Parkinson disease: A complex disease comes to the clinic.

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Ten years ago, Polymeropoulos and co-workers described for the first time the existence of genetic linkage, a concept that reflects the finding of the place in the genome where a gene underlying a character is, between PD and a *locus* in chromosome 4¹. That genetic linkage was then characterized and, a year later, the underlying gene defect was identified: alpha-synuclein was the culprit of the disease in that particular family². Today, we know that familial Parkinson disease (FPD) can be caused by mutations in at least 7 known genes and, possibly, at least other 4 genes still remain to be identified. Despite the media hype surrounding all genetic advances related to this prevalent disorder, the true is that there is a huge gap between our ability to understand the aetiology of the disease in those very few families with familial Parkinson's disease and the known cause(s) of the disease in more than 90-95% of all affected individuals, those with a non-genetic PD³. But this grouping into two apparently separate worlds does not imply that these two types of PD should be considered as different entities. In effect, due to the clinical and pathological similarities existing between FPD and non-genetic, or at least non-monogenic, PD the knowledge of the genes causing the former can bring new ideas and open new doors in the research for the latter.

Moreover, the genetic influence in non-monogenic PD cannot be neglected either.

Epidemiological reports show that there is a genetic risk derived from the genetic makeup of the individuals. Thus, the risk for the disease, the response to treatment or the progression of the neurodegeneration are all factors that might be influenced by common genetic variability. In this

respect, it is worth to note that this variability, unlike that causing FPD, refers to common variants more or less extended in the normal population and that only exert their deleterious, or their protective, effect when appear in combination with other genetic or environmental factors. Thus it is obvious that the identification of genetic factors involved in the commonest form of Parkinson disease is of the outmost importance for a number of reasons, some related with our knowledge of the disease, some related to relevant clinical aspects. Amongst the latter, the possibility of performing predictive genetic testing is, possibly, the most appealing of all. Having the possibility of predicting who and, possibly, when will an individual suffer from PD and which course his/her disease will take will allow clinicians to act before the disease starts once protective therapies are in place.

This possibility, that today may be taken closer to Science fiction than to reality, is not such. In this issue of *The Lancet Neurology*, two separate studies analyze the effect of genes in non-monogenic PD. Both studies follow the initial work published a few months ago by Maraganore and co-workers⁴. In that first analysis, 13 different locations in the genome were apparently related to the appearance of PD in the populations studied by those researchers. In genetic research, almost as important as an initial description of an association between a trait of interest and a gene or a location in the genome related to that trait is the replication of that particular finding. In this respect, several papers appeared in the past cast some doubt on the consistency of the initial findings⁵⁻⁸. In this issue of *The Lancet Neurology* two collaborative studies add some interesting data to this debate. The work published by Elbaz, Nelson, Payami, Ioannidis, Fiske and colleagues is a serious attempt to replicate the finding of Maraganore and colleagues. In this work none of the original thirteen *locus* related to PD found by Maraganore and colleagues was associated with PD by Elbaz, Nelson, Payami, Ioannidis, Fiske *et al.* One of the things that makes this study interesting is the fact that, for the first time, the driving force behind the study is the funding body of the original work. The Michael J. Fox Foundation, as part of its strong commitment to finding the cause of PD, as a

mean to find its cure, asked a number of groups to put their forces together and to find out whether the initial study had found the *Rosetta stone* of the genetics of PD. On a separate work, Fung, Scholz, Matarin, Simón-Sánchez and colleagues, also failed to replicate the findings of the Maraganore *et al* work. The fact that the results of the replication did not confirmed the initial results can be seen as frustrating but, nevertheless, some interesting and helping lessons may be extracted that will help future projects of this type to be developed with higher rates of success. One of the lessons is that size is important. The genetic influence on PD is likely to involve many genes, and not all patients will suffer from their disease as a result of having inherited the same genetic variability. Thus, the chances to discover some or most of the genes behind PD will depend on a number of reasons such as their relative impact on disease risk, or the frequency of the disease-associated allele. As both the heritability of PD⁹ and the penetrance of the disease is low, the size of the population required to detect a genetic effect should be important. Another lesson that can be extracted is clearly shown by the Fung, Scholz, Matarin, Simón-Sánchez and colleagues work: sharing of information. When we are about to witness an explosion in the number of genome-wide association studies (see below for a definition of this type of studies) aimed to uncover genetic variability related to common diseases it becomes urgent the implementation of an “Open Access” policy regarding the availability of data to all researchers interested in a particular subject. This is pioneered by the study led by A. Singleton, their complete genotype data will be made available in order to allow other researchers, now or in the future, to try to interpret these data in a different way, may be selecting groups of patients based upon certain clinical characteristics and looking for some genes related to their disease.

It is also interesting to note that, despite reaching a similar conclusion, both studies are not comparable. Whereas Elbaz, Nelson, Payami, Ioannidis, Fiske and colleagues focus on analyzing the 13 regions identified by Maraganore *et al.* in a large population, the Fung, Scholz, Matarin, Simón-Sánchez and colleagues work have studied few patients but using a large number of markers.

This approach is known as “genome-wide association” analysis. In fact, the aim of this second study was not to replicate Maraganore *et al.* findings, but to obtain (an impressive amount of) data and make it available; but an obvious side effect of this work was to put it in perspective with respect of known data.

As a summary, the two papers published in this issue of *The Lancet Neurology* support the idea that the genetic influence in the common, non-monogenic, form of PD is largely heterogeneous and that no single gene is likely to have a strong effect in the relative ratio for the disease. Moreover, although it will not happen in the close future, starts to set the foundation of what will be routine medical practice in a few years from now, where use of genetic information at the multi-*locus* level will be necessary to fully understand some of the causes of the disease of a particular patient. Waiting for that day, researchers must be granted access to all collected data at the genetic and clinical level, always keeping in mind the ethical aspects associated with the use of this information, to take full advantage of the huge efforts made in order to obtain that data. Only through large collaborative efforts, including patients by the thousands, not a few hundreds, and using a dense map of markers, these endeavours are likely to be successful.

REFERENCES

1. Polymeropoulos MH, Higgins JJ, Myles-Worsley M, *et al.* Mapping of a gene for Parkinson's disease to chromosome 4q21-q23. *Science* 1996;**274**:404-7
2. Polymeropoulos MH, Lavendan C, Leroy E, *et al.* Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 1997;**276**:2045-7
3. Epidemiological estimates
4. Maraganore D, de Andrade M, Lesnick TG, *et al.* High-resolution whole-genome association study of Parkinson disease. *Am J Hum Genet* 2005;**77**:685-93
5. Clarimon J, Scholz S, Fung HC, *et al.* Conflicting results regarding the semaphoring gene (SEMA5A) and the risk for Parkinson disease. *Am J Hum Genet* 2006;**78**:1082-4

6. Farrer MJ, Haugarvoll K, Ross OA, *et al.* Genomewide association, Parkinson disease, and PARK10. *Am J Hum Genet* 2006;**78**:1084-8
7. Goris A, Williams-Gray CH, Foltynie T, Compston DA, Barker RA, Sawcer SJ. No evidence for association with Parkinson disease for 13 single-nucleotide polymorphisms identified by whole-genome association screening. *Am J Hum Genet* 2006;**78**:1088-90
8. Li Y, Rowland C, Schrodi S, *et al.* A case-control association study of the 12 single-nucleotide polymorphisms implicated in Parkinson disease by a recent genome scan. *Am J Hum Genet* 2006;**78**:1090-2
9. Roca WA, McDonnell SK, Strain KJ, *et al.* Familial aggregation of Parkinson's disease: The Mayo Clinic Family Study. *Ann Neurol* 2004;**56**:495-502