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Parkinson Disease and Clathrin Coat Dynamics at Synapses, Why Not?

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In 2013, the missense p.Arg258Gln (R258Q) mutation in the Suppressor of actin (SAC domain) of Synaptojanin 1 (SYNJ1) was linked to a recessive form of early onset of Parkinson's disease (PD) in 3 independent families.^{1–3} Although *SYNJ1* mutations remain rare, there is continued interest in the investigation of this protein in the possible pathogenesis of PD.

Investigation into the proposed function of SYNJ1 as a pre-synaptic phosphatase has primarily focused on the 5-phosphatase domain, with relatively little work on the SYNJ1 Sac phosphatase domain. The work presented by Cao and colleagues⁴ and published in *Neuron* addresses this particular issue.

The authors generate a transgenic mouse line carrying the originally reported PD-associated R258Q; notably this mouse exhibits movement problems at an early stage (3–4 months), suggesting that this line is worthy of investigation as a potential model of PD-linked dysfunction. Because of the role of SYNJ1 in synaptic endocytosis, the authors then explored how the mutation could affect other synaptic and endocytic proteins. Brains from these mice show accumulation of endocytic proteins, suggesting that there may be alterations in the endocytic pathway, something confirmed in cortical neurons from the mutant mice at synaptic terminals.

Ultrastructural observation of these nerve synapses demonstrated a greater abundance of the clathrin-coated vesicles and a concomitant reduction of synaptic vesicles. Taken together with functional studies at the synapses in the cortical neurons, the data suggest that this mutation alters the synaptic vesicle recycling pathway. In particular, the dynamics of clathrin coat regulation, which lead to defects in synaptic vesicle reformation at the synaptic terminal. Supporting this observation, auxilin, another regulator of clathrin coat events, has been linked to juvenile and sporadic forms of PD.^{5,6}

To finally link this interesting observation to the early onset of Parkinson Disease, the nigrostriatal pathway was analyzed in the model. By using immunofluorescence, the authors observed the accumulation of abnormal clusters of dopamine active transporter (DAT), tyrosine hydroxylase (TH), and synaptosomal-associated protein 25 (SNAP25) in the dopaminergic axons, suggesting aberrant nerve fibers. These clusters were selectively

located in the dorsal striatum of the mutant mice and not observed in other areas. Electron microscopy analyses depict accumulation of onion-like plasma membrane at these terminals. In contrast to these data, the number and morphology of dopaminergic neurons in the ventral tegmental area or the substantia nigra were found to remain unaltered, strongly supporting the idea that the abnormalities observed in the mutant mice are a result of a defect in the synaptic pathway at the nerve terminals rather than cell death.

In summary, this work describes that the human disease linked R258Q mutation, when expressed in mice, leads to a synaptic accumulation of clathrin-coated endocytic intermediates that might induce a selective dystrophy in subpopulations of axon terminals in the dorsal striatum. This suggests a link between this particular form of disease and a dysfunctional endocytic pathway.

Although an exciting model, there is much left to do. Linking the accumulation of clathrin-coated vesicles directly to the movement disorder observed in the mice is key, as is the consideration of whether the mechanisms proposed in this paper are generalizable to PD as a whole or are specific to only this genetic form of disease.

References

1. Krebs CE, Karkheiran S, Powell JC, et al. The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive Parkinsonism with generalized seizures. *Hum Mutat.* 2013; 34(9): 1200–1207. [PubMed: 23804563]
2. Olgiati S, De Rosa A, Quadri M, et al. PARK20 caused by SYNJ1 homozygous Arg258Gln mutation in a new Italian family. *Neurogenetics.* 2014; 15(3):183–188. [PubMed: 24816432]
3. Quadri M, Fang M, Picillo M, et al. Mutation in the SYNJ1 gene associated with autosomal recessive, early-onset Parkinsonism. *Hum Mutat.* 2013; 34(9):1208–1215. [PubMed: 23804577]
4. Cao M, Wu Y, Ashrafi G, et al. Parkinson sac domain mutation in synaptojanin 1 impairs clathrin uncoating at synapses and triggers dystrophic changes in dopaminergic axons. *Neuron.* 2017; 93(4): 882–896.e5. [PubMed: 28231468]
5. Edvardson S, Cinnamon Y, Ta-Shma A, et al. A deleterious mutation in DNAJC6 encoding the neuronal-specific clathrin-uncoating co-chaperone auxilin, is associated with juvenile parkinsonism. *PLoS One.* 2012; 7(5):e36458. [PubMed: 22563501]
6. Olgiati S, Quadri M, Fang M, et al. DNAJC6 mutations associated with early-onset parkinson's disease. *Ann Neurol.* 2016; 79(2):244–256. [PubMed: 26528954]