Editorial.

In the last decades, Parkinson's disease (PD) has been studied under a variety of approaches in order to understand its causes and progression and with the objective of designing sound therapeutic approaches that could substitute the symptomatic therapies currently applied to patients with this neurodegenerative condition. Of those approaches, one that has provided a substantial amount of information is Genetics. For almost 20 years now, the application of molecular genetics to PD has revealed important information about which pathways are crucial in the disease. Today, and according to the MIM database (http://www.ncbi.nlm.nih.gov/omim/), 21 *loci* are related to PD. Some of them were identified as part of the analysis of families, in the classical conception of this term: i.e. Mendelian, whereas applying the concept of a complex or multifactorial disease served to identify some others. For those 21 *loci,* some of the genes underlying the disease are known, whereas for the remaining only genetic evidences exist and, in a few of them, contradictory reports put an alert sign on their true relationship with the disorder.

The ultimate cause for PD still remains elusive. Despite all efforts made since its first clinical description in 1817 by James Parkinson [1] or the latter universalization of its name by Charcot, the ultimate causes of this neurodegenerative disorder are mainly unknown. Several turning points in defining the etiology of the disease can be found in the almost 300 years since Parkinson's essay and, among them, the identification of the *substantia nigra* as the first CNS target of the disease, the finding that environmental toxins severely damage this neuroanatomical region and the identification of α-synuclein as the first gene causing familial PD are specially relevant.

Given the genetic influences on traits like disease onset, clinical manifestations, its progression or response to treatment, it is surely ironic that for a long time, the existence of a family history of the disease has been a cause to exclude the diagnosis of PD. This is especially true when one considers that shortly after Charcot proposed to assign the name of James Parkinson to the disease, two of his disciples, Leroux [2] and Lhirondel [3], proposed *heredity* as a possible cause of the disease. Even Leroux was to affirm that "*a true cause of paralysis agitans, and may be the only true cause, is heredity*" pointing to the role that genetic variants may have in the etiology of PD. Nowadays, genetics offer one of the founding blocks on which build our understanding of the disorder by

identifying the proteins which malfunctioning causes, or contributes to, the disease. In this special issue, we aim to offer a review on what is known about the proteins behind those *loci*. In the selection of which proteins should be included in this special issue, we have decided that those causing Mendelian, either autosomal dominan or autosomal recessive, PD should all be included. Also, we took into account those for which there is strong evidence of a relationship to PD either by being related to other disorders but also causing PD or a phenotype that included parkinsonism of PD-features in it or by being related to PD in a non-familial way Finally, we included a miscellaneous chapter were several different *loci* were dealt with. Although in the literature there is an enormous amount of reports showing evidences of association between different *loci* or SNPs with PD, most of them are not included here as the causative gene or polymorphism behind this relationship is not well defined or there are contradictory reports on their relationship to PD risk.

First, Sahay and colleagues review the effects that point mutations in *SNCA* have on how the protein folds, on its ability to form fibrils and on how they oligomerize. These authors also address the intriguing paradox that PD-causing mutations in SNCA seem to act through opposite mechanisms with respect to fibril formation, some mutations enhancing it while others reduce it, or to binding to vesicle membranes, with some mutations showing stronger binding to them and others having it attenuated. The clinical characteristics of those groups of mutations were also different, stressing the complexity of the phenotype.

Blanca Ramírez and coworkers reviewed the effect that mutations have on *LRRK2*, the main genetic cause of familial PD that also plays a role in sporadic (either non-familial or non-Mendelian) disease. Mutations in this gene cause familial PD that is usually indistinguishable from the non-Mendelian form of the disorder. Moreover, variability at this *locus* is also found modifying the risk for the disease with a few variants found to be protective while others, more frequently, increased the risk for the disease. How these genetic alterations modify the function of this multi-domain protein, and how this relates to the appearance of the disease, is treated in this chapter.

Another protein causing, when mutated, autosomal dominant PD is VPS35, a key component of the retromer. In fact, as Follett and colleagues explain in their paper, the retromer is a structure that is being increasingly related to neurodegeneration. How this

mutation, as well as other also related to PD in other retromer components, causes PD is an exciting and intriguing fact that may change our understanding of the disorder.

On their turn, Hauser, Primiani and Cookson summarize the effect that mutations in the genes related to autosomal-recessive early-onset familial PD (AR-EO PD) have. The three proteins covered in this paper are quite different although they share a common theme, other than the fact that they cause AR-EO PD, in that they are related to mitochondrial function, one of the cellular organelles where damage is critical for PD.

A rare cause of autosomal-recessive early-onset PD is mutated FBXO7, treated by Randle and Laman in their paper. FBXO7, a Skp1-Cul1-F box protein –type E3 ubiquitin ligase, may be related to PD through its different functions: signaling, cell cycle, mitophagy and, obviously, proteasome regulation.

Loss-of-function mutations in ATP13A2 also cause a severe autosomal-recessive early-onset PD with a phenotype that includes some atypical features such as supranuclear gaze palsy, dementia or generalized brain atrophy. This lysosomal ATPase transports cations, Zn^{+2} in humans. And mutations in this gene could also cause early-onset PD as well as neuronal ceroid lipofuscinosis.

In the interface between Mendelian and non-Mendelian forms of the disease is UCHL-1. This protein was first related to familial PD although, so far, only on small pedigree has been reported with an apparently causative mutation, p.I93M. But the importance of this protein in PD also lies in the fact that a common polymorphism, p.S18Y, seems to be protective. Finally, a third mutation, p.E7A, is also causing a different early-onset progressive neurodegenerative disorder. How all these changes alter the role of UCHL-1 in the ubiquitin-proteasome system, as well as in other ubiquitin-related functions is the main topic of this paper.

Goo, Rhim and Kang show how mutations in HTRA2 alter the function of this serine protease required for mitochondrial control with a role on stress-related apoptosis and, therefore, cellular death. Again, healthy mitochondria seem to be critical for neuronal survival and brain functional integrity.

Vilageliu and Grinberg discuss on a somewhat different aspect, how mutations in a protein related to a different disorder, Gaucher disease, are also provoking the

appearance of PD, and the relationship of GBA, the causative protein in Gaucher, and α-synuclein.

Finally, Cardona and Pérez-Tur offer a miscellaneous overview on other proteins or genes related to PD among which, MAPT is one of the most widely accepted PD-risk factor, although the variants underlying this association are, so far, not fully understood.

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References

[1] Parkinson, J. *An essay on the shaking palsy.* Sherwood, Neely, and Jones. London, **1817**
[2] Leroux, P.D. *Contribution a l'étude des causes de la paralyse agitante.* Thesis, Paris. **1880**
[3] Lhirondel, G. *Antécédents et causes dans la maladie de Parkinson*. Thesis, Paris. **1883**