**Supplementary clinical information**

**Patient DEL1-1**

A now 40-year-old man of East Asian ancestry developed a tremor affecting his right hand and titubation of the head at age 34 years. Prior to the onset of this symptom, he reported no significance health issues, apart from occasional migraine headaches, gout, and dyslipidemia.  There was no associated event or trigger: he had no fever, no injury, and no recreational drug use. As symptoms worsened he developed impaired balance as well as urinary frequency and orthostatic lightheadedness. Within 6 years, tremors, both small and large amplitude, affecting both hands, made it impossible for him to write or use eating utensils. He reported a constant headache. His gait was unsteady and he had to stop working. He did not have significant swallowing problems and had not lost any weight. He denied any impairment to his vision or hearing. He reported some dysphagia with dry foods. He had an episode of encephalopathy with pneumonia at age 38 years.

Physical examination demonstrated mild obesity (BMI:  29 kg / m^2) and no dysmorphologic features. Cranial nerve examination was normal. He had full motor power initially and then developed spastic weakness in the lower extremities. Sensation was intact. Deep tendon reflexes were brisk with clonus and crossed adductor response. Plantar response not elicitable on the right and up going response on the left. He had impaired finger-to-nose pointing with intention tremor. His voice was breathy, halting, and tremulous. He had a continuous no-no head shaking tremor. He was unable to perform tandem gait. His gait was unstable and spastic.

Normal results were obtained for urine organic acids, plasma homocysteine, very long chain fatty acids, vitamin E, copper, ceruloplasmin, ammonia, plasma amino acids, urine oligosaccharides, urine mucopolysaccharides, cholestenol and galactocerebrosidase. Genetic testing for CADASIL, FXTAS, SCA1,2,3,6,7 were negative. Very long fatty acids and arylsulfatase A were normal. He had normal CSF studies.  There was no family history of similar symptoms.

**Patient DEL2-1**

A 59-year-old, left-handed, male, retired mechanic presented at age 52 years with recurrent leg cramps, particularly at night. There was no history of autonomic dysfunction (e.g. orthostatic hypotension, impotence, or dry skin). In the subsequent years, he developed slowly progressive spasticity in his lower extremities and a wide-based ataxic gait. At 54 years, he developed tremor in his lower limbs, difficulty in fine motor activities, fine end point nystagmus on both right and left lateral gaze, and urinary incontinence. His leg cramps persisted until his death at age 59 years. His vision, hearing, and cognition remained relatively preserved. His medical history was noteworthy for well-controlled hypertension, gastro-esophageal reflux, arthritis, and chronic anxiety. Of his 3 siblings, his sister had similar neurologic symptoms. His mother, who died suddenly of a myocardial infarct in her 50s, had difficulty ambulating and frequent falls, but a more detailed description was unavailable. The patient’s oldest brother died from bone cancer. The patient had no children.

Laboratory investigations during life were inconclusive. Electrolytes, blood counts, and hepatic, renal, and thyroid function tests were unremarkable. Serum lactate, pyruvate, copper and ceruloplasmin, amino acids, arylsulfatase, very long chain fatty acids, beta-galactosidase, and beta-N -acetylhexosaminidase A and B levels were all normal. Urine tests for methylmalonic acid and organic acids were normal. His vitamin B12 levels were borderline low on 1 occasion, prompting supplementation, but without improvement. Electromyography studies were normal.

Genetic tests for *NOTCH3* mutations and spinocerebellar ataxias were negative. His sister who had similar symptoms was tested for *LMNB1* duplications and none were found.

**Patient DEL3-1**

A 40-year-old female of Scottish/Irish and Native American heritage presented with 3-year history of dysarthria and hypophonia followed by progressive difficulties with weakness and clumsiness of her upper extremities and difficulties ambulating due to a combination of imbalance and weakness. She reported no symptoms of dysautonomia such as constipation, urinary incontinence or orthostatic lightheadedness or syncope.

On exam, her mentation was normal except for depressed mood. Speech was hypophonic and dysarthric. She had asymmetrical central facial weakness and poor elevation of the soft palate, bilateral asymmetric spasticity and weakness of all four extremities. Her base of support was wide and she ambulated with a combination of cerebellar and spastic features. Reflexes were brisk throughout and her plantar responses were extensor.

The patient’s sister (DEL3-2) and father (DEL3-3) were deceased after experiencing an illness with similar progressive neurological deterioration.

A spinal tap was unrevealing and EMG and NCV studies were normal. Formal dysautonomia testing including quantitative sudomotor axon reflex test (QSART), heart rate (HR) modulation during deep breathing and valsalva maneuver, and blood pressure and HR during tilt testing were all normal. Dilated eye exam revealed normal optic disks and retinas. Central motor conduction times by transcranial magnetic stimulation (tmsCMCTs) revealed delayed latencies to activation of upper extremity muscles and absent responses to the lower extremity muscles.

**Patient DEL3-2**

A 35-year-old Caucasian female started having symptoms at age 34 years. She initially realized slurring of speech and then recognized hand incoordination. Her gait at the time was only slightly unbalanced. She suffered from progressive neurological worsening and subsequently developed weakness in her hands, left greater than the right, and legs. At the time of evaluation, she could walk unassisted but preferred to hold onto somebody. Her speech had worsened and she realized difficulty expressing. She was able to comprehend when people were talking to her. She developed swallowing difficulties, both to liquids and solids. She was getting tired easily and complained of shortness of breath. Her vision as well as hearing were reported as normal. She had no abnormal movements or numbness and tingling, muscle atrophy or fasciculations. Her memory was reported as preserved. She had recently stopped working because of her neurological illness and drove only on occasion.

Neurological examination was remarkable for apraxia of speech as well as of motor movements such eye closing, wrinkling her forehead or opening her mouth. She had mild bilateral peripheral optic nerve pallor. She had limitation of upward gaze as well as interrupted saccades and pursuit. No obvious nystagmus. Motor examination revealed mild spasticity in the extremities. She had upper motor neuron weakness in her upper extremities of moderate degree, and in the lower extremities of mild degree, left greater than right. Her brisk deep tendon reflexes were brisk with right knee jerk clonus and bilateral non-sustained ankle clonus. Her plantar responses appeared equivocal. Rapid alternating movements were slowed in the upper and lower extremities. Finger to nose testing and heel to shin testing did not reveal a significant coordination problem. Her gait was predominantly spastic with a bouncing quality while her tandem gait was near normal. She was able to stand on her heels and toes for a brief period of time. Romberg could not be assessed because of inability to follow verbal instructions to close her eyes.

Spinal fluid analysis that showed 1 WBC, 1 RBC, normal protein (37 mg/dL), normal glucose (69mg/dL) and negative Lyme titers and cryptococcal antigen. The CSF ACE level was 21.

**Patient DEL3-3**

Onset of symptoms occurred at age 32 in the form of right-handed incoordination noted while playing the guitar. Symptoms were particularly prominent in the afternoons or after a day of vigorous work at a steel mill. Three years later he began dragging his right foot and his right sided weakness gradually worsened in a stepwise fashion; there were periods of rapid decline followed by weeks or months of stability. By age 38 he could walk two miles without a cane but would stumble. At age 39, he noticed weakness in the left leg and left hand. There were no sensory deficits or visual changes. Language was generally preserved although there are some word finding difficulties superimposed on severe dysarthria. There was occasional urinary incontinence due mostly to difficulties getting up to the bathroom. The family was adamant that he was very “heat sensitive”. For example, at age 38, he went into a steam bath and was unable to walk for minutes until he took a long cold shower.

Family history was notable for maternal grandfather given a diagnosis of MS. The mother was one of 12 siblings, was unaffected, but one maternal aunt who had "a mild form” of MS.

On neurological exam, mental status was normal except for minimal difficulties with math calculations. Speech was severely dysarthric. There were no memory difficulties, comprehension deficits, apraxia or neglect. Affect is described as “pseudobulbar”. Cranial nerves were normal. On motor exam, he was unable to stand unsupported and required assistance transferring to a chair. The muscle tone was increased with spasticity worse on the right than on the left along with corresponding asymmetrical weakness of upper and lower extremity muscles, more pronounced in distal muscle groups. There were no cerebellar or sensory deficits. Deep tendon reflexes were exaggerated in both upper and lower extremities but particularly at the ankles where he had 3 to 4 beats of clonus. Upgoing toes were elicited bilateral bilaterally. Neurovascular exam is normal. There was no clinical evidence in support of significant dysautonomia.

EKG was normal. He had a normal electrocardiogram and normal routine blood studies (CBC, electrolytes and routine blood chemistry). Ceruloplasmin was normal. CSF analysis revealed 2 WBC/mm3, 92% lymphocytes, 8% monocytes. Glucose was 54 mg/dl and protein 46 mg/dl. The CSF index was 0.36 with IgG 2.4 mg/dL, albumin 23.7 mg/dL and synthesis rate 0.00. Oligoclonal bands were negative.

ARSA levels, peroxisomal screen, vitamin E, HEXA activity, beta- and alpha-galactosidase activities were normal. Phytanic acid and serum/urine screen for inborn errors of metabolism were negative as well.

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| --- | --- | --- | --- | --- | --- | --- | --- |
| **Family ID** | **Centromeric junction\*** | **Telomeric junction\*** | **Deletion size**  **(Kb)** | **Centromeric repeat** | **Telomeric repeat** | **Microhomology at junctions** | **Distance of deletion junction from LMNB1 ‘ATG’ start site (bp)** |
| ADLD-1-TO | 125386030 | 126046459 | 660 | (TA)n, AluSx | AluSz | 23 bp | 66742 |
| DEL1 | 125857895 | 126108379 | 250 | Alujr | AluSp | None | 4822 |
| DEL2 | 125492412 | 126101296 | 609 | AluSg7 | AluSP | 26 bp | 11905 |
| DEL3 | 125352465 | 126024979 | 673 | 10bp LINE homology | LINE (LIMC5) | None | 88222 |

**Table e-1: Details of genomic deletions upstream of *LMNB1***

\*All coordinates are from GRCh37/hg19

**Table e-2: *LMNB1* expression in patient cells**

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| --- | --- | --- | --- | --- |
|  | **PBMCs** | | **Fibroblasts** | |
|  | **DEL1-1** | **CTRLs** | **DEL1-1** | **CTRLs** |
| **Mean** | 4.69 | 1.01 | 2.45 | 1.00 |
| **± SEM** | 0.12 | 0.04 | 0.05 | 0.03 |
| **p-value** (vs CTRLs) | <0.0001 |  | <0.0001 |  |

\* All data were analyzed using Mann-Whitney *t-test*. Values are calculated relative to controls using average of at least two independent experiments. PBMC- peripheral blood mononuclear cells