Using global team science to identify genetic Parkinson's disease worldwide

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Word count:

Number of characters in the title: 75

Number of words article: 1170

Number of figures: 2

Number of color figures: 0

Number of tables: 1

Supplement: 2 items

Talks on rare diseases in the field of neurology often start with a statement like this: “About 80% of all rare diseases have a neurologic manifestation and about 80% of those are genetic in origin”. Although these numbers probably represent more of an estimate than well-documented evidence, rapidly advancing and cost-effective sequencing technologies have led to the quickly growing identification of patients with hereditary neurological diseases. While the importance of genetics for diagnosis and genetic counseling is undisputed, the recent development of first gene-targeted therapies entering clinical trial[1,2] is adding an important new layer to the (re-)consideration of genetic testing in neurology. However, establishing accurate genotype-phenotype and genotype-treatment relationships requires large sample sizes. Systematic reviews can serve as instruments to combine information from several small samples, but unfortunately, this is often complicated by inconsistent and incomplete reporting of clinical and genetic data across studies. Thus, large multi-center approaches are necessary to systematically and uniformly characterize patients with genetic neurologic conditions and to eventually establish sizable clinical trial-ready cohorts.

Using genetic Parkinson’s disease (PD) as an example and Illustrating the magnitude of the issue, up to ~300,000 patients worldwide are estimated to have hereditary forms of PD, representing 5% of an estimated total of 6 million patients with PD in 2018[3]. Monogenic forms of Parkinson’s disease (PD) can be caused by mutations in *SNCA, LRRK2, VPS35, Parkin, PINK1,* and *DJ1*[4]. These genes have been unequivocally linked to PD according to the criteria established by the International Parkinson and Movement Disorder Society Task Force on Genetic Nomenclature in Movement Disorders[5]. In addition, *GBA* variants represent the strongest known genetic risk factor for PD, with an age-dependent penetrance of ~30% at the age of 80 years[6]. However, *individual* clinical information for patients with genetic PD is only

reported for a fraction of cases (n=1,769; Movement Disorder Society Genetic mutation database; MDSGene, www.mdsgene.org) in the international medical literature and publications are often biased towards unusual presentations of gene mutations. Both clinical expression and penetrance of gene mutations may vary considerably across different populations and ethnicities[7,8], further challenging pooling of data and their interpretation. Finally, given the growing availability of diagnostic genetic testing and the increasing difficulty to publish case reports of mutation carriers in peer-reviewed journals, we expect the proportion of published vs. unpublished cases to rapidly shift towards the latter.

As a result, neurologists commonly lack reliable reference data to be able to offer tailored counseling and treatment to patients with genetic PD and other hereditary neurological diseases.

Since the 1990s, there has been a growing interest and investment in large-scale, team-based research initiatives to address complex and multifaceted problems that require collaboration across *different* disciplines[9]. Likewise, there is an increasing necessity for – ideally global-scale - team science approaches of clinicians and researchers with *similar* interests joining forces to promote advanced research and to improve patient care. Employing novel ways of team science, electronic databases, and global communication, we performed a worldwide survey of genetic PD with an emphasis on availability of demographic, clinical, omics and imaging data as well as of biomaterials, to both foster and exploit global collaboration. In order to identify possible participants for our survey, we compiled the names of corresponding authors from articles included in the Movement Disorder Society Genetic mutation database (MDSGene, www.mdsgene.com) that comprises the following PD genes: *SNCA*, *LRRK2*, *VPS35, Parkin*, *PINK1*, and *DJ1*[7,8]. For *GBA*,

we screened the literature according to MDSGene criteria to identify corresponding authors of eligible articles (articles published in English with clinical information available). In addition, the "Genetic Epidemiology of Parkinson's disease" consortium (https://geopd.lcsb.uni.lu) contributed names of members not already identified as a corresponding author of publications represented in MDSGene. Additional contacts were included upon recommendation of participants (Figure 2). We next developed an online survey and invited the previously identified researchers to report availability of information on their genetic PD patients. To avoid multiple reporting of the same cases, we asked participants to indicate sharing of samples and encouraged participants from the same center to nominate one person to report all cases or to divide up the cases between reporting researchers. The survey was open for contributions for 5 weeks from March until May 2018. Two rounds of email reminders were sent out after two weeks each to enhance the response rate. Participants received no financial compensation for their contribution.

A total of 103 researchers from different centers in 43 countries reported n=8,453 PD patients with mutations in PD genes (Figure 1, for more details please see Supplementary Table 2). The overall response rate to our invitation was 45% and 79% of the respondents completed the survey. Of these, 98% indicated their interest in further collaboration, and 45% sent personal emails expressing their interest to contribute further to this project and/or suggesting additional collaborative projects (Figure 2). Reflecting the worldwide distribution of participating centers, the backgrounds of the reported patient samples were diverse and include Arab, Asian, Ashkenazi Jewish, Caucasian, Hispanic, Indian, Mennonites, and North African. Almost equal numbers of patients (n=~3000) were reported to carry mutations in *LRRK2* or a *GBA* risk allele, followed by pathogenic variants in *Parkin* (n=~1500), *SNCA* and *PINK1* (n=~250 each), *DJ1* and *VPS35* (n=~30 each). The total number of reported monogenic

PD cases in the present study exceeds published cases by a factor of 2.6 (n=5,299 vs. n=2,064 cases (www.mdsgene.org), both excluding *GBA*) indicating that the majority of patients with genetic PD are not reflected in the published literature. Regarding data quality and completeness, information on PD nonmotor signs is particularly scarce in the literature. Even for cognition, published information is available only for about a third of the cases with monogenic PD (www.mdsgene.org)[7,8]. In contrast, our present approach indicates availability of nonmotor signs in general for two thirds of the reported cases (Table 1).

To fill these knowledge gaps, a new collaborative mindset is indispensable. Our worldwide collaborative effort revealed an unprecedented level of data completeness, a paramount prerequisite when aiming to perform meaningful genotype-phenotype correlations and when selecting patients for clinical studies and trials[7,8]. Team science of clinicians and researchers in the field of rare neurological diseases will facilitate sharing of expertise, promote new research opportunities, offer a network to foster new training opportunities for young researchers, and, advance development of individualized therapies. As a future perspective, collecting very large cohorts of monogenic PD may result in powerful enough data sets to perform meaningful natural history studies of individual monogenic forms as well as modifier studies. These can be modeled after studies performed in well-characterized longitudinal cohorts unselected for genetic cause[10]. In a similar vein, our approach may be expanded to mutation-negative early-onset PD patients with a positive family history in order to uncover rare novel mutations.

Based on the enthusiastic responses to our survey and the eager willingness to collaborate, we are confident that we have successfully established a team science approach that will specifically enable i) successfully increasing sample sizes of patients with rare neurological

diseases; ii) leveraging neurology expertise globally; and iii) fostering team science among neurologists worldwide.

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Acknowledgments

Michael J. Fox Foundation: EJV, HM, CK

German Research Foundation FOR2488: NB, KL, MK, CK

Author contributions

A full list of all authors contributing to this manuscript can be viewed in Supplementary Table 1. EJV and CK were responsible for the conception and design of the study; EJV, CK and MK conducted the analysis and interpretation of the data; EJV and CK drafted the manuscript; all authors and the members of the MJFF Global Genetic Parkinson's Disease Study Group contributed to the acquisition of data and to the revision of the manuscript.

Conflicts of interest

The authors have no conflict of interest to declare.

Figure 1: Worldwide centers reporting patients with monogenic PD and PD patients with variants in GBA.

Legend: Please find a detailed list of the participating members of the **MJFF Global Genetic Parkinson's Disease Study Group** in Supplementary Online Table 1.

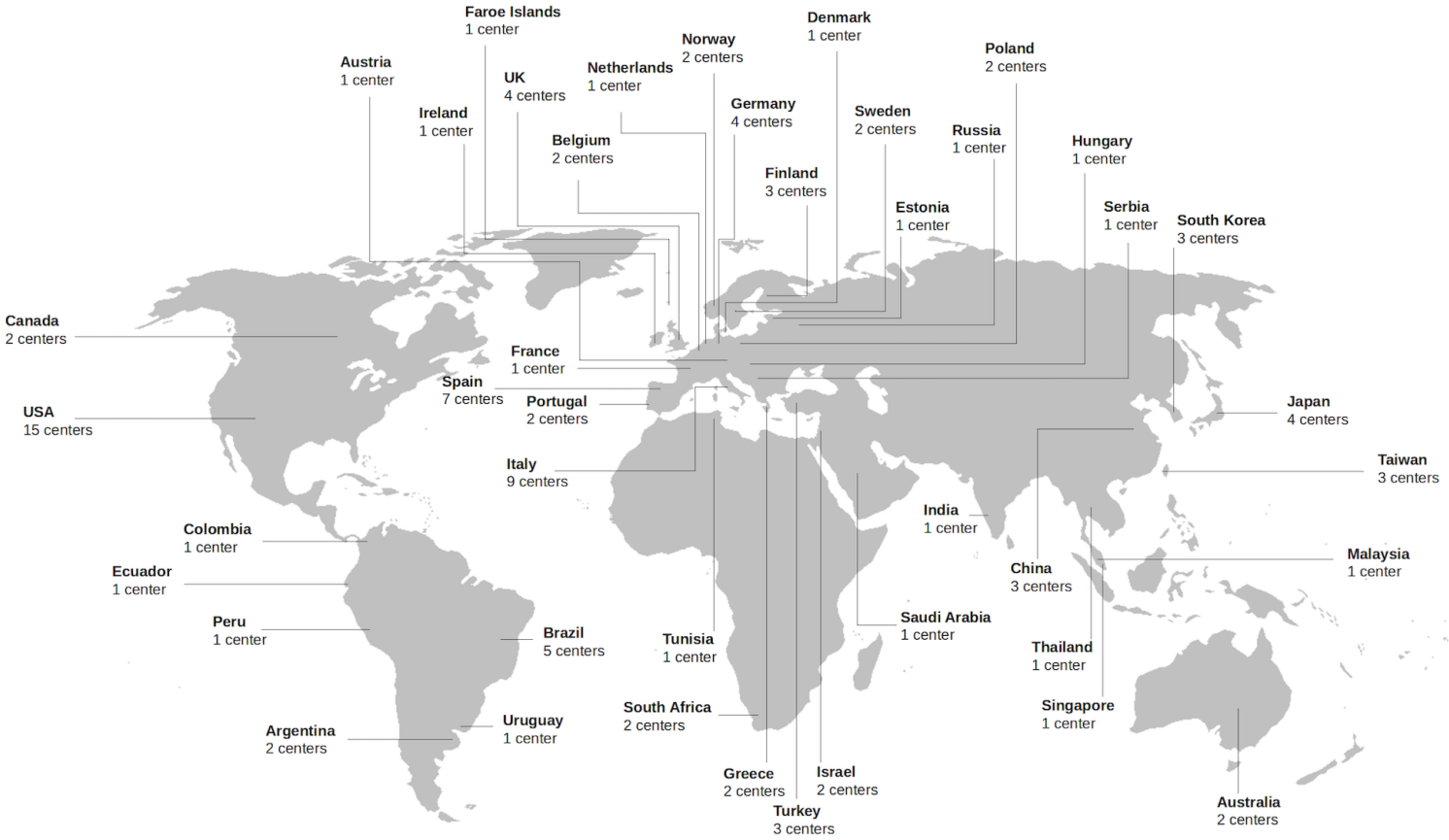

Figure 2: Response analysis.

Legend: *publications on GBA were screened according to the MDSGene protocols.

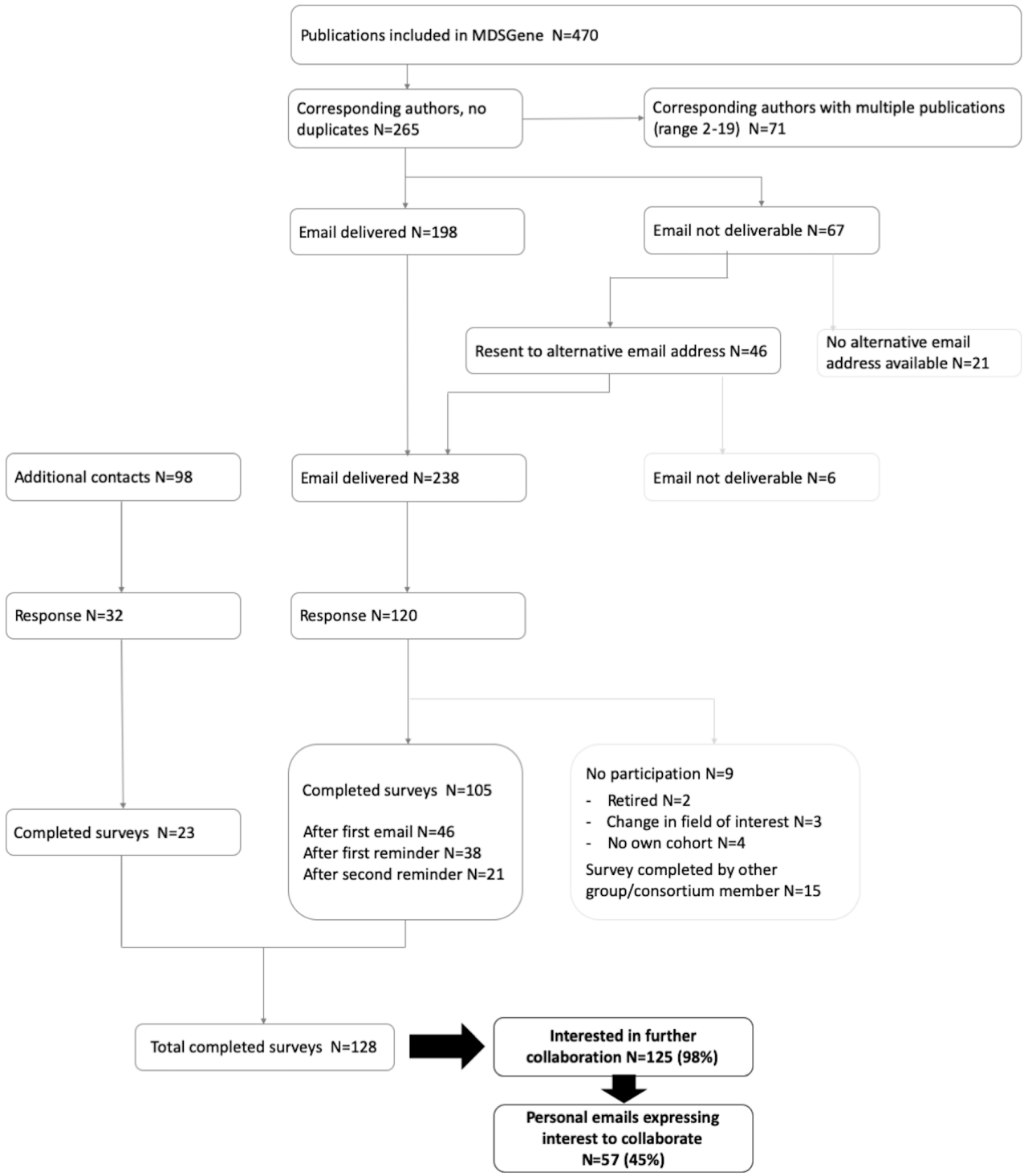

Table 1: Availability of information.

Legend: The participating centers were asked to report availability of an item if the relating data was available for at least a subset of the reported PD patients registered at their center.

	number of centers reporting available information (percentage of total participating centers (n=103))
Age	102 (99%)
Sex	102 (99%)
Ethnicity	101 (98%)
Pedigree	94 (91%)
Age at onset	97 (94%)
Unified Parkinson Disease Rating Scale (UPDRS)	68 (66%)
Hoehn & Yahr Scale	75 (73%)
Dopaminergic medications	79 (77%)
Nonmotor signs	68 (66%)
Environmental exposures	48 (47%)
Life style variables	36 (35%)
Treatment response	76 (74%)
Omics data	17 (17%)
-Genomics	14 (14%)
-Transcriptomics	2 (2%)
-Proteomics	1 (1%)
-Metabolomics	1 (1%)
Imaging	38 (37%)
-MRI	33 (32%)
-SPECT/PET	19 (18%)
-TCS	7 (7%)
DNA	88 (85%)
RNA	22 (21%)
Serum	28 (27%)
Plasma	26 (25%)
Whole blood	23 (22%)
Cerebrospinal fluid	8 (8%)
Fibroblasts	12 (12%)
iPSCs	11 (11%)
Brain tissue	11 (11%)

Supplement

Supplement 1: The MJFF Global Genetic Parkinson's Disease Study Group

Supplement 2: Number of centers and reported genetic PD patients

Supplement 1: The MJFF Global Genetic Parkinson's Disease Study Group

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Supplement 2: Number of centers and reported genetic PD patients

Legend: In total, 103 centers shared numbers of available genetic PD patients (listed in the table), and additional 5 centers completed the survey but did not indicate numbers. Researchers were asked to report all PD patients with mutations in one of the listed genes that were registered at their center. Whether these patients are still available for future studies was not assessed, but given the fact that the genes of interest were all described within the last two decades, the proportion of historic cases included in these numbers should be relatively low.

*Mutations in GBA are considered risk variants for PD. The same applies to certain mutations in LRRK2 in the Asian population (e.g. G2385R), which we did not specifically assess in our survey, but which centers may have included in the reported numbers.

	centers	DJ1	GBA*	LRRK2*	Parkin	PINK1	SNCA	VPS35
Argentina	2	0	0	10	1	0	0	0
Australia	2	0	0	19	11	3	2	4
Austria	1	0	30	1	6	1	0	3
Belgium	2	0	12	43	1	0	1	0
Brazil	5	0	26	39	34	2	1	0
Canada	2	2	34	328	65	62	65	3
China	3	5	90	330	264	10	0	5
Colombia	1	0	13	3	12	0	0	0
Denmark	1	0	0	0	2	0	0	0
Ecuador	1	0	1	0	0	0	0	0
Estonia	1	0	15	25	5	0	1	5
Faroe Islands	1	0	0	1	0	0	0	0
Finland	3	0	15	2	2	0	2	0
France	1	2	124	189	145	19	27	5
Germany	4	1	119	20	23	12	2	2
Greece	2	0	38	1	3	0	77	0
Hungary	1	0	3	1	0	0	0	0
India	1	0	6	2	5	3	0	0
Ireland	1	1	21	2	25	1	0	0
Israel	2	1	240	180	1	0	0	1
Italy	9	3	227	147	117	28	22	0
Japan	4	0	65	20	293	23	19	4
Malaysia	1	0	0	200	0	0	0	0
Netherlands	1	1	15	1	3	0	1	0
Norway	2	0	35	40	5	4	0	0
Peru	1	0	20	1	1	0	0	0
Poland	2	0	0	1	42	2	2	0
Portugal	2	1	0	0	4	1	0	0
Republic of Korea	3	0	0	0	27	6	0	0

Russia	1	1	32	15	40	2	2	1
Saudi Arabia	1	1	0	0	15	4	0	0
Serbia	1	1	78	6	17	1	0	0
Singapore	1	0	20	0	0	0	0	0
South Africa	2	0	13	15	19	4	2	0
Spain	7	2	77	386	72	4	8	0
Sweden	2	2	37	14	2	0	6	0
Taiwan	3	1	27	12	30	11	0	2
Thailand	1	0	24	0	14	0	0	0
Tunisia	1	0	0	559	10	59	0	0
Turkey	3	3	2	2	36	2	2	0
United Kingdom	4	0	115	31	13	5	7	0
Uruguay	1	0	0	12	1	0	0	0
U.S.A.	15	1	1614	561	192	8	9	0