Occurrence of Amyotrophic Lateral Sclerosis in Type 1 Gaucher Disease

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Abstract

Objective
To report the association between type 1 Gaucher disease (GD1) and amyotrophic lateral sclerosis (ALS) in 3 unrelated families and to explore whether GBA variants influence the risk of ALS.

Methods
We conducted retrospective chart reviews of patients with GD1 or their family members diagnosed with ALS. To further investigate whether there is an association between ALS and GD, we performed exploratory analyses for the presence of GBA variants in 3 ALS cohorts from Toronto (Canada), Montreal (Canada), and Project MinE (international), totaling 4,653 patients with ALS and 1,832 controls.

Results
We describe 2 patients with GD1 and 1 obligate GBA mutation carrier (mother of GD1 patient) with ALS. We identified 0 and 8 GBA carriers in the Toronto and Montreal cohorts, respectively. The frequencies of GBA variants in patients with ALS in the Montreal and Project MinE cohorts were similar to those of Project MinE controls or Genome Aggregation Database population controls.

Conclusions
The occurrence of ALS in biallelic or monoallelic GBA mutation carriers described here, in addition to common pathogenic pathways shared by GD1 and ALS, suggests that GBA variants could influence ALS risk. However, analyses of GBA variants in ALS cohorts did not reveal a meaningful association. Examination of larger cohorts and neuropathologic studies will be required to elucidate whether patients with GD1 are indeed at increased risk for ALS.

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Gaucher disease (GD) is a lysosomal storage disorder (LSD) caused by biallelic mutations in the GBA gene. GBA variants are also important risk factors for synucleinopathies, specifically Parkinson disease (PD) and dementia with Lewy bodies (DLB). Of interest, other LSD-related genes have been implicated in neurodegeneration. For instance, SMPD1 variants were recently associated with risk of PD. Although multiple pathways are involved in PD pathogenesis, the main mechanism thought to underlie the association between LSD and PD is dysfunction in the autophagy-lysosomal pathway (ALP).

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease (MND) that also likely results from several pathogenic mechanisms, including ALP dysfunction. Recent case reports of patients diagnosed with both ALS and a LSD, such as Fabry disease or type 3 GD, raise the possibility that common lysosomal abnormalities may underlie the co-occurrence of these disorders. The aims of this study are (1) to report the association between type 1 GD (GD1) and ALS in 3 unrelated families and (2) to explore whether GBA variants increase the risk of developing ALS.

Glossary
AF = allele frequency; ALP = autophagy-lysosomal pathway; ALS = amyotrophic lateral sclerosis; DLB = dementia with Lewy bodies; GD = Gaucher disease; GD1 = type 1 GD; gnomAD = Genome Aggregation Database; LSD = lysosomal storage disorder; MND = motor neuron disease; PD = Parkinson disease; WES = whole-exome sequencing; WGS = whole-genome sequencing.

Standard Protocol Approvals, Registrations, and Patient Consents
Informed consent was obtained from case 1 and next of kin of case 3. Relatives of case 2 were not contactable, and thus, the case description was anonymized. Retrospective review of clinical data was conducted in accordance with the Helsinki Declaration. Informed consent for participation in the genetic study was obtained from the Toronto participants in accordance with the University of Toronto research ethics board (protocol #34754) and from the French-Canadian Montreal participants in accordance with the Montreal Neurological Institute and Hospital research ethics board (approval #2017-2740), affiliated with the McGill University Health Centre research ethics board.

Data Availability
All data relevant from case 1, case 3, and Project MinE are included in the article or uploaded as supplementary information. Anonymized data from case 2 may be shared by request from any qualified investigator.

Methods
Patients
Fifty-six patients with GD1 from the Mark Freedman & Judy Jacobs Program for Gaucher Disease at Mount Sinai Hospital (Toronto, Canada) underwent routine assessment by a neurologist (L.V.K.) between 2017 and 2020. One patient was diagnosed with ALS (case 1), and 1 patient had a first-degree relative with ALS (case 3). One GD1 patient with probable ALS (case 2) was identified at a medical center in Israel.

Genetic Analyses
We examined for GBA variants in 3 ALS cohorts: (1) 125 patients with ALS from Sunnybrook Health Sciences Centre (Toronto, Canada) who underwent whole-genome sequencing (WGS) at Genome Quebec (Montreal, Canada); (2) 162 French-Canadian patients with ALS who underwent whole-exome sequencing (WES) at the Montreal Neurological Institute (Montreal, Canada); and (3) 4,366 patients with ALS and 1,832 age- and sex-matched controls from the international Project MinE WGS data set. Only exons 1–9 were analyzed; exons 10 and 11 were not analyzed due to similarities to the pseudo-GBA gene and limitations regarding reliability of WGS or WES findings in these exons. Only nonsynonymous and loss-of-function GBA variants were analyzed. We used the legacy glucocerebrosidase protein sequence nomenclature to describe the variants. For details, see e-Methods (links.lww.com/NXG/A428).

Results
Patients
Case 1 was diagnosed with clinically probable laboratory-supported ALS. Case 2 presented with probable ALS, but ultimately developed clinically definite ALS. Case 3 was an obligate GBA mutation carrier who was also diagnosed with ALS. She was the mother of a patient with GD1 with PD. Clinical data and genetic investigations are described in table 1, figure e-1 and e-Results (links.lww.com/NXG/A428).

ALS Cohorts
We did not identify any patients with ALS with a GBA variant by WGS in the Toronto cohort. Eight patients in the French-Canadian ALS cohort were found to have one of the following GBA variants: E326K, T369M, N370S, and S52L (table 2). In 2 cases, there was a variant of uncertain significance in an ALS-related gene: (1) CCNF H69Y variant in a GBA T369M carrier and (2) DCTN1 G467A variant in a GBA E326K carrier. The frequency of GBA variants in the French-Canadian ALS cohort was similar to that of European population controls in the Genome Aggregation Database (gnomAD) database. Thirty-five GBA variants were identified in patients with ALS or controls from the Project MinE data set and were rare (table 3). The frequency of these GBA variants in ALS patients was similar to that of Project MinE or gnomAD population controls.
The allele frequency (AF) of N370S present in case 1, case 2, and the daughter of case 3 was 0.003 in the French-Canadian cohort (similar to the AF found in European gnomAD controls) and 0.002176 in ALS Project MinE patients (similar to the AF found in ALS Project MinE controls). W378G, c.84dupG, and P236T found in case 1, case 2, and the daughter of case 3, respectively, were not present in any of the ALS cohorts.

### Discussion

Although the co-occurrence of GD1 with PD and the increased risk of PD among GBA mutation carriers are well established, the association of GD1 with ALS is rare. Of interest, 2 of 3 ALS cases reported here (1 patient with GD1 and 1 obligate GBA mutation carrier) have a family history of PD. Neurodegeneration in PD and ALS results from several shared mechanisms, including lysosomal dysfunction. Furthermore, a complex overlap between parkinsonian and motor neuron syndromes has long been appreciated with parkinsonism and ALS co-occurring within families or even within an individual patient. A genetic basis may underlie some cases of parkinsonism and ALS overlap, most notably nucleotide repeats in C9orf72 or ATXN2. Rare cases with both parkinsonism and ALS have been reported with mutations in DJ-1, TARDBP, or ANG.

One of the patients with ALS reported here (case 1) had GD1 due to W378G and N370S GBA mutations. N370S is one of...
was obtained from a study of over 400 patients with GD. Considering that ALS is approximately one hundred times less prevalent than PD, we expect that examination of much larger numbers of GD patients will be required to elucidate whether indeed there is a link between ALS and GD.

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Table 2 GBA Variants Identified in the Montreal French-Canadian ALS Cohort

| Variant | dbSNP ID | No. of carriers | AF     | AF in gnomAD |
|---------|----------|-----------------|--------|--------------|
| SS2L    |          | 1               | 0.003  | 9 × 10⁻⁶     |
| E326K   | rs2230288 | 3               | 0.009  | 0.012        |
| T369M   | rs75548401| 3               | 0.009  | 0.009        |
| N370S   | rs76763715| 1               | 0.003  | 0.002        |

Abbreviations: AF = allele frequency; ALS = amyotrophic lateral sclerosis = dbSNP = single nucleotide polymorphism database identification number; gnomAD = Genome Aggregation Database. Compared with European population controls.

the most frequent GBA mutations reported to be associated with increased PD risk. W378G is a French-Canadian founder GBA mutation more recently linked to GD1 and synucleinopathies when found in compound heterozygosity with N370S.14 Although case 1 did not have PD, there was a family history of PD and reported DLB (figure e-1, links.lww.com/NXG/A428). He was found to have a variant of uncertain significance in SQSTM1, but it did not segregate with the various neurodegenerative diseases in his family and therefore was not considered pathogenic. The increased risk of synucleinopathies with W378G and N370S raises the possibility of a synucleinopathy mimicking ALS in case 1 and possibly case 3. Lewy pathology can accompany typical MND pathology in patients with co-occurrence of ALS and parkinsonism15 and sometimes in patients with ALS without clinical parkinsonism.16 However, we did not find any definitive reports in the literature of Lewy pathology occurring in isolation (i.e., in the absence of MND pathology in both the brain and spinal cord) in patients presenting clinically with only ALS, without parkinsonian features. Yet, we cannot fully eliminate this possibility because we have no autopsy data for our patients.

Limitations of our study include the lack of neuropathologic data and lack of genetic data for ALS-related genes in 2 cases. In addition, genetic analyses only included exons 1–9 of the GBA gene and thus potentially excluded some GBA variants. This likely had a minimal effect on our results because mutations in the excluded exons in Europeans are rare.17 Identification of complex alleles was also limited with our genotyping methods.

Our analyses of GBA variants among 4,653 patients with ALS and 1,832 controls did not support heterozygosity for a GBA variant (i.e., 1 mutant GBA allele) as a risk factor for ALS. In contrast, a strong association between GBA variants and PD was previously demonstrated in a study of 5,691 patients with PD and 4,898 controls.18 Co-occurrence of GD1 (i.e., 2 mutant GBA alleles) and ALS in our reported cases could be coincidental; however, a previous report of ALS in a patient with type 3 GD6 and the existence of common pathogenic pathways shared by GD and ALS suggest that GD could influence ALS risk. The association between GD1 and PD began with a suggestion from case reports, but definitive proof

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| Variant | ID                  | AF cases | AF controls | AF in gnomAD (WGS)\(^{20}\) | AF in gnomAD (WES)\(^{20}\) |
|---------|---------------------|----------|-------------|-----------------------------|-----------------------------|
| R463P   | chr1:155204986:C:G  | 0.0001145| 0           | NA                          | NA                          |
| D453V   | chr1:155205016:T:A;rs771744004 | 0.0001145 | 0.0002729 | NA                          | 2.03282e-05                 |
| D453H   | chr1:155205017:C:G;rs77958429 | 0.0001145 | 0.0002729 | NA                          | 2.03283e-05                 |
| D443N   | chr1:155205047:C:T;rs75671029 | 0         | 0.0002729   | 0.00219709                  | 0.000512291                 |
| K425T   | chr1:155205100:T:G   | 0.0001145 | 0           | NA                          | NA                          |
| D409H   | chr1:155205518:C:G;rs1064651 | 0.0001145 | 0           | 0.00025895                  | 0.00126416                  |
| R395C   | chr1:155205560:G:A   | 0.0001145 | 0           | NA                          | 4.06128e-06                 |
| E388K   | chr1:155205581:C:T;rs149171124 | 0.0005726 | 0.0002729   | 3.23039e-05                | 0.000178674                 |
| N370S   | chr1:155205634:C:T;rs76763715 | 0.002176  | 0.002186   | 0.0016507                   | 0.00232286                  |
| R359P   | chr1:155206067:C:G   | 0.0001145 | 0           | NA                          | NA                          |
| Q350H   | chr1:155206093:C:G;rs761681845 | 0.000229  | 0           | 3.2329e-05                  | 2.03041e-05                 |
| R329C   | chr1:155206158:G:A;rs374306700 | 0.0001145 | 0           | NA                          | 1.21818e-05                 |
| E326K   | chr1:155206167:C:T;rs2230288 | 0.01649  | 0.01528   | 0.012828                    | 0.0106732                   |
| A269T   | chr1:155207209:C:T;rs368425393 | 0         | 0          | NA                          | 2.03287e-05                 |
| T267I   | chr1:155207214:G:A;rs199628072 | 0.0001145 | 0           | 0.000129232                 | 5.2852e-05                  |
| R262H   | chr1:155207229:C:T;rs140955685 | 0.0001145 | 0           | 0.0008188                   | 0.000290698                 |
| F259L   | chr1:155207237:T:G   | 0.0001145 | 0           | NA                          | NA                          |
| H255Q   | chr1:155207249:A:C;rs367968666 | 0.0003436 | 0           | 6.45995e-05                 | 0.000239828                 |
| S237F   | chr1:155207304:G:A;rs755512507 | 0         | 0.0002734   | NA                          | 8.12942e-06                 |
| F216Y   | chr1:155207367:T:G;rs74500255 | 0         | 0.0002731   | 3.2306e-05                  | 1.22561e-05                 |
| Y212H   | chr1:155207935:A:G;rs121908300 | 0.0001145 | 0           | NA                          | 4.06062e-06                 |
| D140H   | chr1:155208361:C:G;rs147138516 | 0.001038  | 0.0008228   | 9.72321e-05                | 0.000138342                 |
| R131C   | chr1:155208388:G:A;rs398123530 | 0.0001147 | 0           | NA                          | 4.0658e-06                  |
| c.307+1G>T | chr1:155209676:C:A  | 0.0001145 | 0           | NA                          | NA                          |
| T63R    | chr1:155209679:G:C   | 0.0001145 | 0           | NA                          | NA                          |
| R44C    | chr1:155209737:A:T;rs1141812 | 0         | 0.0002731   | 6.46078e-05                 | 8.53187e-05                 |
| R39C    | chr1:155209752:G:A;rs146774384 | 0.0001145 | 0           | 9.69681e-05                 | 9.34336e-05                 |
| Y22F    | chr1:155209802:T:A   | 0.0001145 | 0           | NA                          | NA                          |
| C18*    | chr1:155209813:G:T   | 0.0001145 | 0           | NA                          | NA                          |
| V15M    | chr1:155209824:C:T   | 0         | 0.0002729   | NA                          | NA                          |
| Q(-8)R  | chr1:155210441:T:C   | 0.000229  | 0.0002729   | NA                          | NA                          |
| V(-22)E | chr1:155210483:A:T   | 0         | 0.0002729   | NA                          | NA                          |
| L(-25)S | chr1:155210492:A:G;rs1141802 | 0.0001145 | 0           | 6.45911e-05                 | 3.66202e-05                 |
| K(-27)R | chr1:155210498:T:C;rs150466109 | 0.0001145 | 0           | 0.0224392                   | 0.00544965                  |
| C(-29)S | chr1:155210505:A:T   | 0.0001145 | 0           | NA                          | NA                          |

Abbreviations: AF = allele frequency; ALS = amyotrophic lateral sclerosis; ID = variant identification; gnomAD = Genome Aggregation Database; NA = not available; WES = whole-exome sequencing; WGS = whole-genome sequencing.
**Appendix**

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