Journal of Parkinson's Disease 9 (2019) 443–444
DOI 10.3233/JPD-191569
IOS Press

Letter to the Editor

Revisiting the History of the 1997 Alpha-Synuclein Discovery in Parkinson's Disease

To the Editor:

In the review article published in the *Journal of Parkinson's Disease* and titled "The Identification of Alpha-Synuclein as the First Parkinson Disease Gene" (The Nussbaum Review) [1], Dr. Nussbaum's account of the events that led to the discovery of the first gene for Parkinson's disease contains certain factual errors or omissions that could lead many readers to be confused on who led and directed this discovery.

The recollection of Dr. Nussbaum about this discovery is vastly different than mine. The Nussbaum Review is limited in accuracy given Dr. Nussbaum's viewpoint of an eyewitness and not the viewpoint of the leader or director of this discovery. In attributing credit, I suggest that we start by carefully examining the annotated authorships of the key references, in none of which Dr. Nussbaum appears as the first or the corresponding author as he did not lead or direct that discovery. The Nussbaum Review may have led the reader to think differently.

At the time of the discovery in 1997, I was the Section Chief of the Gene Mapping Unit and I had already spent 14 years at the National Institutes of Health (NIH), long before Dr. Nussbaum arrived. By the time of the synuclein discovery, my laboratory had mapped a number of human disease genes, discovered and mapped numerous genetic markers, and pioneered large scale gene mapping.

Dr. Nussbaum repeatedly associates the discovery as governed by "luck" and "serendipity", but I would disagree and suggest that we think of "perseverance" instead, but let us take a closer look at the facts.

Dr. Nussbaum states that after meeting with Dr. Duvoisin and colleagues that he and his team "... undertook genome wide mapping". Dr. Nussbaum's recollection is incorrect. Neither Dr. Nussbaum nor his own laboratory participated or planned to participate in this mapping project. Dr. Nussbaum invited me to meet with the Robert Wood Johnson team at the NIH. I immediately offered to collaborate with the RWJ team and began a whole genome analysis. Dr. Nussbaum is correct that my team's effort started from chromosome 4 but he is incorrect on why. Susan Ide, my graduate student at the time, had identified the location of the Ellis van Creveld gene to the short arm of chromosome 4 and it was where she started. The Wolfram syndrome project, to which Dr. Nussbaum is referring, was performed three years before and published in 1994.

Dr. Nussbaum writes "soon after we published the paper showing the map location for the Parkinson's disease gene in the Contursi kindred, we received a call from the White House". While it is true that the mapping was published in 1996 in *Science*, the word "we" needs to be clarified. As the principal investigator, I wrote and submitted the 1996 *Science* paper [2] with myself as the first and corresponding author and Dr. Nussbaum as second to last author, in acknowledgment of introducing me to the project. Another correction is on the timing of when the White House contacted the NIH Public Relations department. I took that call with White House staffers a year later, in 1998, and after the alpha-synuclein discovery of 1997.

Dr. Nussbaum goes on to suggest that "the physical map was quickly constructed by a team led by Christian Lavedan". This is incorrect as the physical "contig map" was constructed under my leadership and direction by a team of scientists from the Institute, including Dr. Lavedan. In the publication of this

"contig map" in *DNA Research* in 1998 [3], I was the last and corresponding author, with Dr. Nussbaum listed as the second to last author.

Dr. Nussbaum's account of the actual alpha-synuclein mutation discovery is incorrect, as he describes a discussion between the two of us that we "looked at each other . . . " and both said "let's have a look" and then goes on to say "Christian Lavedan and his colleagues . . . sequenced the alpha synuclein gene . . . (and) they found a missense change". Dr. Lavedan only became involved in the project in February of 1997, after we first sequenced the alpha-synuclein gene in November of 1996. Dr. Elizabeth Leroy and Susan Ide in my laboratory first sequenced the alpha-synuclein gene in November of 1996 from cDNA extracted from a Contursi pedigree patient cell line. At that time, we found no mutation in the alpha-synuclein gene and excluded alpha-synuclein from further inquiry. It was later in April of 1997 when armed with the intron-exon structure of the alpha-synuclein gene, which we had resolved, that I asked Susan Ide in my laboratory to sequence the alpha-synuclein gene again, now from genomic DNA material. This is how Dr. Ide, rather than Dr. Lavedan, first sequenced the missense mutation. The earlier failure to detect the mutation in late 1996 was confirmed to be due to a cell line switch with an unaffected individual. The discovery was published in *Science* in 1997 [4] with myself as the first and corresponding author and Dr. Nussbaum as the last author. Dr. Nussbaum also refers to Drs. Leroy, Ide, and Dehejia, all three of whom were members of my laboratory and none of whom reported to Dr. Lavedan or Dr. Nussbaum.

Dr. Nussbaum also refers to the alpha-synuclein protein discovery in Lewy bodies by stating that "we were in the process of demonstrating the same thing". Here it is important to clarify who the "we" characters were. In June of 1997, I led a collaboration with Mike Brownstein and Eva Mezey at the NIH on immunohistochemistry of synuclein in Parkinson's disease brain samples, results of which were published in 1998 [5] with myself as the last and corresponding author with Dr. Nussbaum as third to last author.

I am humbled to have led and directed the discovery of alpha-synuclein as the first genetic factor for Parkinson's disease, a discovery that has inspired a generation of scientists in the last 20 years in their pursuit of a treatment for the patients suffering from this devastating disease. I am grateful to all who contributed in many ways toward this discovery, and to the editors of this journal for giving me the opportunity to correct the record.

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