Supplemental data

**Diverse myopathological features in the congenital myasthenia syndrome with GFPT1 mutation**

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Figure S1. Repetitive nerve stimulation (RNS) at 3Hz in patient one revealed positive decrement of compound muscular action potential (CMAP) in the deltoid. RNS at 3Hz in patient two revealed positive decrement of CMAP in the deltoid and abductor digiti minimi muscle.
Table S1. Description of the *GFPT1* gene variants.

| Chr | Pos  | rsIDs     | Ref | Alt | Transcript | Protein | VEP Annotation | Clinical Significance | Allele Freq |
|-----|------|-----------|-----|-----|------------|---------|----------------|------------------------|--------------|
| 2   | 69590695 | rs201322234 | G   | A   | c.331C>T   | p.Arg111Cys | missense         | Pathogenic (ClinVar)   | 0.000139211  |
| 2   | 69590694 | rs189717232 | C   | T   | c.332G>A   | p.Arg111His  | missense         | Pathogenic (ClinVar)   | 0.000010625  |
| 2   | 69556825 | rs1024585946 | G   | A   | c.1534C>T  | p.Arg512Trp  | missense         | Disease (HGMD)         | 0.000003978  |

Source gnomAD database v2.1.1 @http://gnomad.broadinstitute.org; http://www.hgmd.org.
Table S2. The clinical summarization of GFPT1-related CMS patients with muscle biopsy.

| Age at onset/age at report (in years) | Clinical features | CK Elevations x | EMG | Muscle biopsy TAs | Therapy Response to AChE inhibitors |
|--------------------------------------|-------------------|----------------|-----|-------------------|----------------------------------|
|                                      | Clinical features |                |     |                   |                                  |
|                                      | Symptom at onset/motor milestones | Facial/bulbar/respiratory muscle weakness/other | Limb girdle weakness/fluctuation/course | RNS: decrement at 3Hz%/muscle | Abnormal SFEMG/Myopathic changes |
|                                      |                   |                |     |                   |                                  |
| P1/m/NA/Iran/p.D348Y,homozygous      | 6/31              | Muscle weakness, fatigue, worse in summer/normal | Yes/no/no/distal limb | X 1.5 | Yes/Proximal | ND/ND | Yes | Positive, side effects |
|                                      |                   |                |     |                   |                                  |
| P2/f/Turkey/p.W240X,homozygous       | 6/26              | Muscle weakness, fatigue and pain/normal | None | Yes/yes/worsening | Normal | 14/distal | Yes/yes | Yes | Positive |
|                                      |                   |                |     |                   |                                  |
| P3/NA/Libya/p.R111C,homozygous       | 6/23–35           | Muscle weakness, fatigue/normal | None | Yes, shoulder > pelvic girdle/ND/ND | Normal | 65–35/Trapezius | ND/yes | Yes | Partially positive |
|                                      |                   |                |     |                   |                                  |
| P4/m/Spain/p.M492T and c.*22C > A    | 14/55             | Weakness in the upper limbs/normal | No/no/no/distal limb | X1.5 | 21/deltoid | Yes/yes | Yes | Positive |
|                                      |                   |                |     |                   |                                  |
| P5/m/Spain/p.M492T and c.*22C > A    | 10/50             | Weakness, falls/normal | No/no/no/distal limb | X1.5 | 26/deltoid | Yes/yes | Yes | Positive, +3,4 DAP |
|                                      |                   |                |     |                   |                                  |
| P6/m/Germany/p.D43V and p.I121T      | 5/16              | Muscle weakness/normal | None | Yes/yes/slight worsening | X2–8 | Yes | ND/ND | Yes, on re-revision | Positive |
|                                      |                   |                |     |                   |                                  |
| P7/m/UK/p.R385H and p.R434H          | 8/23              | Fatigue on walk/slight delayed | Yes/no/slight/slight neck and distal limb weakness | X2 | Yes/anconeus | Yes/ND | Yes | Positive, +3,4 DAP |
|                                      |                   |                |     |                   |                                  |
| P8/m/UK/p.T15M and p.R496W           | 6/37              | Repeated falls/normal | Yes/no/no/distal limb | X5–10 | Yes | Yes/ND | Yes | Positive, +3,4 DAP |

**Note:** Table entries are based on clinical observations and laboratory results. CK = creatine kinase; EMG = electromyography; RNS = repetitive nerve stimulation; SFEMG = single fiber electromyography; AChE = acetylcholinesterase; ND = normal; DAP = disease-associated protein.
| Case # | Gender | Nationality | Mutation | Age at onset/age at report (in years) | Clinical features | CK Elevations x | EMG | Muscle biopsy TAs | Therapy Response to AChE inhibitors |
|--------|--------|-------------|----------|--------------------------------------|------------------|----------------|-----|------------------|-----------------------------------|
| P9/I/Germany/ p.V199F and c.*22 > A | f | 13/26 | Fatigue/normal diabetes | None | Yes/yes/stable | Normal | 30-60/ trapezius | ND/yes | Yes, on revision |
| P10/I/Senegal/ p.R512W, homozygous | f | 1/7 | Muscle weakness, falls/normal | None | Yes/yes/worsening | Normal | 35/ trapezius | ND/yes | Suggestive |
| P11/m/Spain/ p.M491T, homozygous | m | 7/19 | Muscle weakness/normal | None | Yes/no/stable | Normal | No/distal | ND/yes | One Inclusion |
| P12/m/Spain/ c.1278_1281dup and c.*22C > A | m | 1/37 | Muscle weakness, falls/slight delayed | No/no/no/neck and distal muscles | Yes/yes/worsening | Normal | 67/ Proximal | Yes/yes | Unspecific myopathic changes |
| P13/m/Spain/ c.1278_1281dup and c.*22C > A | m | First decade/39 | Muscle weakness/normal | No/no/no/neck muscles | Yes/yes/worsening | Normal | 14/deltoid | Yes/yes | Yes |
| P14/m/Italy/ p.T15A and c.621-622del | m | 10/55 | Muscle weakness/normal | None | Yes/no/worsening | Slightly | Yes/ trapezius | ND/yes | Yes |
| P15/m/Italy/ DNA not available | f | 7/36 | Muscle weakness/normal | None | Yes/no/ND | Slightly | Yes/ Proximal | ND/yes | Yes |
| P16/m/Italy/ p.222-223insA and p.R111C | m | First decade/40 | Muscle weakness/normal | None | Yes/yes/worsening | Normal | X12 | 50/ proximal | Yes/yes | Positive, +3,4 DAP |
| P17/I/Malta/ p.M491T and c.714_715insA | f | 8/9 | Frequent falls, fatigability when walking/delayed | Learning difficulties | Yes/yes/worsening | Slightly | No/distal | ND/ND | No |
| P18/m/Malta/ p.M491T and c.714_715insA | m | 7/13 | Difficulties in running, fatigability/normal | Learning difficulties | Yes/yes/worsening | Slightly | ND | ND/ND | No |

**Clinical features:**
- CK Elevations x:
  - Normal
- EMG:
  - RNS: decrement at 3Hz%/muscle
  - Abnormal SFEMG/Myopathic changes
- Muscle biopsy TAs:
  - ND/yes
- Therapy Response to AChE inhibitors:
  - Positive
  - Suggestive
  - One Inclusion
  - Positive, +3,4 DAP
  - Positive
  - Positive, +3,4 DAP
  - Positive
  - Positive
  - Positive, +3,4 DAP
  - Positive at first, but worsening after 2 years of treatment. Improvement with addition of 3,4 DAP
  - Positive at first, but effect lost after 3 years of treatment
| Patient | Gender/ | Age at onset/ | Symptom at onset/ | CK | EMG | Muscle biopsy TAs | Therapy Response to AChE inhibitors |
|---------|---------|--------------|------------------|----|-----|------------------|-----------------------------------|
| P19     | m/Korea/p.E256Q and p.M499T | 13/15 | Difficulties in climbing stairs and lifting heavy objects, fatigue/normal | None | Yes/NA/NA | X 1.5 | 67.1/trapezius 17.1/flexor carpi ulnaris | Yes/yes | Yes | Positive |
| P20     | m/NA/c.1700-1716delp17 and c.*22C > A | 0/16 | Poor cry, apneic spells/delayed | No/no/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | Yes | Positive, +3,4 DAP |
| P21     | l/NA/p.Arg545Pro and c.*22C > A | 8/12 | Difficulty climbing steps/NA | No/yes/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | Yes | Positive, +3,4 DAP |
| P22     | f/NA/c.606-8A>G and c.*22C > A | 12/20 | Unable to squat/NA | No/yes/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | No | Positive, +3,4 DAP |
| P23     | m/NA/p.Asp113Gly and p.Met492Thr | 19/56 | NA/NA | No/yes/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | Yes | Positive, +ephedrine |
| P24     | m/NA/p.Arg17X and c.*22C > A | 12/12 | Unable to keep up with peers/NA | No/yes/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | No | Positive, +3,4-DAP, albuterol |
| P25     | f/NA/c.686-2A>G and p.Arg304X | 0/1 month | Hypotonia, arthrogryposis, weakness of all except the ocular muscles/NA | Yes/yes/yes/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | Yes | Limited response to pyridostigmine, 3,4-DAP |
| P26     | m/NA/p.Arg111Cys, homozygous | 10/18 | Difficulty climbing steps/NA | No/yes/no/distal limb | Yes/NA/progressive | NA | Yes | NA/yes | Yes | Positive |
|   | Clinical features | CK Elevation n x times | EMG | Muscle biopsy TAs | Therapy Response to AChE inhibitors |
|---|-------------------|------------------------|-----|------------------|-----------------------------------|
|   | Age at onset/age at report (in years) | Symptom at onset/motor milestones | Facial/bulbar/respiratory muscle weakness/other | Limb girdle weakness/fluctuation/course | RNS: decrement at 3Hz%/muscle | Abnormal SFEMG/Myopathic changes |   |
| P27/f/NA/ p.T350I and c.1337delA | 9/64 | Difficulty walking /NA | No/no/no/distal limb | Yes/NA/progressive | Mildly elevated | Yes | NA/yes | Yes | Positive |
| P28/m/NA/ p.Met1fsX2 and p.Thr15Met | 4/9 | Difficulty walking, clumsy /NA | No/no/no/distal limb | Yes/NA/stable | NA | Yes | NA/yes | Yes | Positive, +3,4 DAP |
| P29/f/USA/ c.IVST-8A>G and c.*22C>A | 13/68 | Difficulties with running, climbing stairs and keeping her arms up/NA | Yes/no/no/neck and distal muscles | Yes/NA/NA | Mildly increased | ND | ND/yes | No | Positive, +3,4 DAP |
| P30/f/ Australia/ c.686-2A>G and p.M358V | 0/13 | Congenital hypotonia/delayed | Yes/no/no/contractures, scoliosis | Yes/NA/NA | Normal | Yes | NA | No | Positive |
| P31/m/Turkey c.686-2A>G, homozygous | 13 month/s/17 | Difficulties in rising from the floor/normal | No/no/no/neck and distal muscles, mild scoliosis | Yes/NA/NA | X4 | NA | NA/yes | No | NA |
| P32/NA/France / p.Gly39_Lys75 delinsGlu and p.Arg111His | First decade/68 | Muscle weakness, fatigability/NA | No/no/no/distal limb | Yes/yes/worsening since 50 years | X 1.5-3 | 20/trapezius 44/quadriceps 21/abductor digiti minimi 38/tibialis anterior | NA | Yes | Moderate improvement with AChEI and 3,4-DAP |
| P33/NA/France / p.Arg111Cys, homozygous | 1/49 | Muscle weakness/NA | No/Mild/N/0/distal limb | Yes/yes/worsening since 45 years | X 2 | 50/trapezius | NA | Yes | The same as P32 |
| P34/NA/France / p.Thr392Pro and p.Met499Arg | 6/18 | Fatigability/NA | No/no/no/distal limb | Yes/yes/NA | X1.5 | 52/trapezius 49/ancones 45/tibialis anterior | NA | Yes | The same as P32 |
| Clinical features | CK Elevations | EMG | Muscle biopsy | Therapy Response to AChE inhibitors |
|-------------------|---------------|-----|---------------|-----------------------------------|
| Age at onset/age at report (in years) | Symptom at onset/motor milestones | Facial/bulbar/respiratory muscle weakness/other | Limb girdle weakness/fluctuation/course | RNS: decrement at 3Hz%/muscle | Abnormal SFEMG/Myopathic changes | |
| P35/f/France/ p. Arg111Cys, homozygous | 6/16 | Fatigability/NA | No/no/no/slight transient ptosis, distal limb | Yes/yes/stable | Normal | 34/trapezius 38/ancones 33/tibialis anterior | NA | Yes | The same as P32 |
| P36/f/France/ p. Arg111Cys, homozygous | 2.5/15 | Muscle weakness/NA | No/no/no/distal limb | Yes/yes/worsening then stability in the last 4 years | Normal | 50/trapezius 54/ancones 19/abductor digiti minimi 57/tibialis anterior | NA | Yes | Moderate improvement, slight improvement with 3,4-DAP |
| P37/NA/France / p. Arg111His and p. Met317Leu | 15/21 | Muscle weakness/NA | No/no/no/distal limb | Yes/yes/slight worsening | X2 | 68/trapezius 28/ancones 40/tibialis anterior | NA | Yes | Moderate improvement with AChEI and 3,4-DAP |
| P38/m/Nepal/ p. Arg14Leu, homozygous | 5/7 | Proximal weakness/basically normal | No/no/no/bilateral retinoschisis | Yes/NA/NA | Normal | Yes | No/yes | No, maintained fascicular architecture; focal areas of degeneration, regeneration; ragged red fibers | Positive |
| P39/m/Afghan/ p. Thr151Lys, homozygous | 0/5 | Delayed walking/delayed | None | Yes/NA/NA | NA | NA | NA | The same as P38 | NA |
| P40/f/Japan/ c.722_723insG, homozygous | 1.5/38 | Difficulties in walking and running/normal | None | Yes/yes/worsening | Normal | 22.5/right median nerve | No/yes | Yes | Positive |
| P41/m/China/ p. Lys154Asn and p. Asn363Ser | 5/23 | Fatigability/NA | None | Yes/yes/stable | Normal | 55/trapezius 62/quadriceps 46/abductor digiti minimi | NA/yes | Yes | Positive |
| P42/m/Mexica/ p. Arg230Ter, homozygous | 0/8 | Congenital hypotonia, low muscle bulk, dysphagia requiring gastrostomy/delayed | Yes/yes/yes/head and distal muscles | Yes/no/worsening | NA | 14/abductor pollicis minimi 39/trapezius | Yes/NA | No, a population of abnormally small muscle fibers that was suggestive of a myopathy | NA, negative with 3,4-DAP |
| Sample ID | Age at Onset/Onset at Motor Milestone | Symptom at Onset | Facial/Respiratory Muscle Weakness | Limb Girdle Weakness/Flexion/Foot Drop | CK Elevation Times | EMG | Muscle Biopsy TAs | Therapy Response to AChE Inhibitors |
|-----------|--------------------------------------|-----------------|----------------------------------|----------------------------------------|-------------------|-----|-----------------|-----------------------------------|
| P43       | 0/2                                  | Intubated       | Yes/yes/head and distal muscles  | Yes/no/worsening                      | NA                | NA  | NA              | No, a mild necrotizing myopathy with extensive autophagic vacuolar pathology |
| P44       | 4/15                                 | Frequent falls, difficulties in walking, running and jumping/normal | No/no/no/mild bilateral ptosis, hilar muscles of the upper limbs | Yes/yes/worsening at age 11          | X2.5              | 42/50/18       | Yes/yes | Yes, with rimmed vacuoles Aleviated partially, improvement with albuterol |
| P45       | 0/4                                  | None            | Yes/NA/NA                        | Normal                                 | Yes               | No/no | Mild changes or non-specific myopathies | NA |
| P46       | 6/14                                 | None            | Yes/NA/NA                        | X1.5                                  | Yes               | NA  | NA              | Positive |
| P47       | 5/18                                 | None            | Yes/NA/NA                        | X2                                    | Yes               | NA/yes | Yes             | Positive |
| P48       | 0/17                                 | None            | Yes/NA/NA                        | Normal                                 | Yes               | NA/yes | Yes             | Positive |
| P49       | 17/47                                | None            | Yes/yes/cervical weakness        | Yes/NA/NA                              | Normal            | Yes  | NA/yes | Yes             | Positive |
| P50       | 3/14                                 | None            | Yes/NA/NA                        | Normal                                 | Yes               | NA/yes | Mild changes or non-specific myopathies | Positive |
| P51       | 7/15                                 | None            | Yes/NA/NA                        | Normal                                 | Yes               | NA  | Yes             | Positive |
The above cases in table S1 came from 14 literatures (Patient 1-18, Patient 19, Patient 20-28, Patient 29, Patient 30, Patient 31, Patient 32-37, Patient 38-39, Patient 40, Patient 41, Patient 42-43, Patient 44, Patient 45-51), which are listed in the order of publication time.

**Abbreviations:**
- P1: patient 1
- LGM: limb-girdle muscle weakness
- M: male
- F: female
- NA: not available
- ND: not done
- TAs: tubular aggregations
- CK: creatine kinase
- EMG: electromyography
- 3, 4-DAP: 3, 4-Diaminopyridine
- RNS: repetitive nerve stimulation
- SFEMG: single fiber EMG
- AChEI: acetylcholinesterase inhibitors