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HIGH LIGHT

Phenotypic variation in a large Swedish pedigree due to *SNCA* duplication and triplication

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Abstract—*Background:* The "Lister family complex," an extensive Swedish family with autosomal dominant Parkinson disease, was first described by Henry Mjönes in 1949. On the basis of clinical, molecular, and genealogic findings on a Swedish and an American family branch, we provide genetic evidence that explains the parkinsonism in this extended pedigree. *Methods:* Clinical methods included a detailed neurologic exam of the proband of the Swedish family branch, MRI, and ([123]I)–beta–CIT SPECT imaging. Genomic analysis included α-synuclein sequencing, *SNCA* real-time PCR dosage, chromosome 4q21 microsatellite analysis, and high-resolution microarray genotyping. The geographic origin and ancestral genealogy of each pedigree were researched in the medical literature and Swedish Parish records. *Results:* The proband of the Swedish family branch presented with early dysautonomia followed by progressive parkinsonism suggestive of multiple system atrophy. Molecular analysis identified a genomic duplication of <0.9 Mb encompassing α-synuclein and multimerin 1 (*SNCA-MMRN1*), flanked by long interspersed repeat sequences (LINE L1). Microsatellite variability within the genomic interval was identical to that previously described for a Swedish American family with an α-synuclein triplication. Subsequent genealogic investigation suggested that both kindreds are ancestrally related to the Lister family complex. *Conclusion:* Our findings extend clinical, genetic, and genealogical research on the Lister family complex. The genetic basis for familial parkinsonism is an *SNCA-MMRN1*1 multiplication, but whereas *SNCA-MMRN1* duplication in the Swedish proband (Branch J) leads to late-onset autonomic dysfunction and parkinsonism, *SNCA-MMRN1* triplication in the Swedish American family (Branch I) leads to early-onset Parkinson disease and dementia.

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The hypothesis that heredity underlies the etiology of Parkinson disease (PD) has traditionally found little support from epidemiologic data.[1] However, a growing proportion of apparently sporadic cases are now explained by pathogenic mutations (e.g., in the *LRRK2* gene)[2] or by genetic polymorphisms of more modest effect (e.g., within the *SNCA* locus).[3,4] These genetic insights were partly made through linkage analysis of pedigrees in which multiple individuals are affected by parkinsonism.[5] Past clinicogenetic studies have identified many such families,[6-8] but few have been followed longitudinally and for most the genetic cause remains to be identified.

Missense mutations in the α-synuclein gene (*SNCA*; A30P, A53T, and E46K) were the first identified in autosomal dominant parkinsonism.[5] Later, α-synuclein was recognized as a component of Lewy bodies and Lewy neurites, the major neuronal pathology associated with PD and dementia with Lewy bodies (DLB).[9,10] In addition, α-synuclein immunocytochemistry highlights neuronal and oligodendroglial cytoplasmic inclusions (GCIs) in multiple system atrophy (MSA).[11]

We have previously shown that *SNCA* genomic triplications can also lead to autosomal dominant, early-onset, rapidly progressive parkinsonism–dementia with autonomic dysfunction.[12] *SNCA* genomic

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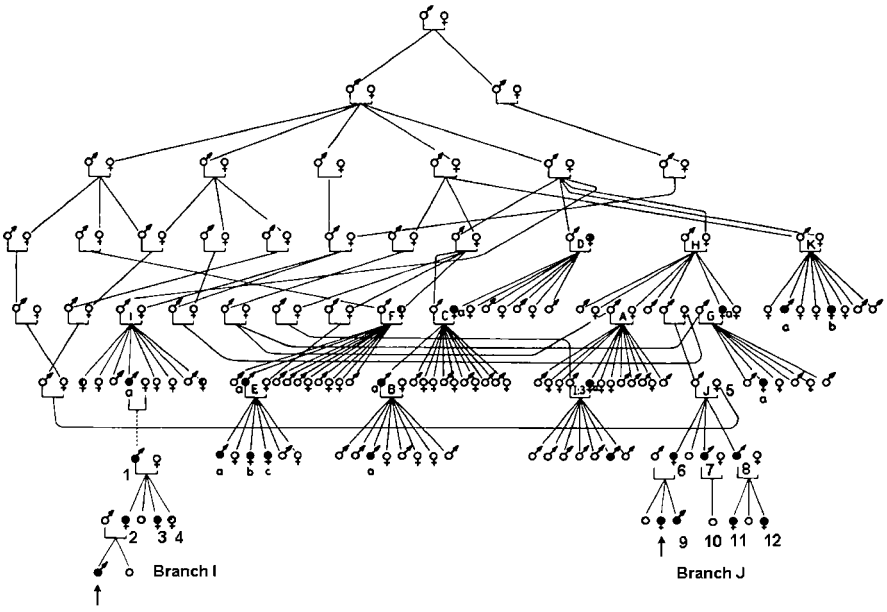

Figure 1. Extended pedigree of the Lister family complex. Classic symbols for males and females are indicated; open circles refer to multiple siblings for which the number and gender remain unspecified (for patient confidentiality). Filled symbols with alphabetic subscripts highlight subjects with parkinsonism, half-filled symbols are indicative of myoclonus, whereas a quarter-filled symbol indicates postural/essential tremor. Subpedigrees were historically denoted by A through K; the alphabetic subscripts denote patients for whom clinical diagnoses were documented in 1949.[7] For these patients, the mean age at symptom onset was 42 ± 11 (SD) years (range 28 to 61 years, n = 10), and the mean age at death was 63 ± 13 years (range 39 to 86 years, n = 10).[7] The arrows indicate probands of Branches I and J, respectively. Additional clinical data are available for family members (numbered) in Branches I and J and are summarized as follows. Branch I: 1) By history, the maternal grandfather was affected with parkinsonism and died at age 52. 2) The disease in the mother of the proband began in her 40s, with asymmetric resting tremor in one arm after injury. Two brain surgeries to alleviate parkinsonian symptoms were performed, without much benefit, and the patient had a severe stroke during the second intervention, 3) Aunt of the proband with parkinsonism, with onset in her early 60s, 4) Another aunt was newly diagnosed with essential tremor in her 80s, but had no parkinsonism. Branch J: 5) Grandmother of index patient, died of "brain tumor" according to family history. 6) Mother of index patient with symptom onset at age 59, with rapidly progressive bradykinesia and postural disturbance. She lived several years in a nursing home and died after a 10-year disease duration. 7 and 8) Parkinson disease (PD) according to family history. 9) Diagnosed with idiopathic PD, symptom onset at age 62 with rapidly progressive bradykinesia and rigidity, but with no or slight tremor and only a weak response to l-dopa. He died at age 69, with a disease duration of 7 years. 10) One individual within this sibpair is reported by family members to have had a psychiatric illness. 11) Onset of parkinsonism at age 40, with slow progression and on–off symptomatology. She died at age 60 with a disease duration of 20 years. 12) Symptom onset at age 62 characterized initially by hemiparkinsonism with bradykinesia, rigidity, slight to moderate rest, and action tremor and moderate response to l-Dopa. Initially disease had a slow progression, but after 4 to 5 years' progression was more rapid. After 7 years of disease, the subject was wheelchair bound and received gastrostomy because of severe dysphagia. Oral dyskinesias were reported at one point, and severe psychiatric problems with depression and anxiety were present even before motor symptoms. Later the patient had long episodes of paranoid psychosis with visual hallucinations. No dementia was present, when evaluated at age 67. The patient died at age 74 years after a disease of 12 years' duration.

triplication leads to a doubling of wild-type α-synuclein expression in the brain and appears sufficient to cause the phenotype.[13] Subsequently, we and others have reported several families with *SNCA* duplication mutations in which disease more closely resembles PD, with later-onset parkinsonism, with slower progression, and largely without evidence of autonomic dysfunction, cognitive decline, or dementia.[14-16]

Herein we describe and compare clinical, genetic, and genealogic findings in two independently ascertained kindreds, residing in Sweden (Branch J) and the United States (the Swedish American kindred[13]; Branch I), whose pedigrees and geographic origin are consistent with the "Lister family complex" (figure 1) originally described by Henry Mjönes in 1949.[7] The clinical features of late-onset parkinsonism and early dysautonomia in Branch J and early-onset parkinsonism with dementia and dysautonomia in Branch I,[17] are explained by a duplication and triplication of a 0.9-Mb genomic region containing two genes, *SNCA* and *MMRN1*. We postulate a molecular mechanism for this dynamic *SNCA* genomic multiplication.

Methods. Pedigrees were constructed based on information from each proband and closely related family members. Sibships and dates of birth and death for individuals in Branch I and Branch J were compared with historical data on Swedish families with autosomal dominant PD.[7] The geographic origin of the grandfather of the proband in the Swedish American family (Branch I) was deduced from Swedish church registers, which include place of birth and date of emigration.

For each proband, clinical assessments included a complete medical history and neurologic examination with appropriate rating scales for parkinsonism, dementia, and autonomic dysfunction.[13,18] For deceased family members, clinical assessment was made from medical records if available and family history. The presence of at least two of the following signs—resting tremor, cogwheel rigidity, bradykinesia, and postural reflex impairment—were required for the diagnosis of parkinsonism, at least one fea-

Table 1 *SNCA-MMRN1* markers and allele sizes

Microsatellite	Position, Mb	Branch J	Branch I
Centromeric			
D4S2460	90.190827	183/187	183/187
D4S2461	90.589769	178/179	173/179
D4S3483	90.659137	293/297	296/297
D4S3484	90.679668	177/189/203‡	189†/203‡
D4S2304	90.808432	293†/302‡	293†/294/302‡
D4S3475	91.025407	204/208†‡	204/208*‡
D4S3476	91.028115	332/334†‡	332/334*‡
D4S3477	91.066322	254/254‡	254/254‡
D4S3480	91.070466	221†/224‡	221†/224‡
D4S3479	91.087762	163/167/169‡	163†/167/169‡
D4S3481	91.124217	261/261‡	261/261‡
D4S3474	91.143057	199/203†‡	199/203*‡
D4S2458	91.272658	117/119/121‡	117†/119/121‡
D4S3245	91.419322	102/102‡	102†/110‡
D4S3485	91.478360	199†/203‡	199†/201‡
D4S410	91.754287	213/215	213/215
Telomeric			

Primer sequence and genomic DNA controls are available on request.

* Equimolar peak heights for these genotypes are indicative of four alleles.
† Duplicated or triplicated alleles.
‡ Region of multiplication.

ture being either resting tremor or bradykinesia. Blood was drawn with informed consent, and genomic DNA was extracted using standard protocols. The project was approved by the local Ethics Committees for Research.

Sequence analysis of SNCA coding regions. Methodology for *SNCA* sequencing (exons 1 through 6) was as previously described, using BigDye Terminators on an ABI PRISM 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA)[13,19].

Quantitative real-time PCR–dosage assay. Quantitative real-time gene dosage analysis was performed on a LightCycler (Roche Diagnostics GmbH, Mannheim, Germany). Duplex PCR was performed using two sets of sequence specific hybridization probes binding within exon 2[20] and 3 of the *SNCA* gene (*SNCA*; GenBank L08850.1). Positive (*SNCA* triplication; sample ND00139, available from Coriell Cell Repositories, NJ) and negative controls were included in each assay. A standard curve over two orders of magnitude was generated and a regression curve based on cross-point values was calculated. The use of an internal control (β-globin) allowed for calculation of the α-synuclein/β-globin ratio to obtain the *SNCA* dosage value. A ratio between 0.8 and 1.2 was considered as normal, a heterozygous duplication was indicated by a ratio between 1.3 and 1.7 and a homozygous duplication or triplication between 1.8 and 2.2.

Genomic microsatellite markers and dosage analysis. Sixteen microsatellite markers within and flanking the *SNCA* gene were selected for analysis (table 1). As previously reported, DNA fragments around these polymorphic markers were amplified by PCR within the log-linear range using fluorescently tagged primers.[13] The resultant products were denatured and electrophoresed on an ABI PRISM 3100 Genetic Analyzer running GeneMapper v3.5 software (Applied Biosystems). Marker sizes were determined with length standards (GeneScan 500 Rox Size Standard; Applied Biosystems) consistent with CEPH genotype standards (http://www.cephb.fr/cephdb/php/eng/). The ratio of peak heights (first/second peak) of heterozygous individuals was calculated and compared between patient samples, diploid and *SNCA* triplication controls.

Affymetrix 250K microarray genotyping and single-nucleotide polymorphism dosage analysis. Total genomic DNA samples for the probands of Branch I and Branch J were processed according to the Affymetrix GeneChip Mapping 500K Assay Manual (Affymetrix, CA). In brief, 250 ng of genomic DNA was digested and ligated to an *Nsp*1 Adaptor (Affymetrix) using T4 DNA ligase (New England Biolabs, Beverly, MA). Amplification was performed over 30 cycles, using ethylenediaminetetraacetate to terminate each reaction and verified on a 2% gel. Pooled product was then eluted through a DNA Amplification Clean-Up plate (Clontech Laboratories, CA). The amplified DNA was subsequently fragmented into products less than 150 bp in length. Fragments were end-labeled, denatured, and hybridized to a GeneChip Mapping 250K *Nsp* array (Affymetrix). Incubation, washing, and staining were carried out according to the GeneChip Mapping Assay Manual, using standard protocols on an Affymetrix Fluidics Station 450. Arrays were scanned once with the Affymetrix GeneChip Scanner 3000 and analyzed with Affymetrix GTYPE Software to generate genotype calls.

GTYPE exported genotype calls and signal intensities (.cel files) were used to estimate copy number using the dChipSNP program.[14,21,22] This algorithm uses a rigorous "within and between" array normalization method to compute estimates of the normal signal values for genotype calls observed with a set of arrays. Deviations from the normal signal values seen for any particular genotype in the set of abnormal DNA samples were compared with values observed for a set of nine samples with normal 2N copy numbers. Copy number changes were then inferred by median smoothing or a hidden Markov model.

Bioinformatics. The reference sequence for the human genome is based on NCBI Build 34 (hg17, May 2004), produced by the International Human Genome Sequencing Consortium. Sequence alignment comparisons were made using VISTA and repetitive elements identified using CENSOR.[23,24]

Results. *Genealogic studies.* Dates of birth and genders of the maternal siblings in Branch J are consistent with part of the Lister family complex originally published by Henry Mjönes (1949). Parish records from the same region of southern Sweden subsequently identified birth and emigration records for the grandfather of the proband in the Swedish-American kindred (Branch I).[13] Details on this individual's father were consistent with an affected male (Ia) in the Lister family complex (figure 1). Mjönes documents this individual with disease onset at age 33 and death at age 54, similar to the proband with *SNCA* triplication (Branch I). However, whereas genetic, geographic, and clinical data are consistent with the pedigree drawn, the genealogic relationship illustrated remains hypothetical (dashed line; figure 1). Historical records indicate the grandfather[1] was adopted, which we speculate was necessitated by his parent's early death.[7]

Clinical findings in Branch J with SNCA duplication. The proband presented with symptomatic orthostatic hypotension at age 71, followed by progressive parkinsonism within 1 year. The motor symptoms were poorly responsive to L-dopa and progressed rapidly. The orthostatic hypotension was severe, requiring drug treatment with midodrine, which decreased the frequency of syncopes. The clinical diagnosis of MSA was raised though remained doubtful owing to a positive family history of PD. Four years after the onset of parkinsonism, the tremor at rest was minimal, but the patient was wheelchair bound due to rigidity and frequent falls and had moderate urinary incontinence. Spontaneous myoclonus in the distal upper extremities developed within 5 years. There was no ataxia, dystonia, or clinical signs of polyneuropathy. MRI showed only a slightly widened left Sylvian fissure and mild white matter

Table 2 *Clinical comparison of probands with SNCA-MMRN1 multiplication*

	Branch J	Branch I
Age at onset, y	71	31
Rigidity	Yes	Severe, generalized
Bradykinesia	Yes	Yes
Rest tremor	Mild, intermittent	Yes
Postural instability	Pronounced with falls	Mild to moderate
Response to l-dopa	Slight	Dramatic effect initially
Orthostatic hypotension	Early, symptomatic, required drug treatment	Moderate to severe, early in illness, required drug treatment
Urinary incontinence	Moderate	Late in illness
Dementia	Late, MMSE 20/30	Early, severe
Paranoia, anxiety	Short episode	Early, pronounced
Depression	Short episode	History of depression between ages 13 and 19, suicidal later in illness
Hallucinations	Visual, olfactory, and auditory upon treatment with amantadine, persistent after discontinuation	Pronounced, visual, auditory, and olfactory
Glabella/snouting reflex	Positive	Late in illness
Apomorphine test	Negative	Not done
Motor fluctuations	Moderate	Severe dykinesias
Olfaction	Not tested	Impaired sense of smell
Myoclonus	Late, in distal upper extremities	No
Essential tremor	No	Yes

MMSE = Mini-Mental State Examination.

disease. The signal intensity in the posterior lateral putamen on T2-weighted images was reduced. ([123]I)–beta–CIT SPECT 5 years after onset of motor symptoms showed a pronounced, symmetric reduction in dopamine transporter binding in the striatum (putamen > caudate; 3.6/4.0 dx/sin [ref > 8.1]) (see figure E-1 on the *Neurology* Web site at www.neurology.org), consistent with a diagnosis of MSA.[25] On examination at 78 years, 6 years after onset of motor symptoms, the proband showed severe bradykinesia and rigidity. Evaluation with the Unified Multiple System Atrophy Rating Scale gave a score of 25 of 48 points on the activities of daily living part, 41 of 56 on the motor part, and a global disability scale rating of 4 of 5.[26] The Schwab and England Activities of Daily Living rating was 20% and the Hoehn and Yahr Parkinson scale was stage 5. The proband had a history of deep venous thrombosis and died at age 80 owing to gastric bleeding, possibly exacerbated by warfarin treatment for an earlier pulmonary embolism. The family declined to give consent for an autopsy.

In Branch J, 7 of 19 family members in the last two generations were affected by parkinsonism, consistent with an autosomal dominant pattern of disease inheritance (figure 1). Limited clinical data for other affected family members were obtained from medical records and proxy interviews and are summarized in the legend to figure 1.

Clinical findings in Branch I with SNCA triplication. Early-onset parkinsonism, cognitive decline, dementia, and autonomic failure has previously been described for the proband of the Swedish American family (Branch I) and were comparable with those previously documented for *SNCA* triplication carriers.[13,17] In brief, the proband first presented at age 31 with rapidly progressive parkinsonism, including tremor, bradykinesia, and rigidity that was L-dopa responsive. At age 45, he developed both visual and auditory hallucinations, accompanied by marked paranoia. Past medical history revealed that he had had depression between ages 13 and 19 and was treated with thorazine. Later in his illness he had a brief suicidal ideation. He showed an impaired sense of smell and interestingly he was a smoker (2 packs/day). Postural hypotension was severe, and a diagnosis of MSA was raised on two occasions. With disease progression, intellectual impairment became evident, and by age 47 he had become increasingly confused and difficult to understand. Over the next 5 years, he became severely demented and apathetic with unintelligible speech. He had severe, generalized rigidity and died of pneumonia at age 52 in a persistent vegetative state requiring tube feeding. The proband's mother, aunt, and grandfather developed parkinsonism and subsequently dementia at a relatively young age, consistent with autosomal dominant inheritance of disease (figure 1). No myoclonus was reported. A comparison of the clinical findings in the *SNCA-MMRN1* duplication and triplication probands is summarized in table 2.

In Branch I, postmortem examination of brain tissue has previously been described.[13] In brief, neuronal degeneration in the substantia nigra and locus ceruleus was severe with occasional Lewy bodies. These inclusions were more numerous in the hypothalamus, the basal nucleus of Meynert, the temporal cortex, and the cortex on the convexity of the brain. Neuronal loss was also prominent in the basal nucleus of Meynert and in the cornu ammonis (CA 2/3) region of the hippocampus, a feature common to

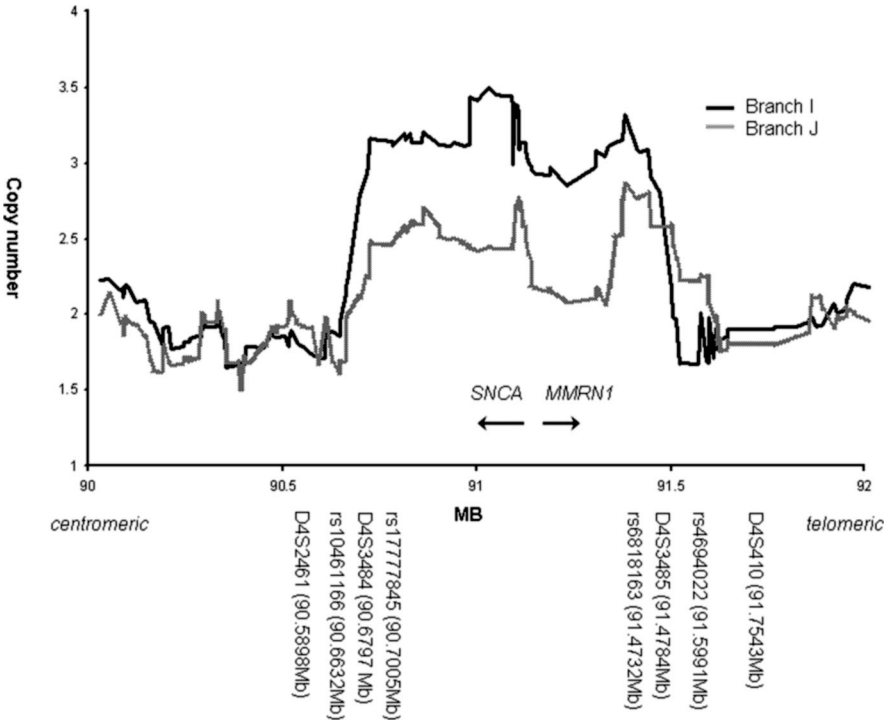

Figure 2. Genomic dosage of probands across the SNCA-MMRN1 locus. Copy number estimates based on analysis of GeneChip Mapping 250K Array data for chromosome 4q21, 90- to 92-Mb centromeric to telomeric. Estimates were derived using dChipSNP software to compare signals and genotypes for all the probe features in a set of arrays (see http:/ /biosun1.harvard.edu/complab/dchip/index.html for additional details and software). A value of 2.0 indicates normal diploid genomic copy number; results for the proband of Branch J are in black and for the proband of Branch I in red. Flanking marker and gene annotations are to scale. No other chromosomal regions showed any significant copy number changes in these probands. Note the highest copy number changes are for Branch I and throughout the multiplied region, whereas Branch J has less amplification.

patients with *SNCA* missense and multiplication mutations.[17,27,28] The end-stage pathology was most consistent with a diagnosis of diffuse Lewy body disease.

In Branch I, each generation had a family member affected by early-onset parkinsonism consistent with an autosomal dominant pattern of disease inheritance (figure 1).[13] Limited clinical data for other affected family members were obtained from medical records and proxy interviews and are summarized in the legend to figure 1.

Genomic analysis. For Branch J, DNA was available only from the proband. Sequencing of the α-synuclein gene proved normal; however, real-time PCR dosage analysis of *SNCA* exons 2 and 3 found abnormal values (between 1.35 and 1.77) indicative of a duplication mutation. Analysis of polymorphic microsatellite repeat markers around chromosome 4q21 confirmed this result; D4S3484, D4S2485, and D4S3479 had three distinct alleles, whereas D4S2304, D4S3475, D4S3476, D4S3480, D4S3474, and D4S3485 had peak area ratios suggestive of three alleles (table 1). Genotypes within and flanking the duplicated region in the proband were identical to genotypes in the Swedish American family (Branch I) albeit with a *SNCA* triplication,[13] and were indicative of a common founder. Higher-resolution qualitative and quantitative genomic analysis was achieved using standard 250K Affymetrix arrays. On chromosome 4q21, 62 contiguous single-nucleotide polymorphisms (SNPs) showed evidence for an increase in dosage in both Branch I and Branch J, from rs17777845 to rs6818163 (90.7005 to 91.4732 Mb), containing only the coding sequence of α-synuclein (91.00 to 91.12 Mb; *SNCA*) and multimerin 1 genes (91.17 to 91.23 Mb; *MMRN1*) (figure 2). The array results were consistent with an *SNCA* duplication in Branch J and an *SNCA* triplication in Branch I. Hybridization signals and allele calls within each peak suggest a tandem multiplication of the same genomic interval. The centromeric breakpoint lies between SNP rs10461166 and microsatellite D4S3484 (90.663 to 90.680 Mb), in an interval of 17 kb and the telomeric breakpoint between microsatellite D4S3485 and SNP rs4694022 (91.478 to 91.599 Mb), in an interval of 120.7 kb. Simple alignment of both flanking sequences revealed a noncoding fragment of 5.2 kb with 92.8% nucleotide sequence identity (cen 90668488 to 90673680 bp and tel 91506765 to 91511959 bp), which corresponds to long interspersed repeat elements (LINE L1).

Discussion. *SNCA* missense and multiplication mutations are a rare cause of parkinsonism, dementia, and autonomic failure.[11] To date, 10 families have been identified with de novo chromosome 4q21 duplication or triplication mutations[13-16] (unpublished data) involving the *SNCA* locus (table E-1). However, the size of these genomic rearrangements varies between families and typically includes adjacent genes. Given this background and the limited number of families and individuals affected, it has been difficult to make a direct comparison of clinical and genetic findings. Here we report two branches of a Swedish family with a 0.7987- to 0.9359-Mb chromosome 4q21 duplication (Branch J) and triplication (Branch I), which include only the *SNCA-MMRN1* loci encoding genes for α-synuclein and multimerin 1. Genealogic and geographic data suggest both Branch I and J are ancestrally related to the Lister family complex, which Henry Mjönes was so careful to document.[7] Genetic evidence for a common founder is supported by shared microsatellite allele sizes within the duplicated *SNCA-MMRN1* region, and both genealogic and genetic data are consistent with the same *SNCA* multiplication having been inherited from a common ancestor.

Parkinsonism was the predominant and present-

ing feature in the five families with *SNCA* duplications previously reported.[14-16] When reported autonomic dysfunction was mild and did not require treatment, only one patient had hallucinations and cognitive decline. In contrast, clinical symptoms of the index patient of Branch J resembled symptoms usually seen in MSA (summarized in table 2 and Results). Clinical comparison of these families clearly suggests that the clinical phenotype of *SNCA* duplication carriers can be more variable with regard to disease progression, age at onset, and symptoms than previously anticipated and does not necessarily resemble that of idiopathic PD. Although *SNCA* duplication cases have yet to come to autopsy, GCIs as found in MSA are also observed in *SNCA* triplications.[13,17,29,30] The proband of Branch I with an *SNCA-MMRN1* triplication has features comparable with affected individuals within the Iowa kindred,[17,29] with rapidly developing clinical symptoms of DLB.[13] Interestingly, families with *SNCA* A53T and E46K missense mutations have been noted to have similar symptoms.[27,28]

Both *SNCA-MMRN1* multiplication families described here share a common founder. The mechanism responsible for large-scale genomic duplications is most likely due to recombination and unequal crossing-over.[31] Classic examples from neurogenetics include chromosome 17p12 duplication in Charcot–Marie–Tooth (type 1) and deletion in hereditary neuropathy with liability to pressure palsies, both of which involve a 1.4-Mb region flanked by two 24-kb low copy number repeats.[32] Comparison of microsatellite variability at D4S3479 suggests the initial duplication found in Branch J was caused through recombination of the 163 allele onto a 167 or 169 background. Subsequently, we propose the 163 allele was subject to a tandem duplication in Branch I. Comparative sequence analysis suggests unequal crossing-over in 4q21 may have been mediated by flanking centromeric and telomeric LINE L1 repeats, a retrotransposon family specific to mammalian genomes. Bioinformatic analysis has yet to determine whether homologous L1 regions are found at the centromeric and telomeric breakpoints of all *SNCA* multiplication mutations.

As these families share the same haplotype, albeit with three or four copies of the *SNCA MMRN1* locus, the difference in their clinical phenotype may be directly attributed to an increased dosage of these two genes. *MMRN1* encodes multimerin 1, a specific Factor V/Va binding protein found in platelets and endothelium.[33] Multimerin deficiency is associated with Factor V Quebec, an inherited bleeding disorder, but the consequences of overexpression are unknown. In this regard, it is interesting to speculate *MMRN1* overexpression may have contributed to the deep venous thrombosis and pulmonary embolism noted in the proband of Branch J. Multimerin is not expressed in brain; thus, wild-type overexpression of α-synuclein appears responsible for the predominant, neurologic phenotype. Functional studies in brain tissue have previously demonstrated that *SNCA* genomic copy number and gene expression are directly related.[13,17,29] Three or four copies of *SNCA* results in a 50 and 100% increase in wild-type α-synuclein expression and clearly has a dramatic effect on disease onset, severity, and progression. Hence, therapies that seek to lower α-synuclein expression may be neuroprotective in *SNCA* multiplication kindreds.

The expanded Lister family complex now provides an unparalleled opportunity to look at the natural history of this form of parkinsonism, to explore the relationship of phenotype to *SNCA* dosage, to assess early clinical features and biomarkers of disease/progression, in affected and asymptomatic carriers, and to investigate potential disease-modifying therapies.

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RETIRED MEMBER CONSORTIUM MEETS TO EXPLORE FUTURE OPPORTUNITIES

The AAN's new Retired Member Consortium for members who have retired or are nearing retirement will have its first meeting on Wednesday, May 2, 2007, from 7:30 am to 9:00 am at the Hynes Convention Center during the AAN Annual Meeting. The consortium will explore how the Academy may best serve its retiring members and provide a sense of community for those who are considering retirement or no longer actively practice neurology. For more information visit am.aan.com/retired or contact Laurie Weyandt at lweyandt@aan.com or (800) 879-1960.

BACK BY POPULAR DEMAND: CLAY WALKER RETURNS TO GALA AUCTION

The AAN Foundation Gala is delighted to welcome Country music star Clay Walker back to the Gala Auction at the 2007 AAN Annual Meeting in Boston. Walker and his band will entertain Gala attendees with a live performance of a variety of hit music. Join us Wednesday, May 2, for a memorable evening of dinner, dancing, and a live auction to raise support for research in neurology. Bring your colleagues and reserve a department table. Visit am.aan.com/gala for more information.

Phenotypic variation in a large Swedish pedigree due to *SNCA* duplication and triplication

J. Fuchs, C. Nilsson, J. Kachergus, et al.

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