis, from listing available certified laboratories to harmonizing next generation sequencing panels for specific disorders.

In addition to the lack of genetic expertise in different regions, financial/economic barriers also play a significant role in inequality of access. Whereas the majority of European respondents reported that genetic testing was performed for free, this was not the case for the other regions, including North America. Specifically, this region encompassed Canada and United States, which have, respectively, a public- and insurance-based healthcare system. Higher per capita income and health insurance coverage might explain why United States respondents reported more access to genetic testing. It is critical to improve availability and to promote lower costs for testing, in addition to improving access to expert interpretation of test results.

Our results revealed inequality of access to genetic testing at a worldwide level and overall a challenging access in more than half of cases for all types of testing, even in Europe and North America. These results are consistent with a survey promoted by the European Reference Network for Rare Neurological Diseases (ERN-RND) [21]. This survey collected responses from 80 European experts in atypical parkinsonism, dystonias/paroxysmal dyskinesia, HSP and ataxia, choreas. Similar to our data, whereas access to chorea testing

was available in European countries, genetic investigations for HSP/ataxia and dystonia were difficult to access.

The data presented here expand previously reported findings and provide novel data about genetic testing accessibility in different world regions obtained from a large sample of respondents (1269 from 109 countries). Online surveys are a generally accepted investigational method [22], with many advantages, including the opportunity to access a large sample of individuals, cost-efficiency, automation and real time access, and convenience for respondents**.** The limitations of this method include sampling methods, accuracy, ambiguity when interpreting some questions and the inability to properly validate the provided information [23]**.** The estimated average response rate for online surveys is highly variable, ranging from 20-30%, and the minimum acceptable response rate still under discussion in the literature. Our survey had a good worldwide representation (respondents from 109 countries) with an overall response rate of 16.2%. This rate is higher compared to a recent survey paper on functional movement disorders administered to IPMDS members (864 responses out of 7689 members from 92 countries, 11% response rate) [24].

In conclusion, our survey paper explored availability and accessibility of genetic testing for movement disorders worldwide, highlighting frequently challenging access but also major inequalities between Europe and North America and the rest of the world. Future studies will help to identify the real and practical needs for advances in diagnosis, testing, and potential interventions in movement disorders, possibly by the creation of effective collaborative international networks.

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APPENDIX:

International Parkinson Disease and Movement Disorder Society Rare Movement Disorders Study Group (in addition to the authors):

Alberto Albanese, Ignacio Amorin, Kailash Bhatia, Melanie Brandabur, Francisca Canals, Francisco Cardoso, Adriana Cardozo, Vanessa Carvalho, Anabel Chade, Pedro, Alejandra Chana Darling, Leonor Correia Guedes, Andrés De la Cerda, MAJ de Koning-Tijssen, Marcus V Della Coletta, Antoine Duquette, Alberto Espay, Jose Etcheverry, Joaquim Ferreira, Jennifer Friedman, Victor Fung, Christos Ganos, Pedro Garcia Ruiz, Oscar Gershanik, Kenneth B.V. Gross, Kim Han-Joon, Joseph Jankovic, Ruyji Kaji, Katya Kotschet, Andres Lescano Da Rosa, Irene Litvan, Naomi Lubarr, Massimo Marano, Maria Josep Martí, Daniel Martinez Ramirez, Janis Miyasaki, Alexander Münchau, Daniela Muñoz Chesta, Pramod Pal, María Cecilia Peralta, Nicolás Phielipp, Giulietta Maria Riboldi, María Cruz Rodríguez Oroz, Federico Rodriguez-Porcel, Harini Sarva, Ludger Schoels, Maria Stamelou, Claudia Uribe Roca.

LEGENDS TO FIGURES

Figure 1. A) Access to general neurologists, movement disorders (MDS) neurologists and pediatric neurologists in different world regions. B) Access to geneticists and genetic counsellors in different world regions. *significant differences compared to Europe, p≤0.004. #significant differences compared to North America, p≤0.004. Number or respondents for each item are shown in x-axis.

Figure 2. Access to genetic testing for parkinsonism, chorea, dystonia, ataxia, hereditary spastic paraplegia (HSP), metabolic disorders across world regions (question #10: Do you or your institution offer any of the following genetic testing?). *significant differences compared to Europe, p≤0.004. #significant differences compared to North America, p≤0.004. §significant difference between Europe and North America, p≤0.004. Number or respondents for each item are shown in x-axis.

Figure 3. Poor access to whole exome sequencing (WES) in all world regions compared to Europe and North America. *significant differences compared to Europe, p≤0.004. #significant differences compared to North America, p≤0.004. Number or respondents for each item are shown in x-axis.

Figure 4. A) Access to geneticists in case of ambiguous genetic test results. B) Presence of national genetic networks. *significant differences compared to Europe, p≤ 0.004. #significant differences compared to North America, p≤0.004. Number or respondents for each item are shown in x-axis.

Figure 5. A) Modality of funding for genetic testing for movement disorders across world regions. B) Access to free-of-charge genetic testing in different world regions. *significant differences compared to Europe, p≤0.0001. Number or respondents for each item are shown in x-axis.

ETHICAL COMPLIANCE STATEMENT

Ethic Committee approval was not required for this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CONFLICT OF INTERESTS

This study did not receive any industry funding.

FULL FINANCIAL DISCLOSURE FOR THE PREVIOUS 12 MONTHS

Martin Cesarini had received research funding from Roche – CHDI foundation ENROLL HD.

Giovanni Cossu: Speaking honoraria from UCB Pharma, Bial, AbbVie, Zambon, Boston. Research support from "Fondazione di Sardegna".

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AUTHORS CONTRIBUTION:

Emilia M Gatto: 1C, 1B, 2C, 3A, 3B

Ruth H Walker: 1C, 1C, 2C, 3B

Claudio Gonzalez: 1C, 2A, 2B, 2C, 3VB

Martin Cesarini: 1C, 2B, 3B

Giovanni Cossu: 1C, 3B

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Mayela Rodriguez Violante: 1B, 1C, 3B

Joseph Jankovic: 1C, 3B

Francesca Morgante: 1C, 2A, 2B, 2C, 3B

H. A Jinnah: 1C, 2A, 2B, 2C, 3B

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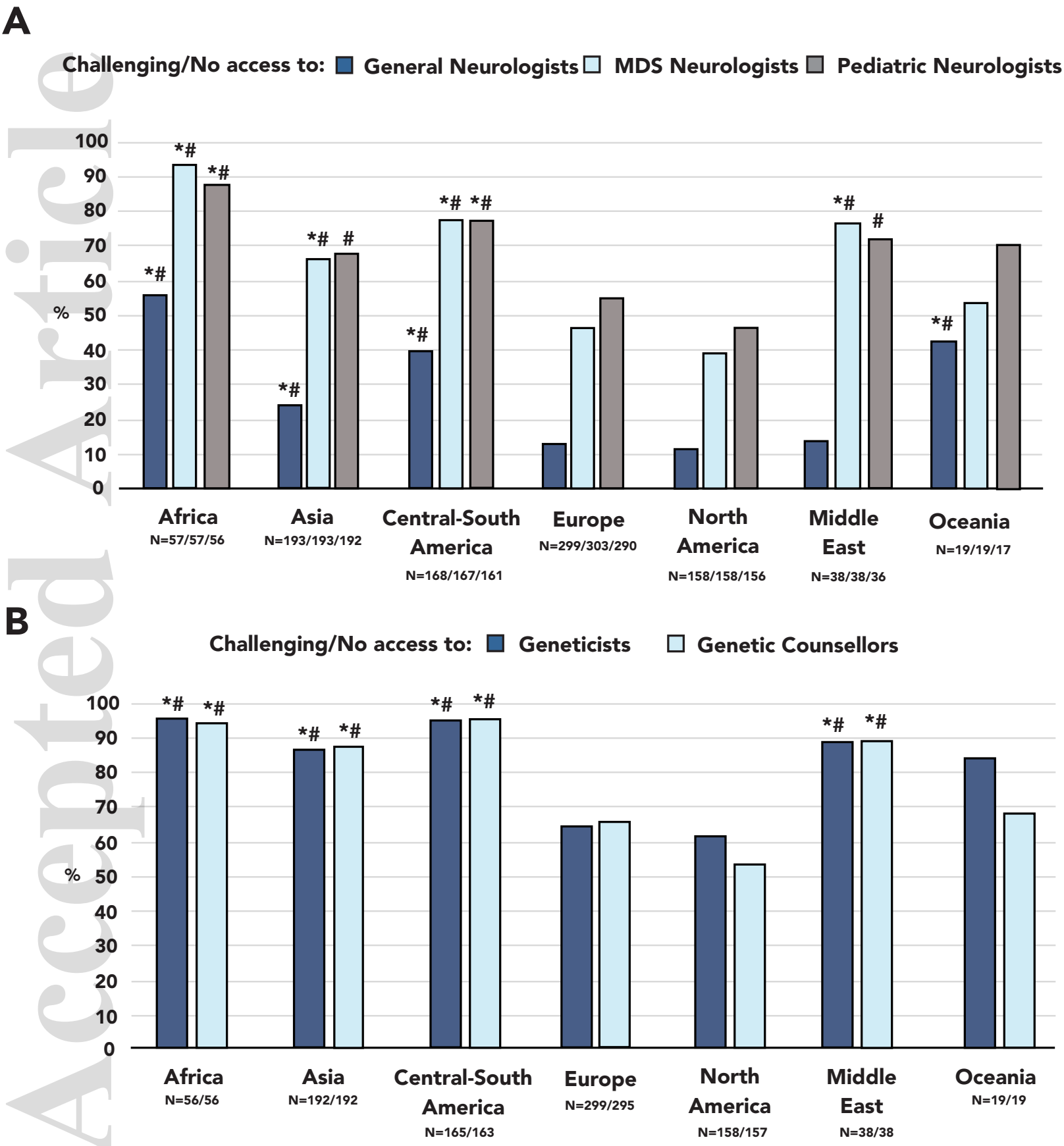
Table: Relative availability of genetic tests as compared with Chorea

DISORDER	RATE RATIO	95% CI (KATZ)
CHOREA (REFERENCE)	1.00	----
METABOLIC DISORDERS	1.02	0.94-1.11
ATAXIAS	1.05	0.97-1.15
DYSTONIAS	1.14	1.05-1.24
OTHER GENETIC TESTS	1.19	1.09-1.28
PARKINSONIAN DISORDERS	1.19	1.10-1.28
HEREDITARY SPASTIC PARAPARESIS	1.23	1.14-1.33
WHOLE EXOME SEQUENCING	1.26	1.17-1.37

Rate ratios and 95% confidence intervals (95% CI). Chi^2: $p<0.0001$ – Linear trend $p<0.0001$.



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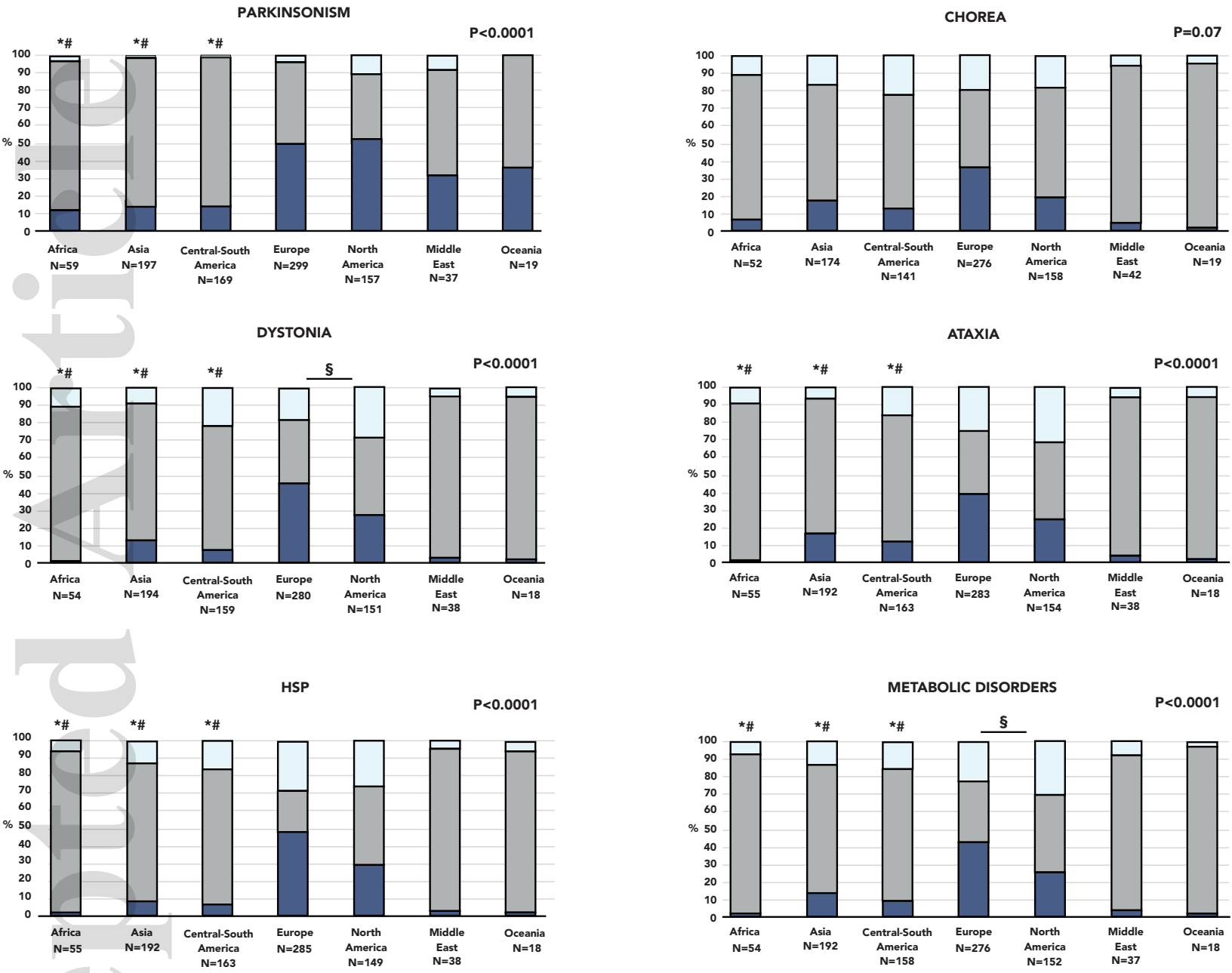

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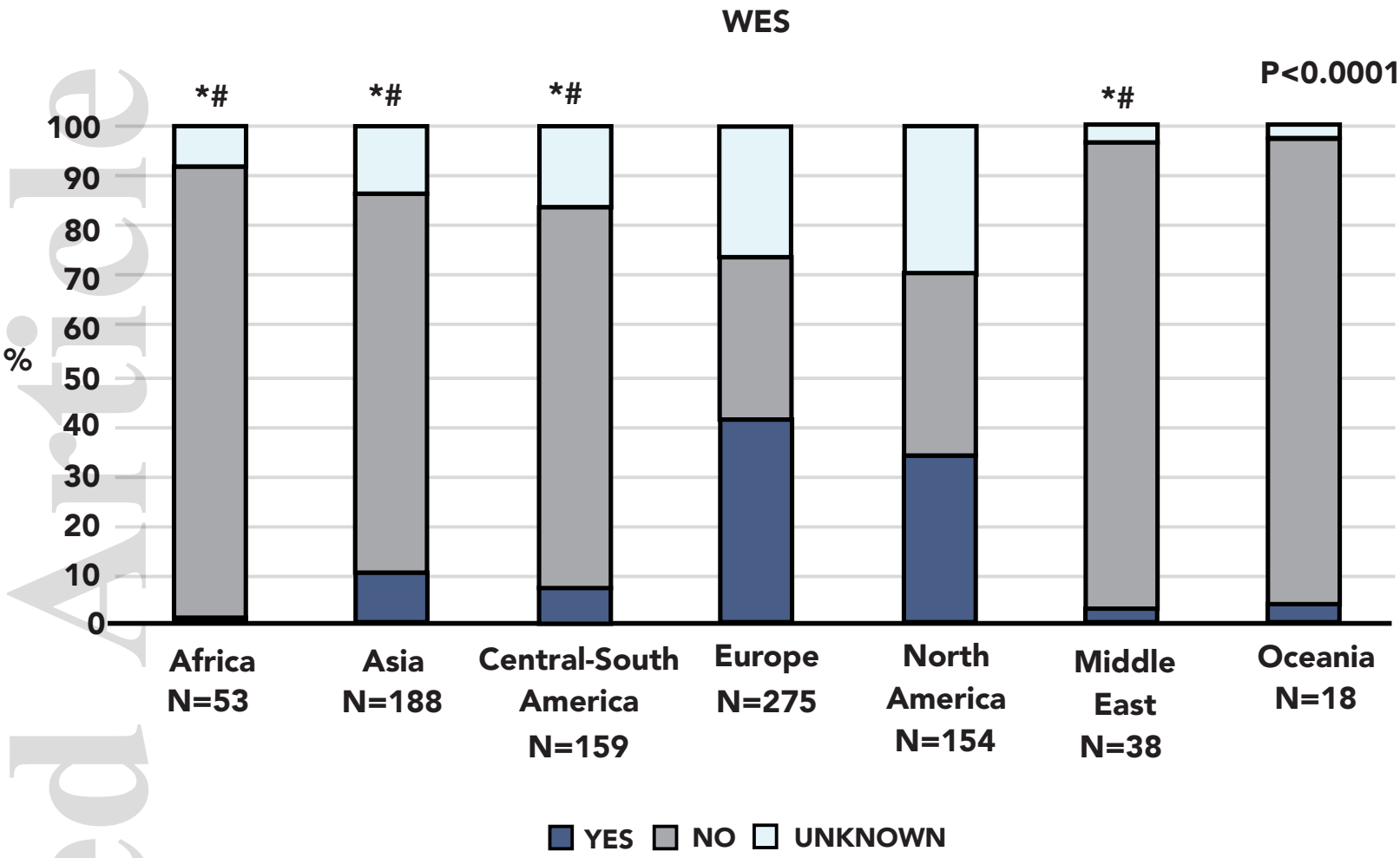

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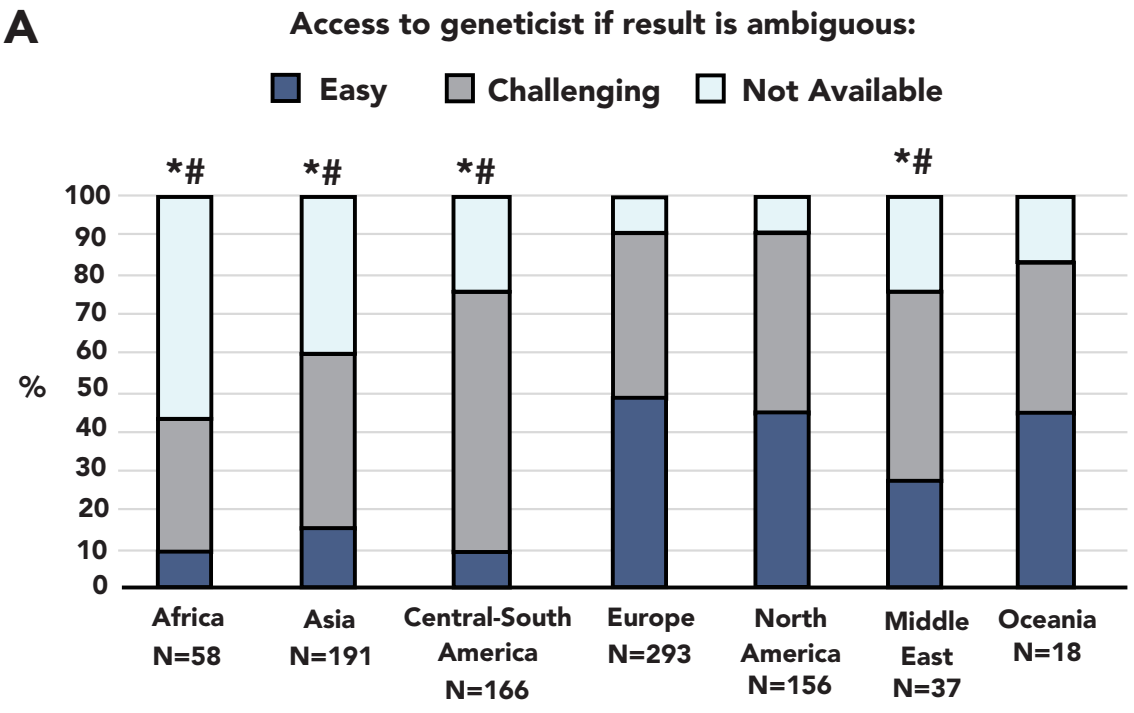

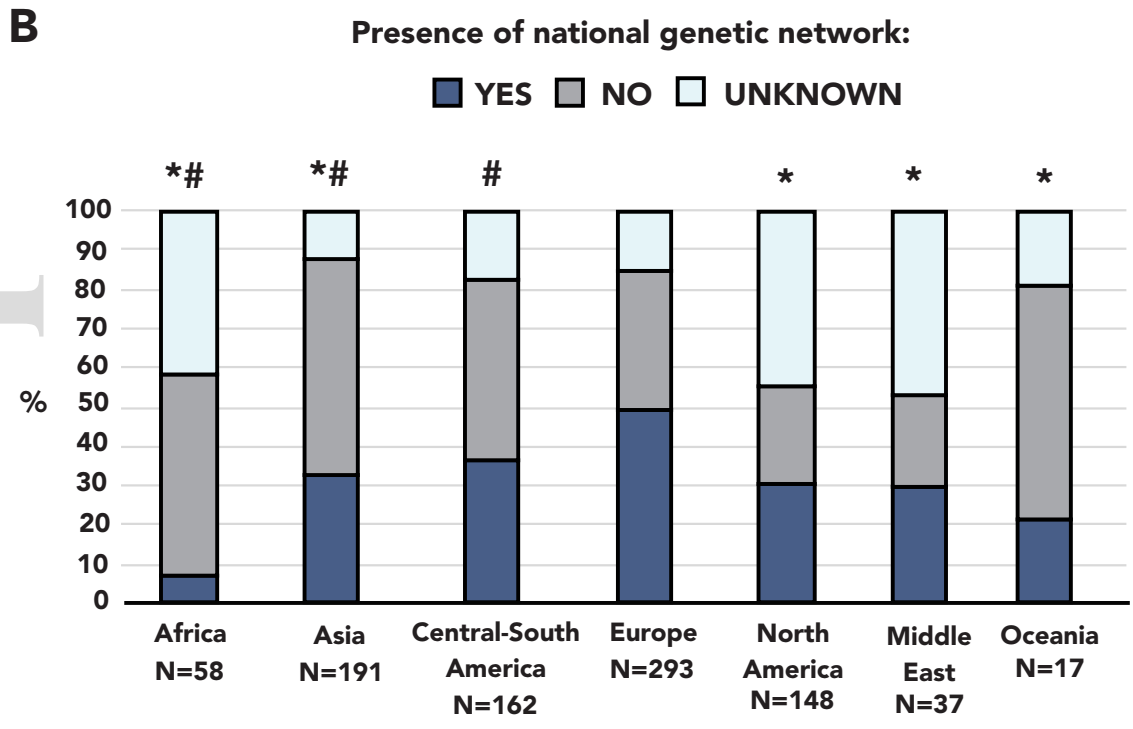

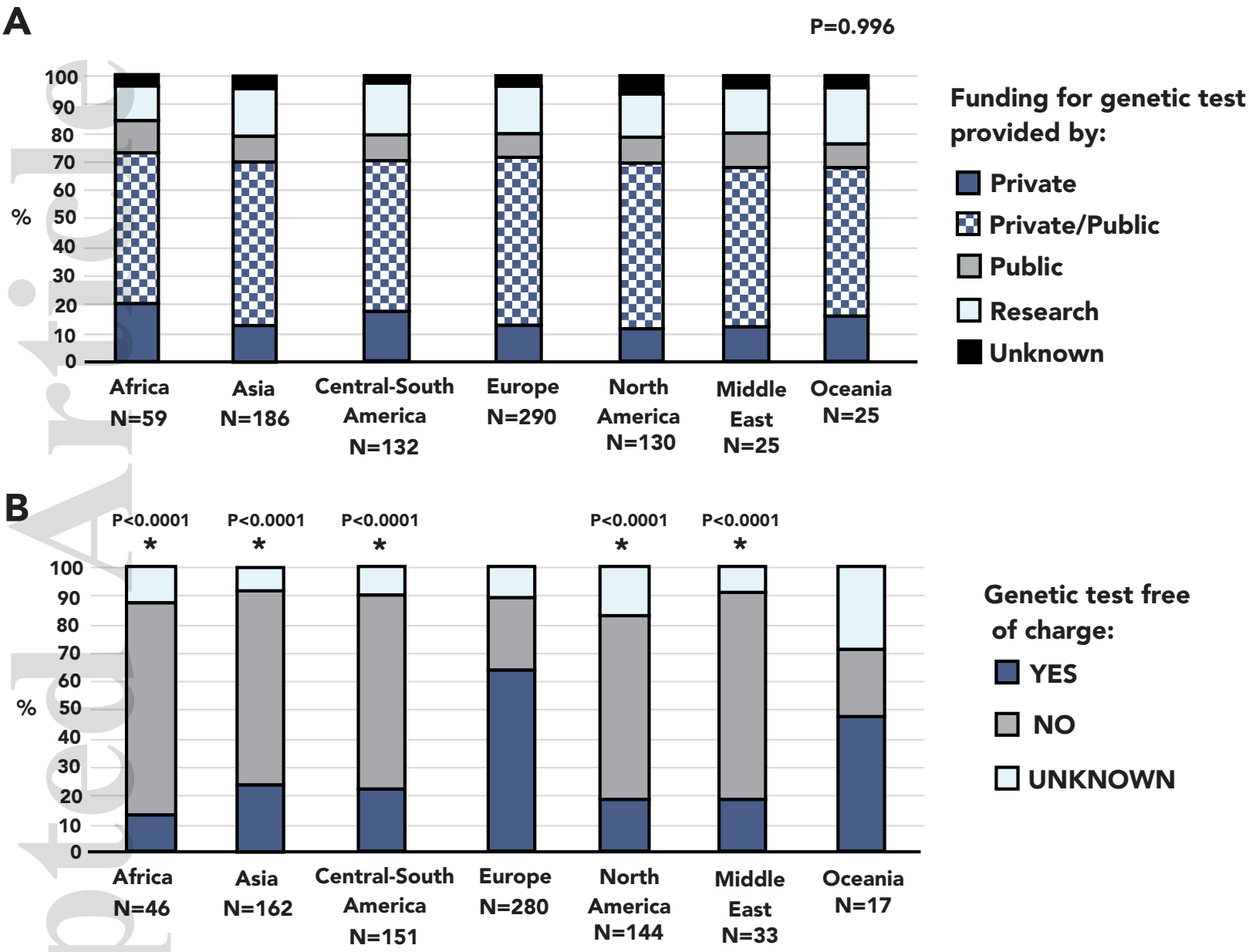

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