FREQUENTLY ASKED QUESTIONS (FAQS) FOR CONTRIBUTING SUSPECTED PD CASES/FAMILIES

First of all, **thank you** very much for your interest, and for taking the time to read this document.

Please note that some more **general** issues that apply to both Monogenic and Complex (Sporadic) PD (e.g., locations for sample analysis and data storage; publication strategies and authorship rules) can be found on the main GP2 homepage: https://parkinsonsroadmap.org/gp2/

1. Why refer potential monogenic cases or families to the Monogenic Portal?

Known monogenic forms of PD (e.g., those caused by pathogenic variants in single genes which are transmitted following Mendelian inheritance) account for only 5-10% of PD cases worldwide, and factors influencing penetrance, phenotypic expression and response to treatment are poorly characterized. Moreover, the spectrum of PD-related genetic variants in underrepresented populations has only been scarcely explored.

Knowledge of the genes (and their associated molecular pathways) contributing to the development and progression of PD has the potential to **advance diagnosis and treatment** for patients with PD. For example, clinical trials are now taking place for treatment of *LRRK2*- and *GBA*-related PD, with the hope of finding treatments that will modify the course of this currently incurable disease (so-called "disease modifying treatments").

A major aim of GP2 is to discover **novel genetic causes** of PD. Thus, a focus of the Monogenic Network is to investigate PD cases with **early onset** (<50 years) and/or those with a **family history** of the condition, unusual presentation, or coming from less well-studied (**underrepresented**) populations. We encourage the submission of **both patients without a genetic diagnosis** and **those already known to carry pathogenic variants** in PD genes.

For **patients**, besides the possibility of participating in clinical trials or benefiting from new treatments, knowledge of one's genetic status can provide valuable information regarding **prognosis** (likelihood of developing, or passing on, the disease; disease course; etc.), which may be helpful in life planning. Notably, **all patients enrolled** into the monogenic arm of GP2 **will undergo genotyping with the Genome Diversity Array (GDA)** which, based on its PD-related mutation custom content, will result in the identification of a sizable number of patients with known mutations in PD genes.

For **clinicians and researchers**, this project provides a great opportunity to better understand the **genetic architecture** of PD in their respective communities/countries. Other benefits of partaking in this global effort include opportunities for **scientific collaborations** and joint **publications** and grants. Contributors become **members of GP2** (a formal document of GP2 membership will be provided), and will be able to access shared (deidentified) **data** from all other GP2 collaborators worldwide, as well as **other resources**.

2. How do I contribute cases/families?

This involves a **2-step** process: Firstly, there is a **registration** step (through the web-based Monogenic Portal). This initial step requires contributors to fill in a simple **Ethics Checklist**, and upload their institutional **ethics consent form**. Once this is deemed "eligible" for data/sample sharing, Data Transfer Agreement (**DTA**) and/or Material Transfer Agreement (**MTA**) forms will need to be signed. While we recognize that this process may seem

somewhat cumbersome, we would like to reassure you that we are going to do our utmost to minimize any inconvenience and speed up the process. Importantly, this also serves to **protect your rights as a contributor**, and will need to be done **only once**.

After the above registration has been completed, the second step will be for the contributor to log in and then submit the details of cases/families using the electronic case report form (**eCRF**).

3. What happens if the patient consent form is deemed "not eligible"?

In general, to be able to participate in GP2, the consent form should include some elements regarding **data and/or sample sharing** (or at least not clearly limit their use to the specific institution at which the study was conducted). If your consent form is deemed "not eligible", the Monogenic Network in conjunction with the GP2 Compliance Group will be happy to help you prepare a new Participant Information and Consent Form to submit to your local ethics committee for prospective cases/families, and to reconsent previously recruited patients.

4. What happens after I have submitted a case/family?

In general, **all samples** will first undergo genotyping using the Genome Diversity Array (**GDA**) with custom content representing known mutations in PD genes. Samples that test negative on the GDA will be then prioritized for whole-genome sequencing (**WGS**) based on multiple factors. These include: availability of high quality **DNA**; **number of samples** from affected individuals available per family; availability of samples from both non-affected **parents**; **age** at PD onset; consanguinity; and ancestry from **underrepresented** populations (i.e., countries with "upper middle income" or below, based on the World Bank's classification of economies: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-group).

The current plan is to perform WGS in **>5,000 cases** within the 5-year duration of the GP2 project, which means that there is a **very high likelihood** for submitted cases/families that fulfill these criteria to be selected for WGS.

5. What if I have *many* potential cases/families to contribute?

In this scenario, rather than filling an eCRF for each case/family, please **directly contact** us first (contact details for the Monogenic Network secretariat are here: monogenic@gp2.org), to work out a way which may be easier and more convenient to contribute your cohort.

6. Will I be informed of the results of the genetic studies?

Yes, results will be returned to the contributor. An underlying aim of the GP2 project is to **democratize access** to, and analysis of, genetic data. However, the specific details (how, what, etc.) are still being worked out and will be updated to contributors as and when they become available.

7. Should I also refer cases/families for whom a genetic diagnosis has already been achieved?

Yes, the clinical and genotypic data, including genotype-phenotype correlations, are of significant interest and we would very much **value** such contributions.

Additional genotyping may also be done on these cases, for example, to try to understand the genetic **modifiers** of disease development and progression.

8. Will contributors be paid?

The cost of **shipping** the samples to a central laboratory, and of **genotyping and sequencing** (GDA, WGS, long-read sequencing, etc.) will be fully covered by GP2.

Small reimbursements can also be made for **patient travel**.

If you have any other query, please do not hesitate to contact Monogenic Network members.

Thank you very much again for your valuable time and contribution.

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