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Mutations in *PDYN* are Not Responsible for Multiple System Atrophy

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We read with great interest the work by Fawcett et al. examining the prevalence of variation in the *PDYN* gene within a large UK cohort of sporadic and familial ataxia patients, demonstrating this to be a rare genetic cause of spinocerebellar ataxia in this group [1] as previously suggested by work from other populations, [2,3] including our own sample of 119 US patients with sporadic ataxia. [4]

While *PDYN* variants do not appear to be a common cause of spinocerebellar ataxia, it remains possible that mutations could play a role in other phenotypes. For example, we identified one patient with a known *PDYN* mutation (p.R138S) [2] who was originally classified as having possible multiple system atrophy (MSA) using the Gilman et al. criteria. [4,5] As the clinical phenotype of SCA23 overlaps with that of the cerebellar variant of MSA (MSA-C), Fawcett et al. explored this possibility in their UK sample by examining 190 patients diagnosed with MSA-C without finding any pathogenic variants, suggesting that *PDYN* mutations are also not a significant cause of MSA in this population. [1]

Extending the findings reported by Fawcett et al., we examined a group of 60 US patients with MSA for variations in the *PDYN* gene. Using the criteria of Gilman et al., 52 (87%) of these patients met the definition of probable MSA, [5] 36 (60%) were women, and the average age was 62 ± 7.7 years. Based on initial clinical presentation, 56 (93%) were classified as MSA-C and 4 (7%) as MSA-P. [5] The majority (70%) were white, non-Hispanic. All study protocols were approved by the UCLA Institutional Review Board and all participants gave informed consent to participate. The entire *PDYN* coding region was

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Author Contributions:
BLF and GC were responsible for the conception and design of the research project. CB and AC were responsible for project execution. SLP and DHG supervised the clinical phenotyping and the molecular aspects of the project, respectively. BLF wrote the manuscript and BLF, GC, SLP, and DHG were responsible for its review and critique.

sequenced as previously described. [4] Sequences were compared to the human genome GRCh37/hg19 build. We identified no known pathogenic variants in *PDYN* although we did identify 9 individuals (15%) heterozygous for a common polymorphism (chr20:1,961,134 A>G, p.(=), rs6045819), a frequency consistent with that observed in normal human variation databases. [4] One of these individuals was also heterozygous for a second rarer polymorphism also seen in normal human variation (chr20:1,961,159 T>A, p.Glu192Val, rs45469293). During the course of the study, two patients with possible MSA were found to have alternate genetic diagnoses (see Table). One was found to carry the premutation associated with the Fragile X tremor/ataxia syndrome. [6] The second patient (who also carried rs6045819) was found to harbor a novel frameshift variation in the transglutaminase 6 gene (*TGM6)* associated with spinocerebellar ataxia type 35 (SCA35), [7] chr20:2,397,971–2,397,981del, c.1430delGGGGTCGCTGT, p.Gly477Ala fs*2. Of note, this patient ultimately developed a phenotype consistent with progressive supranuclear palsy (PSP), an interesting observation given that transglutaminases have been previously suggested to play a role in PSP. [8,9]

In summary it would appear that multiple lines of evidence suggest that *PDYN* variants, while important to consider in very rare cases of familial ataxia, are uncommon causes of cerebellar ataxia worldwide, including multiple system atrophy. Our work further illustrates the challenge of diagnosing a patient with MSA and emphasizes the need to consider rare clinically overlapping genetic disorders in cases with atypical features.

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Table

Patient Gene/Mutation[a]	Initial Clinical Presentation	Initial Diagnosis[b]	MSA Progressive Clinical Features	MSA-Atypical Progressive Clinical Features
PDYN chr20:1961320 C>A p.R138S	Cerebellar ataxia Urinary urgency Urinary frequency Erectile dysfunction	MSA-C (possible)	Cerebellar ataxia	None
TGM6 chr20:2,397,971– 2,397,981del p.Gly477Ala fs*2	Parkinsonism Urinary urgency Urinary frequency	MSA-P (possible)	Parkinsonism Cerebellar ataxia	Cognitive impairment Brother with PSP phenotype
FMR1 109 CGG repeats (normal 5–44)	Cerebellar ataxia Urinary incontinence Brain MRI with cerebellar atrophy	MSA-C (possible)	Parkinsonism	Cognitive impairment Brain MRI with T2-weighted hyperintensities in middle cerebellar peduncles

[a] *PDYN* patient previously reported [4] and included here for comparison.

[b] Based on Gilman et al. criteria. [5]