Current Date

To Whom It May Concern,

Mr. John Doe is from the 5th generation of individuals (see attached partial genetic chart) in the first American family known to have the autosomal dominate genetic mutation identified in 2009 as MATR3 gene, DNA Sequence Variation c.254 C>G, which results in the amino acid substitution p.Ser85Cys. Frequently referred to as simply MATR3, Ser85Cys.

This mutation has been shown to result in two condition;

- Amyotrophic Lateral Sclerosis 21 (ALS 21).

and

- Distal Myopathy Type 2 (aka VCPDM)

As of 2015, 36 active cases have been identified within the US.

National Institutes of Health (NIH) published its genetic findings in March of 2014 that established the connection between this mutation and familial ALS [Traynor, B. *et al. Nature Neuroscience* **17**, 664–666 (2014)]. NIH is currently conducting detailed clinical exams as the second phase of its research with a report anticipated in 2016. For additional research information contact Dr. Bryan Traynor MD, Chief of the Neuromuscular Disease Unit, NIH.

During 2014 and 2015, family members have had the diagnosis of familial ALS confirmed by; Dr. R. S. Bedlack at Duke Medical Center, Dr. Benjamin Brooks of Carolinas HealthCare Systems, and Dr. S. P. Ringel at University of Colorado Hospital.

NIH neurological exam results for 6 family members has been attached along with a typical medical report for from an ALS Clinic.

Sincerely,
Ralph E. Thompson
Researcher, VCPDM.org

Attached;

- 5 Generational Inheritance Chart - Doe, John
- Typical Medical Report from an ALS Clinic
- 2013 NIH Neurological Exam Results for 6 Family Members (USALS#4)

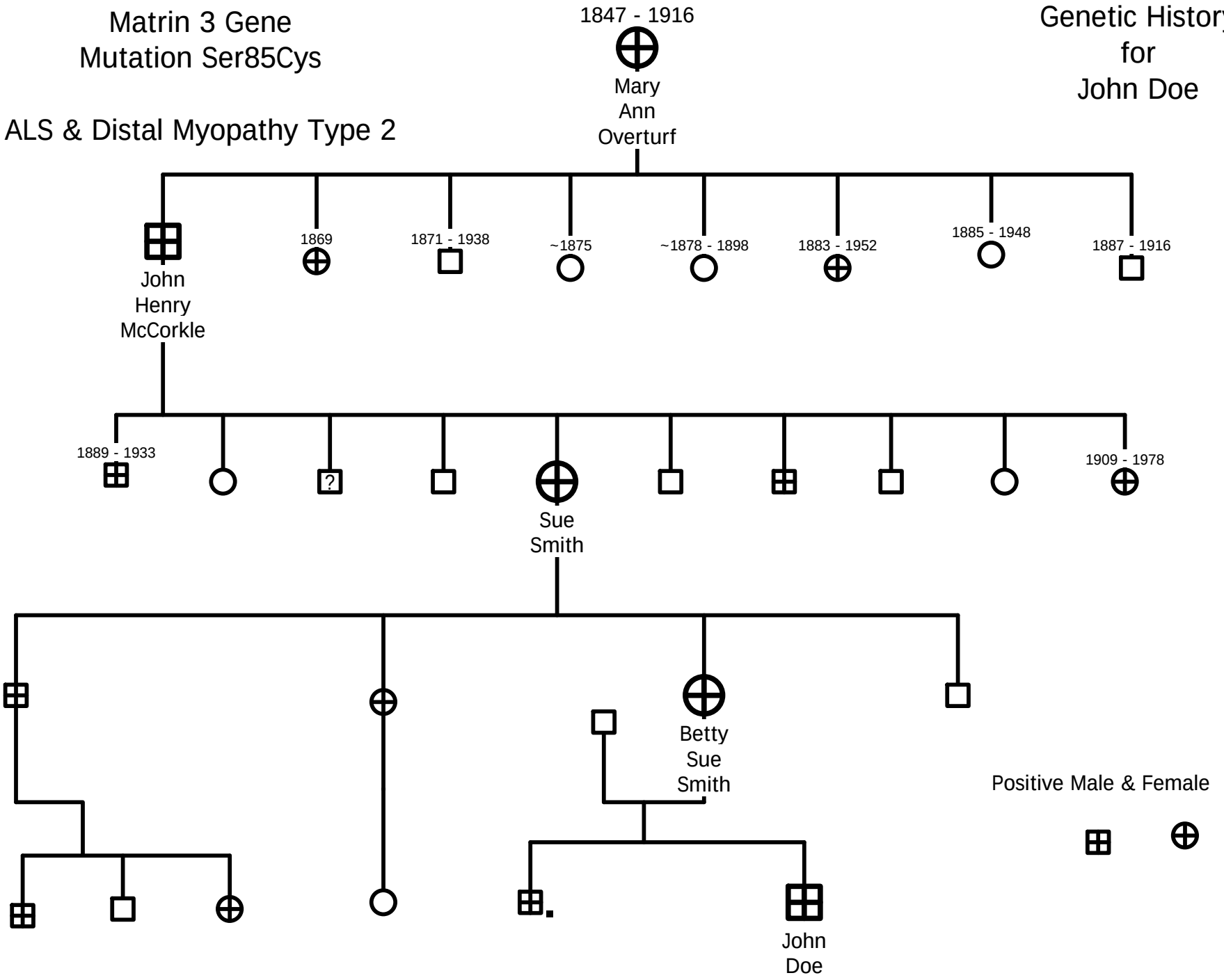
Sample

DRAFT

Matrin 3 Gene
Mutation Ser85Cys

ALS & Distal Myopathy Type 2

Genetic History
for
John Doe



Typical Medical Report

[redacted]

[redacted]

University of Colorado Hospital

UNIVERSITY OF COLORADO HEALTH

[redacted]
6/12/2014 Office Visit
MRN : [redacted]

Dept **720-848-2080**
Phone:
Encounter [redacted]
#:

Description: [redacted]
Provider: **Ringel, Steven P, MD**
Department: **Neurology Op**

Diagnoses

Familial ALS (amyotrophic lateral sclerosis) - Primary
Distal myopathy

Reason for Visit

Follow-up

Vitals - Last Recorded

BP	Pulse	Temp	Ht	Wt	BMI
150/68	97	36.1 °C (97 °F) (Temporal Artery)	1.727 m (5' 8")	[redacted]	[redacted] kg/m2

Progress Notes

Ringel, Steven P, MD 6/12/2014 12:06 PM Signed
Assessment and Plan:

	ICD-9-CM
1. **Familial ALS (amyotrophic lateral sclerosis)**	**335.20**
2. Distal myopathy	359.1

Medications Placed This Encounter
Medications
[redacted]

The patient has an extremely rare autosomal dominant form of familial ALS due to a mutation in the Matrin 3 gene. This causes progressive weakness, dysphagia, respiratory muscle weakness and frontotemporal dementia. I am recommending:
- talk to pulmonologist (William Kelly MD) about starting BIPAP at night for his restrictive lung disease
- see speech therapy in Grand Junction for swallowing assessment
- acquire a motorized wheelchair.(we will arrange for a loaner chair from MDA until he receives Medicare and can order a new power chair). Since he has a diagnosis of familial ALS, he will be eligible for Medicare immediately after he receives disability
[redacted]

Subjective:

Patient ID: [redacted] is a [redacted] male who presents to Neurology for follow up.
HPI

The patient saw me on one previous occasion two years ago because he was experiencing increasing weakness in his feet and hands over many years. The patient's father, 3 uncles and 3 brothers all have this disease. His father and one brother died of respiratory muscle failure. The family was reported in 1998 (Am J. Hum Genet1998;63:1732-42:) A second family was reported in 2009 (Am J Hum Gen 2009;84:511-18). The disorder is caused by a missense mutation in the gene encoding the nuclear matrix protein - matrin 3.

Description of the USALS#4 pedigree (Ser85Cys)
NIH Exams – January 2013

The proband of the USALS#4 family, developed right foot drop at 44 years of age. Muscle weakness spread to the remaining limbs over the next 2 years. A diagnosis of Charcot-Marie-Tooth disease was made at the age 46 on the basis of a neurogenic pattern observed in an electromyogram and nerve conduction studies (EMG/NCS). Reevaluation 2 years later led to the patient's illness being reclassified as non-Scandinavian distal myopathy. The patient's condition progressed, with the development of dysarthria and mild dysphagia by the age of 53 and respiratory failure requiring nocturnal noninvasive ventilation by the age of 56. Currently, at age 65, the subject uses a power wheelchair for mobility.

Neurological examination at age 65 revealed mild dysarthria, perioral fasciculations, a brisk jaw jerk and moderately weak neck extension. There was generalized muscle wasting and pyramidal-distribution weakness in all four limbs. In the upper limbs, shoulder abduction was 3/5 bilaterally, elbow extension was 4/5, wrist extension and finger extension were 1/5, and finger abduction, finger adduction and thumb abduction were 3/5, whereas shoulder adduction, elbow flexion, wrist flexion and abductor digiti minimi were 5/5 bilaterally. In the lower limbs, hip flexion was 4/5 bilaterally; ankle dorsiflexion, ankle plantar flexion and extensor hallucis longus were 0/5, whereas hip abduction, hip adduction, knee flexion and knee extension were 5/5 bilaterally. Tendon reflexes were absent, and toes were mute on Babinski testing. Proprioception and vibration sensation were diminished to the level of the ankles and knees, respectively, bilaterally. The patient was able to stand and walk slowly using a walker and with the assistance of one person.

Patient V:2. A cousin of the proband noticed right foot drop at 42 years of age. Within 5 years, the muscle weakness had spread to involve both hands. The patient developed dysarthria and mild dysphagia at age 47 and respiratory failure requiring supplemental oxygen and noninvasive ventilation at 49. The patient had an episode of aspiration pneumonia at age 55 that required prolonged intubation and ventilation. Currently, at age 57, the patient uses a power wheelchair but can walk slowly using a walker.

Neurological examination at age 57 revealed mild dysarthria, mild facial weakness, poor palate elevation and a brisk jaw jerk. Limb examination showed generalized muscle atrophy and a pyramidal pattern of weakness. In the upper limbs, shoulder abduction and elbow extension were 4/5 bilaterally, wrist dorsiflexion was 1/5, finger extension and thumb abduction were 3/5, and finger flexion and abductor digiti minimi were 4/5, whereas shoulder adduction, elbow flexion and wrist flexion were 5/5 bilaterally. In the lower limbs, hip flexion was 4/5 bilaterally, and ankle dorsiflexion, ankle plantar flexion, toe flexion and toe extension were 1/5, whereas hip abduction, hip adduction, knee flexion and knee extension were 5/5 bilaterally. Deep tendon reflexes were absent in the upper limbs. The right knee jerk was 2+, and the left knee jerk was brisk (3+). Ankle jerks were absent and toes were mute on Babinski testing. There was loss of pinprick and temperature sensation to the mid-calf level bilaterally.

Patient V:7. A cousin of the proband observed right leg weakness at 33 years of age. Symptoms progressed to the point that the patient has been using a power wheelchair since 57, although continuing to walk slowly using a rollator walker as part of an exercise regimen. Hand weakness developed at age 60, and the subject had an episode of aspiration pneumonia requiring prolonged intubation and hospitalization at age 63. The patient has required nocturnal noninvasive ventilation and daytime oxygen supplementation since that time. Mild dysphagia and occasional choking episodes required changes in food consistency.

Neurological examination at age 65 revealed mild dysarthria, mild facial weakness and a brisk jaw jerk. Generalized limb atrophy and pyramidal-distribution weakness was evident. In the upper limbs, shoulder abduction, elbow flexion and elbow extension were 4/5 bilaterally, wrist extension was 3/5, finger extension was 4/5 and thumb abduction was 3/5, whereas shoulder adduction, wrist flexion and adductor digiti minimi were 5/5 bilaterally. In the lower limbs, hip flexion was 4/5 bilaterally, hip abduction and hip adduction were 3/5, knee flexion and knee extension were 1/5, ankle dorsiflexion and ankle plantar flexion were 0/5, and toe extension was 1/5 bilaterally. Deep tendon reflexes were absent in all four limbs, and toes were mute on Babinski testing. Temperature sensation was diminished to the mid-calf level bilaterally.

Patient V:8. A cousin of the proband presented with dysarthria and choking at 47 years of age. The patient developed left ankle weakness at age 52. Weakness had

spread to both hands by age 58. Currently, at age 63, the patient has difficulty using eating utensils and walks with the aid of a walker.

Neurological examination at age 63 revealed dysarthria with nasal air escape, poor palate elevation, tongue fasciculations and a brisk jaw jerk. There was marked distal atrophy and weakness. In the upper limbs, wrist extension was 4/5 bilaterally, finger extension and thumb abduction were 3/5, and left abductor digiti minimi was 4/5, whereas bilateral shoulder abduction, shoulder adduction, elbow flexion, elbow extension, wrist flexion and right adductor digiti minimi were 5/5. In the lower limbs, ankle dorsiflexion and ankle invertors were 3/5 bilaterally and extensor hallucis longus was 4/5, whereas hip flexion, hip extension, hip abduction, hip adduction, knee flexion, knee extension, ankle plantar flexion and foot evertors were 5/5 bilaterally. Triceps reflexes were brisk (3+) bilaterally, whereas other deep tendon reflexes in the upper limbs were normal (2+). Knee jerks were brisk (3+) bilaterally, ankle jerks were absent, and toes were mute on Babinski testing. Vibration sensation was diminished to the level of the ankles bilaterally.

Patient V:13. A cousin of the proband noticed mild dysarthria and throat-clearing difficulties at 42 years of age. At age 44, the subject developed right leg weakness that spread to involve the left leg and both hands by age 51. The patient occasionally chokes when eating. Currently, at age 58, the patient remains mobile with the aid of bilateral ankle orthotics.

Neurological examination, at age 58, revealed trace dysarthria. There was prominent distal muscle atrophy. In the upper limbs, right shoulder abduction was 4/5 bilaterally and wrist extension and finger extension were 3/5, whereas shoulder adduction, elbow flexion, elbow extension, wrist flexion and finger flexion were 5/5 bilaterally. In the lower limbs, left hip flexion was 4/5, ankle dorsiflexion was 2/5 bilaterally and extensor hallucis longus was 3/5, whereas hip extension, hip abduction, hip adduction, knee flexion, knee extension and ankle plantar flexion were 5/5 bilaterally. In the upper limbs, reflexes were diminished (1+). In the lower limbs, knee jerks were brisk (3+ with crossed adductors), ankle jerks were absent, and the toes were mute on Babinski testing. All sensory modalities were intact.

Patient V:15. A cousin of the proband developed hand weakness at 49 years of age. Currently, at age 50, the patient complains of fatigue, frequent cramping of the right foot, and mild dysarthria when fatigued.

Neurological examination, at age 50, revealed bilateral thenar and first dorsal interossei muscle atrophy. In the upper limbs, wrist extension, finger extension and thumb abduction were 4/5 bilaterally, whereas shoulder abduction, shoulder adduction, elbow flexion, elbow extension, wrist flexion and finger flexion were 5/5 bilaterally. In the lower limbs, extensor hallucis longus was 4/5 bilaterally, whereas all other muscle groups were 5/5. Reflexes in the upper limbs were 2+ with the exception of the left brachioradialis, which was diminished (1+). In the lower limbs, knee jerks were brisk (3+ with crossed adductors) bilaterally, ankle jerks were absent, and toes were downgoing on Babinski testing. Vibration sensation was diminished to the level of the ankle bilaterally. The patient had difficulty with heel walking and toe walking.

In summary, the clinical features of patients in the Ser85Cys *MATR3* kindred were consistent with a progressive, fatal motor neuron disease with combined upper and lower motor neuron signs, bulbar dysfunction and respiratory failure.