Biallelic POC1A variants cause syndromic severe insulin resistance with muscle cramps

Biallelic *POC1A* variants cause syndromic severe insulin resistance with muscle cramps

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Abstract

Objective: To describe clinical, laboratory and genetic characteristics of three unrelated cases from Chile, Portugal and Saudi Arabia with severe insulin resistance, SOFT syndrome, and bi-allelic pathogenic *POC1A* variants.

Design: Observational study.

Methods: Probands' phenotypes, including short stature, dysmorphism and insulin resistance, were compared with previous reports.

Results: Cases 1 (female) and 3 (male) were homozygous for known pathogenic *POC1A* variants: c.649C>T, p.(Arg217Trp) and c.241C>T, p.(Arg81*), respectively. Case 2 (male) was compound heterozygous for p.(Arg217Trp) variant and the rare missense variant c.370G>A, p.(Asp124Asn). All three cases exhibited severe insulin resistance, acanthosis nigricans, elevated serum triglycerides and decreased HDL-cholesterol, and fatty liver, resembling three previously reported cases. All three also reported severe muscle cramps. Aggregate analysis of the six known cases with bi-allelic *POC1A* variants and insulin resistance showed decreased birth weight and length [mean (SD) -2.8 (0.9) and -3.7 (0.9) SDS, respectively], severe short stature [mean (SD) height -4.9 (1.7) SDS] and moderate microcephaly [mean occipitofrontal circumference -3.0 (range -4.7 to -1.2)]. These findings were similar to those reported for patients with SOFT syndrome without insulin resistance. Muscle biopsy in Case 3 showed features of muscle involvement secondary to a neuropathic process.

Conclusions: Patients with SOFT syndrome can develop severe dyslipidaemic insulin resistance, independent of the exonic position of the *POC1A* variant. They also can develop severe muscle cramps. After diagnosis, patients should be regularly screened for insulin resistance and muscle complaints.

Introduction

SOFT syndrome (MIM#614813), denoting Short stature, Onychodysplasia, Facial dysmorphism, and hypoTrichosis, is the name coined for a rare primordial dwarfism syndrome encompassing severe growth failure of prenatal onset, craniofacial dysmorphism, sparse hair, and digital abnormalities (1). In 2012, two groups reported that the syndrome was caused by bi-allelic variants in *POC1A*, encoding the Proteome Of Centrioles 1A (POC1A) protein (1-3). POC1A is an important luminal component of centrioles, playing roles in the function of centrosomes, spindle poles, and ciliary basal bodies (4-6).

Since these initial reports (1-3), 12 additional affected kindreds have been described (7-16). In addition to the cardinal syndromic features, three of 31 patients reported to date also manifested severe dyslipidaemic insulin resistance (IR) (7, 11, 16). All 3 harboured pathogenic variants in exon 10, raising the possibility of a distinct, exon-specific "variant POC1A-related" (vPOC1A) subsyndrome (11). However, an exon 9 variant in the most recently reported patient with IR (16), and variants outside exon 10 in two further individuals with early-onset type 2 diabetes (DM2) (2), suggest that IR may be part of the wider SOFT syndrome phenotype, and not uniquely associated with exon 10 variants.

We now present clinical, biochemical and genetic characteristics of three unrelated patients carrying biallelic pathogenic *POC1A* variants outside exon 10 who show clinical features of SOFT syndrome plus severe dyslipidaemic IR, providing further evidence that severe IR with or without DM2 is a frequent component of SOFT syndrome. All three also suffer from severe muscle spasms and cramps, reported only in one patient to date (2).

Case reports and methods

Study approval

Patients were enrolled in genetic research projects or were referred for diagnostic genetic testing. All investigations were conducted according to Declaration of Helsinki principles. Clinical data and images

were collected with signed informed consent from participants/families. Permission was obtained to publish images in **Figures 1-3** and **Supplementary Figure 1**.

Case reports

Detailed clinical information on the three cases is presented in the **Supplementary Information on clinical presentations** and their developmental history, clinical history and physical examination findings are summarized in **Table 1**.

Case 1 is a 21.5-year-old Chilean woman born to healthy parents of normal height (**Figure 1A**) with an extremely low birth size and poor postnatal growth (**Table 1, Figure 1B**). Further clinical features include microcephaly; bilateral hip pain; prominent forehead; deep-set eyes; hypoplastic nostrils; smooth philtrum; thin upper lip; light skin; café au lait macules; joint hyperlaxity; broad hands and feet with broad thumbs/big toes; and broad upper legs (**Figure 1.C-H**). Radiographs showed short phalanges, cone epiphyses of the distal phalanges, pseudo-epiphysis in the middle phalanx of the second finger and fifth finger clinodactyly with bone age 7.9 years (chronological age 8.7 years) (**Figure 1.K).** Femoral necks were asymmetrical with abnormal remodelling, shortening and deformity (**Figure 1.L**). Endocrine assessment showed transient elevated serum IGF-I, increased plasma insulin concentration (**Supplementary Table 1**) and a normal GH response to clonidine. Breast development was relatively early but menarche was delayed and followed by oligomenorrhoea. Hair became progressively dry, sparse and brittle (**Figure 1.J**), with increased scalp sensitivity.

Recombinant human growth hormone (rhGH) plus a GnRH analogue was administered from 10.1 to 11.6 years resulting in a small increase of height SDS, but was discontinued due to the poor growth response and development of acanthosis nigricans and hypertension. From 18 years onward, muscle cramps have been the major complaint, affecting limbs, abdominal muscles, tongue and jaw. The EMG needle triggered painful vastus lateralis spasms, leading to prolonged continuous muscle activity (**Fig**

1.I). Cramps subsided with amitriptyline. Metabolic evaluation (**Supplementary Table 1**) showed progressive IR (treated with metformin), elevated serum triglycerides and fatty liver.

Case 2 is a 25-year-old man, the only child of unrelated Portuguese parents. His mother is healthy and normal-statured. His father is short (-2.1 SDS), with a prematurely aged appearance, hearing impairment, obesity, premature loss of dentition, but normal intellectual ability (**Figure 2A**). The proband was born with a low birthweight and showed poor postnatal growth (**Table 1**, **Figure 2B**) and centripetal adiposity (body mass index 2.5 SDS) (**Figure 2C-F**). Further clinical features include brachydactyly; mild fifth finger clinodactyly with broad, short nails; scattered depigmented patches on the abdomen; irregular café au lait patches on the lower back; joint hypermobility; supernumerary teeth; and mild acanthosis nigricans. Rapid, patchy hair loss was noted at age 25 years.

rhGH therapy from 9.5 to 10.5 years yielded no benefit, and was discontinued due to excessive weight gain. Metabolic assessment showed extreme fasting hyperinsulinaemia without diabetes, reactive hypoglycaemia, fatty liver, and mildly elevated serum creatine kinase (**Supplementary Table 2**). From 13.6 years he has intermittently complained of muscle cramps. At 25 years old, he reported severe muscular pains, significantly worse than in teenage years. These were spasmodic, associated with paraesthesia in the fingers, and were exacerbated by cold.

Case 3 is a 32-year-old Saudi Arab male born to parents who are first cousins and were diagnosed with DM2 at 42 years of age (**Figure 3A**). The proband was born small for date (**Table 1**) and showed poor postnatal growth (**Figure 3B**) and delayed developmental milestones (current IQ 68). Further clinical features include several facial dysmorphisms **(**detailed in **Supplementary Information**); brachydactyly; posteriorly rotated, low set ears; small, broad hands and feet with hypoplastic distal phalanges and nails; widely spaced first and second toes; single palmar creases; alopecia; and centripetal adiposity (**Fig 3B**). A skeletal survey (**Figure 3C**) revealed short femoral neck and phalanges, short left third metacarpal and metatarsal bone, hypoplastic distal phalanges and nails, and short, thick long bones.

GH deficiency was suspected and rhGH therapy given from 8 years of age for 6 years, but information on serum IGF-I, GH stimulation testing and growth response is unavailable. Metabolic assessment showed nuchal and axillary acanthosis nigricans, DM2, non-proliferative diabetic retinopathy, persisting fatty liver, hypercholesterolaemia and hypertriglyceridaemia (**Supplementary Table 3**). For the borderline low plasma testosterone no cause was found. At 26 years, muscle cramps in legs and chest on exertion and at rest were reported, with elevated serum creatinine kinase concentration. Muscle biopsy (**Supplementary Figure 1**) showed nonspecific myopathic changes suggestive of a secondary neuropathic process.

Laboratory investigations

Details of genetic analysis are presented in **Supplementary information on genetic analyses**. Biochemical investigations were undertaken in accredited hospital laboratories. The presented reference ranges are as provided by these laboratories, except for fasting plasma insulin, triglycerides, cholesterol, HDL-cholesterol and LDL-cholesterol. Reference ranges for fasting insulin in prepubertal children (to 11 years) were from Peplies et al (17), for pubertal adolescents from Ballerini et al (18), and for young adults from Tohidi et al (19). For plasma lipids we used the recommendations of the Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (20).

Analysis of facial characteristics

Frontal facial photographs and clinical and genetic information of the three cases presented and eight previously reported [three from (3), single patients from (7, 9, 13, 14, 16)] were uploaded to the Face2Gene (FDNA inc, USA) platform. A “DeepGestalt” of the facial features of SOFT syndrome was generated, as previously reported for other syndromes (21).

Results

In Case 1 a rare homozygous *POC1A* missense variant [c.649C>T, p.(Arg217Trp)] was found, as previously reported in a Chilean girl with SOFT syndrome (13). In Case 2 and his mother the same p.(Arg217Trp) variant was identified in heterozygous form. A second rare heterozygous missense variant [c.370G>A), p.(Asp124Asn)] was detected in Case 2 but not his mother. The father was unavailable for study, but based on these findings the *POC1A* variants in the proband were deemed highly likely to be compound heterozygous. Case 3 harboured the same homozygous truncating variant in *POC1A* reported by Shaheen et al in a Saudi family (3) [c.241C>T, p.(Arg81*)]. Further details on these genetic variants are shown in **Supplementary Table 4**.

All known cases with SOFT syndrome and IR or DM2 are summarised in **Supplementary Table 5**. All six fully documented cases had acanthosis nigricans, insulin resistance, elevated triglycerides, and fatty liver. Data from three members of the large Arab pedigree reported by Shalev et al (2), two of whom were reported to have DM2, are also shown. For these cases evaluation of plasma insulin, acanthosis nigricans and fatty liver was unavailable, but serum triglycerides were increased [4.6, 6.2 and 5.5 mmol/L (reference < 1.3 (20)] and HDL-cholesterol levels were low [0.9, 1.1 and 1.1 mmol/L, reference >1.2 (20), personal communication, Dr. Shalev].

Supplementary Table 6 shows the anthropometric profile of all reported cases, stratified by presence of IR. All except two patients without IR were younger than 15 years. In contrast, all patients with IR were older than 22 years. Auxological findings were similar between groups. Birth weight and length were low except for patients with the p.(Leu171Pro) variant (2). In contrast, head occipitofrontal circumference (OFC) at birth was normal in almost all patients resulting in relative macrocephaly. Average height was -5 to -6 SDS, with a wide range (-9 to -2 SDS), while OFC was relatively spared (mean approximately -3 SDS).

Based on analysis of facial characteristics of our patients and 8 reported previously, a general facial representation of patients with SOFT syndrome ("DeepGestalt") was generated (**Supplementary Figure 2)**, featuring a prominent nose with a broad tip and broad mouth. Subjective

inspection showed a triangular face in young children, less striking in older subjects. The syndrome is not yet recognized by the algorithms, which require further images for training (21).

Discussion

This report conveys two main messages. First, it solidifies dyslipidaemic IR and fatty liver as being associated with loss of *POC1A* function, showing this is not exclusive to pathogenic variants in exon 10. Second, it suggests that muscle involvement, likely secondary to neuronal dysregulation, is a novel phenotypic feature of SOFT syndrome.

Besides the dyslipidaemic IR in our three cases and three previously reported (7, 11, 16), we know of three cases with early onset DM2 in a family reported in 2012 (2). Two of these were reported, with one further case diagnosed at 26 years' old (Dr. Shalev, personal communication). Nine cases of SOFT syndrome with reported dyslipidaemic IR, or 26% of all reported cases, are thus known. In most cases with IR, *POC1A* variants are outside exon 10, and anthropometric data do not discriminate cases with or without IR (**Supplementary Table 6**). We believe there is no basis to classify patients with bi-allelic *POC1A* variants and IR as having a specific subsyndrome as previously suggested (11). The prevalence of IR in SOFT syndrome would likely be higher if patients were biochemically screened from childhood onward. All but two previously reported cases without IR were younger than 15 years, while 8 of 9 cases with IR were adult at IR diagnosis (**Supplementary Table 6)**, suggesting that IR development is age-dependent.

The mechanism linking dyslipidaemic IR to *POC1A* variants is unknown, but other forms of monogenic IR offer clues. Dyslipidaemia and fatty liver are common and severe in monogenic IR caused by adipose tissue defects, and the trajectory of dyslipidaemic IR in SOFT syndrome is reminiscent of lipodystrophies, where metabolic derangement commonly becomes clinically manifest peripubertally (22). In contrast, primary insulin signalling defects (in *INSR* or *PIK3R1*) do not result in dyslipidaemia or fatty liver (23, 24). Interestingly, several other genetic defects affecting the centrosome/primary cilium also feature dyslipidaemic IR, including Alström Syndrome (e.g. (25), caused by biallelic *ALMS1* variants

(26) and Osteodysplastic Primordial Dwarfism of Majewski Type 2 (27), caused by biallelic *PCNT* variants (28). This suggests a possible unifying mechanism linking certain forms of centrosome dysfunction to IR, possibly mediated by effects on adipose tissue. Addressing this experimentally will be challenging due to the numerous functions of the centrosome, but viability of mice with *Poc1a* deficiency, which recapitulate skeletal manifestations of SOFT syndrome (29), will permit future studies.

Regarding the question of how loss of POC1A causes the broad clinical phenotype, we can only speculate. POC1A protein expression is nearly ubiquitous, so the pattern of tissue involvement cannot easily be explained by expression pattern alone. Given preliminary evidence of abnormal mitotic kinetics and perhaps shorter cilia in POC1A deficiency, and given recent evidence that cilia play a key role in adipocyte development in vivo (30), inefficient adipogenesis, or deranged kinetics of a mesenchymal stem cell pool, may impair the crucial function of adipose tissue in metabolic homeostasis. A similar phenomenon could be present in other tissues such as the epiphyseal growth plate, hair follicles, muscle and gonads. The effect of rhGH treatment in cases 1 and 2 was minimal, and in case 3 the low adult height achieved renders a positive effect of rhGH treatment unlikely. In case 1 this treatment coincided with worsened IR and increased blood pressure and in case 2 with increasing obesity. We therefore suggest that rhGH treatment is not indicated in SOFT syndrome.

To date, muscular cramps have not been included in SOFT syndrome (MIM # 614813), although reported in one Arab case (2). After we identified them as prominent complaints in our three cases, we approached a previously described patient with IR (7). She also reported severe muscle cramps in hands, neck, abdomen and legs from early childhood, usually at night, and more commonly in winter. A further patient described by Giorgio et al (11) subsequently also complained of muscle cramps (Drs. E. Rubino, A. Brusco; personal communication). Sica et al (31) (MIM %600771) reported two brothers with short stature (130-132 cm), sparse scalp and absent body hair, low set ears, large noses, high-pitched voices, enlarged cardiac ventricles, and severe “undulating” painful muscle spasms from 8-10

years. We believe these siblings likely had SOFT syndrome on clinical grounds. We therefore speculate that muscle cramps may be a common, albeit so far unrecognised, feature of the syndrome.

Muscle cramps and pain generally increased with exercise, associated with fasciculation-like twitches in limbs and elevated blood creatine kinase concentration. Electrophysiological evaluation, and some aspects of muscle biopsy, suggested a likely neurogenic origin. Further investigation and case descriptions are needed to elucidate the pathophysiology of neuromuscular involvement. Of note, the association between IR and muscle involvement is not unique to SOFT syndrome, however. The entity "acanthosis nigricans with muscle cramps and acral enlargement" (MIM 200170), was described in 1980 (32, 33) and features of severe IR with phenytoin-responsive muscle cramps have been reported (33, 34). No features clearly conforming to SOFT syndrome were described. Other conditions such as some laminopathies and congenital generalised lipodystrophy type 4, feature myopathy and lipodystrophic IR (35).

The composite image of SOFT syndrome generates a step towards automated assistance to clinicians in making diagnoses on upload of a facial image and clinical features (21). Since SOFT syndrome is rare, the database could ultimately be a value in facilitating early diagnosis and screening for complications, however further images are required to train recognition algorithms fully. Although modern diagnostic procedures in high-income countries tend to use a hypothesis-free approach (e.g. next generation sequencing techniques like exome sequencing (ES) and whole genome sequencing in the near future), we believe that visual recognition of a facial phenotype remains important, particularly in countries where genetic testing is not available or reimbursed.

In conclusion, patients with SOFT syndrome often manifest severe dyslipidaemic IR and muscle cramps, independent of the position of the *POC1A* variant. After diagnosis, patients should be regularly screened for IR and muscle complaints. Further studies are needed to clarify the pathophysiology of these clinical features of SOFT syndrome.

Figure Legends

Figure 1. Case 1. A: Pedigree (using INVITAE Family pedigree tool). M/M indicates a bi-allelic *POC1A* variant, M/W a heterozygous carrier. B: Growth curve (height for age) against CDC chart. C and D: Frontal and lateral photographs aged 8.8 years. E: Chest at 8.8 years showing the café au lait spot. F: Hands show brachydactyly and mild fifth finger clinodactyly and broad thumbs. The nails were broad and short. G: Feet show broad big toes. H: Broad upper legs. I: Muscle cramps aged 21.5 years. J: Scalp aged 21.5 years. K: The hand X-ray aged 8.7 years shows short phalanges, cone epiphyses of the distal phalanges, pseudo-epiphysis in middle phalanx of the index, clinodactyly of the little finger and slight delay in bone maturation. L: The pelvic X-ray aged 8.7 years shows asymmetric involvement of the femoral necks with abnormal remodelling, shortening and deformity.

Figure 2. Case 2. A: Pedigree (using INVITAE Family pedigree tool). M/M indicates a bi-allelic *POC1A* variant, M/W a heterozygous carrier. B: Height plotted against CDC charts. C-F: Frontal and lateral photographs aged 22.3 years.

Figure 3. Case 3. A: Family pedigree (using INVITAE Family pedigree tool). M/M indicates a bi-allelic POC1A variant, M/W a heterozygous carrier. B. Clinical features demonstrating the abnormal findings: 1) Short stature; 2) High forehead and frontal bossing; 3) Posterior low set ear; 4) Gynaecomastia; 5) Acanthosis nigricans; 6) Hypoplastic distal phalanges and nails; 7) Wide space between big and second toes. C. Radiological abnormalities: 1) Short third metacarpal; 2) Metatarsal bone; 3) Short Femoral neck; 4) Empty sella turcia.

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Declaration of interest

All authors declare no competing interests.

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Author contribution statement

VM, IH-D, DA, JB, CC, KA and RKS contributed by performing, interpreting and describing the clinical assessment of the patients. CdB advised on endocrine assessment, YH was responsible for uploading and interpreting facial dysmorphology, and EB advised on the diagnosis of the muscle phenotype. FSA, ML and RKS performed the genetic analyses. JMW coordinated the writing process. All authors contributed in data interpretation and various revisions of the manuscript and have approved the submitted manuscript.

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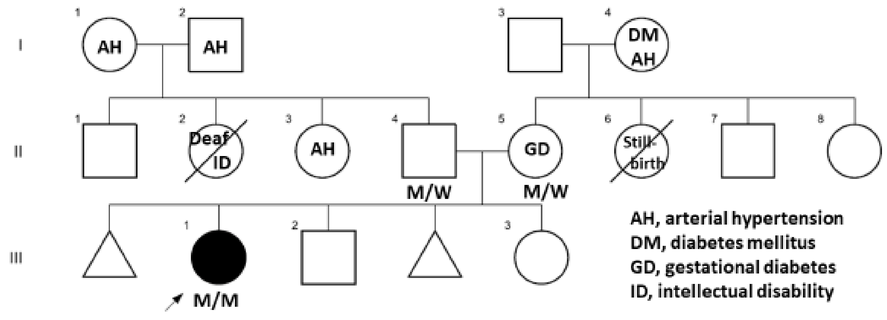
448

Table 1. Developmental history, clinical history and physical examination findings in the three cases

	Features	Case 1	Case 2	Case 3
Development	Gender	Female	Male	Male
	Current age	21 years	25 years	32 years
	Parents	Reportedly unrelated	Not related	First cousin consanguineous
	Birth weight	1520 g (-4.4 SDS)	2450 g (-3.2 SDS)	1800 g (-2.8 SDS)
	Birth length	39 cm (-5.5 SDS)	NR	45 cm (-3.0 SDS)
	Birth OFC	31 cm (-2.4 SDS)	NR	33 cm (-1.2 SDS)
	Psychomotor development	Normal	Normal	Delayed
	Linear growth	Severe growth failure. Adult height 120 cm (-6.6 SDS)	Severe growth failure. Adult height 127 cm (-7.2SDS)	Severe growth failure. Adult height 138 cm (-5.8 SDS)
Clinical observations	Insulin resistance	Insulin resistance which progressed to Type 2 diabetes	Insulin resistance with reactive hypoglycaemia	Insulin resistance which progressed to Type 2 diabetes
	Hypertension	Present, treated	NR	Absent
	Hyperlipidaemia	Diagnosed at 11 years	Diagnosed at 22 years	Diagnosed at 22 years
	Ophthalmological assessment	Astigmatism	NR	Mild non-proliferative diabetic retinopathy
	Pubertal development	Tanner B2 at 9.8 years, menarche at 15.3 years	Tanner G2 at 11 years; G3 (testes 8 ml) at 13.5 years	Absent (G1 at 21 years), gynaecomastia
	Muscle cramps	Onset aged 2 years	Onset aged 13 years	Onset aged 22 years
	Alopecia	Present	Present	Present
	Centripetal obesity	Absent (waist circumference 72 cm)	Present	Present
	Acanthosis Nigricans	Present from 10.1 years	Present from 13.5 years	Present from 21 years
	Hypotonia	NR	NR	Present
	High pitched voice	Present	Present	Absent
	Adult gonadal status	Partial ovarian failure (due to IR?)	NR	Borderline low plasma testosterone
Laboratory	Insulin	Increased	Increased	Increased
	Creatine Kinase	Increased	Increased	Increased
Additional findings	Empty sella turcica	NR	NR	Present
	Diffuse fatty liver	Present	Present	Present
	Kidney anatomy	Normal kidney ultrasonography	NR	Left ectopic kidney
	Electromyography (EMG)	Reduced recruitment of MUAPs firing at increased frequency with increased amplitude, polyphasic potentials. Spontaneous fasciculations.	NR	Rare fibrillations and positive sharp waves. Normal MUAPs, morphology and recruitments. Muscular cramps induced by leg exercise accompanied by fasciculation
	Colonoscopy	NR	NR	Transverse colon polyp, no dysplasia or malignancy

Abbreviations: MUAPs, Motor Unit Action Potentials; NR, Not Reported; OFC, occipitofrontal circumference; SDS, standard deviation score

A



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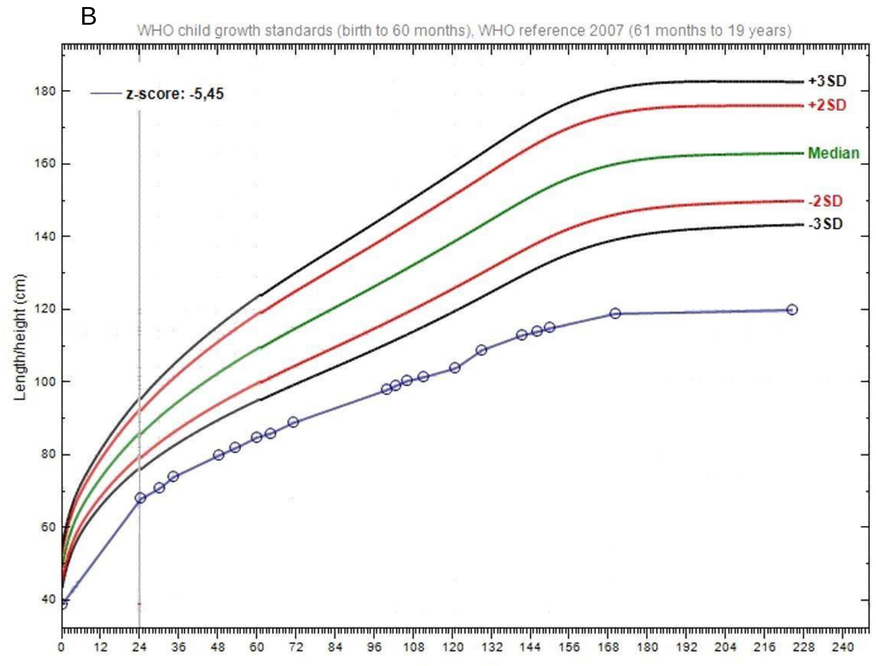

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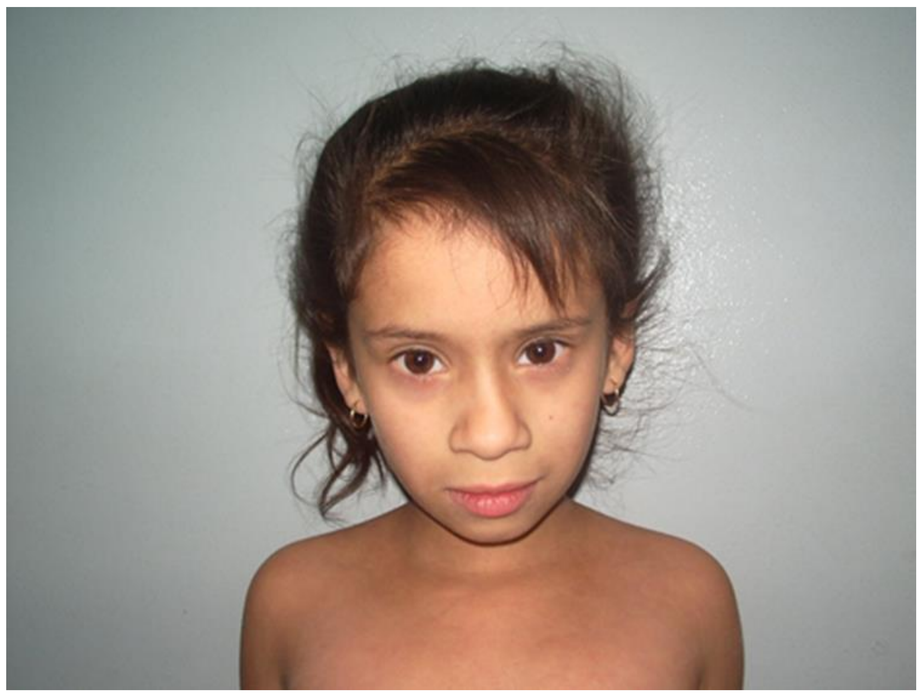

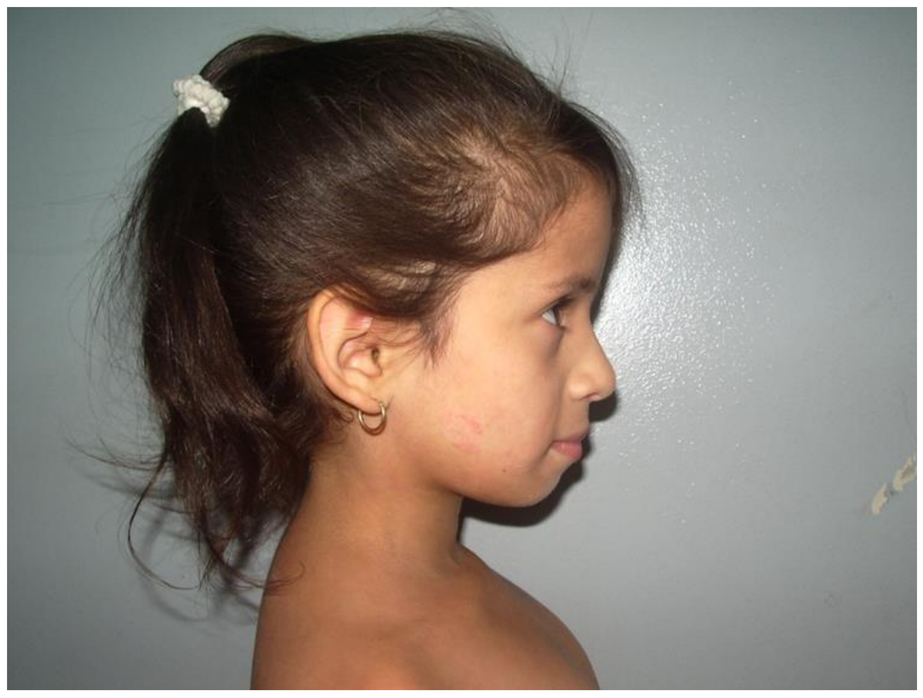

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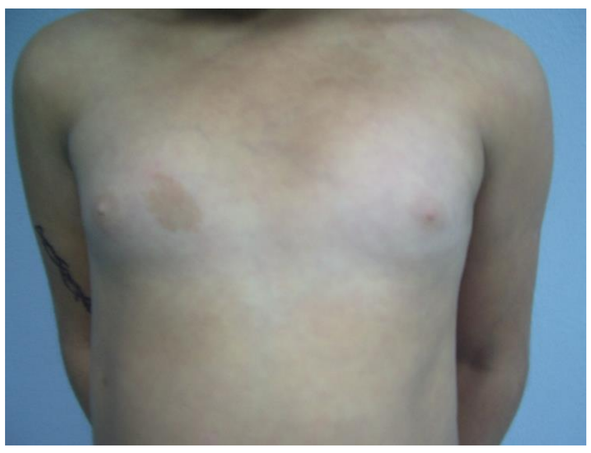

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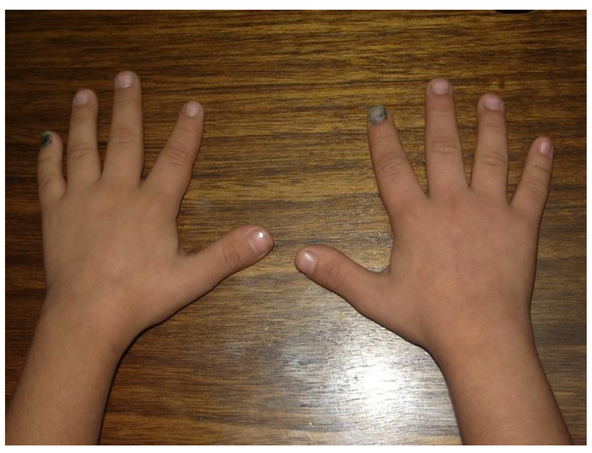

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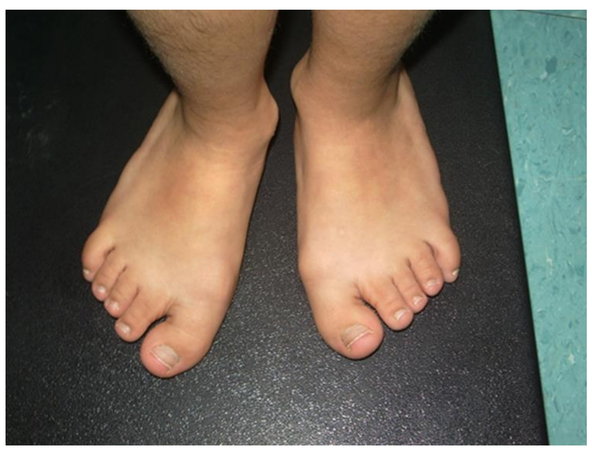

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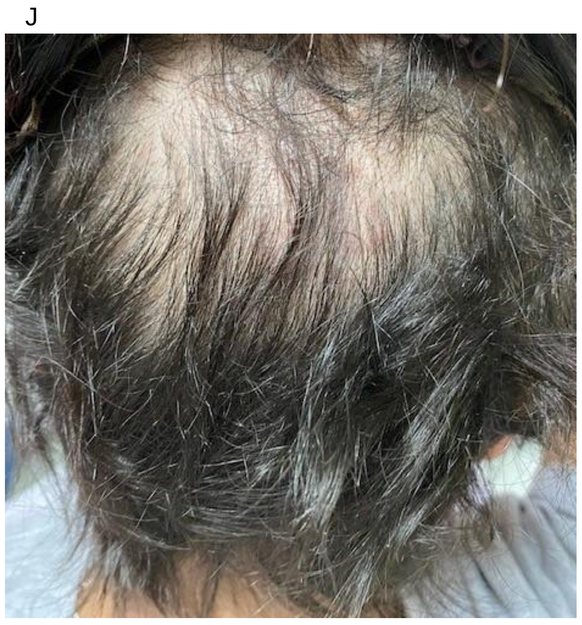

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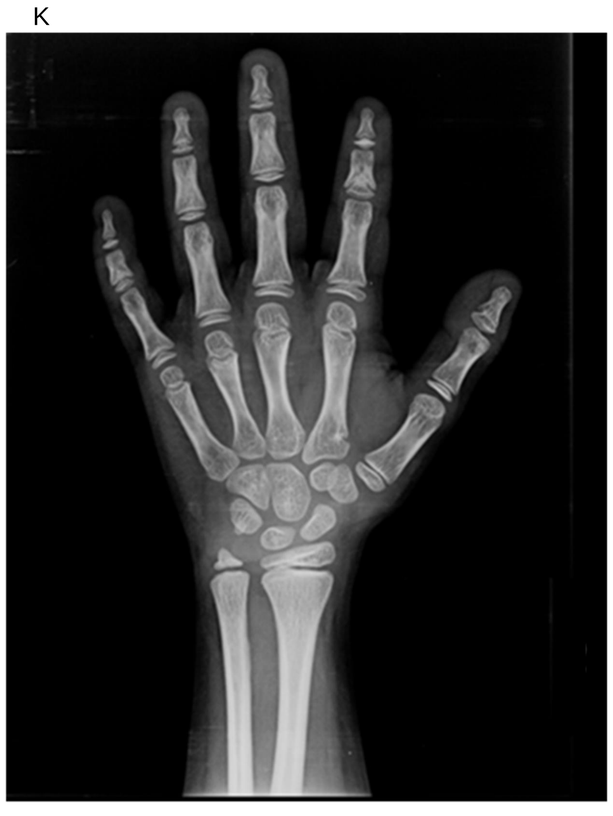

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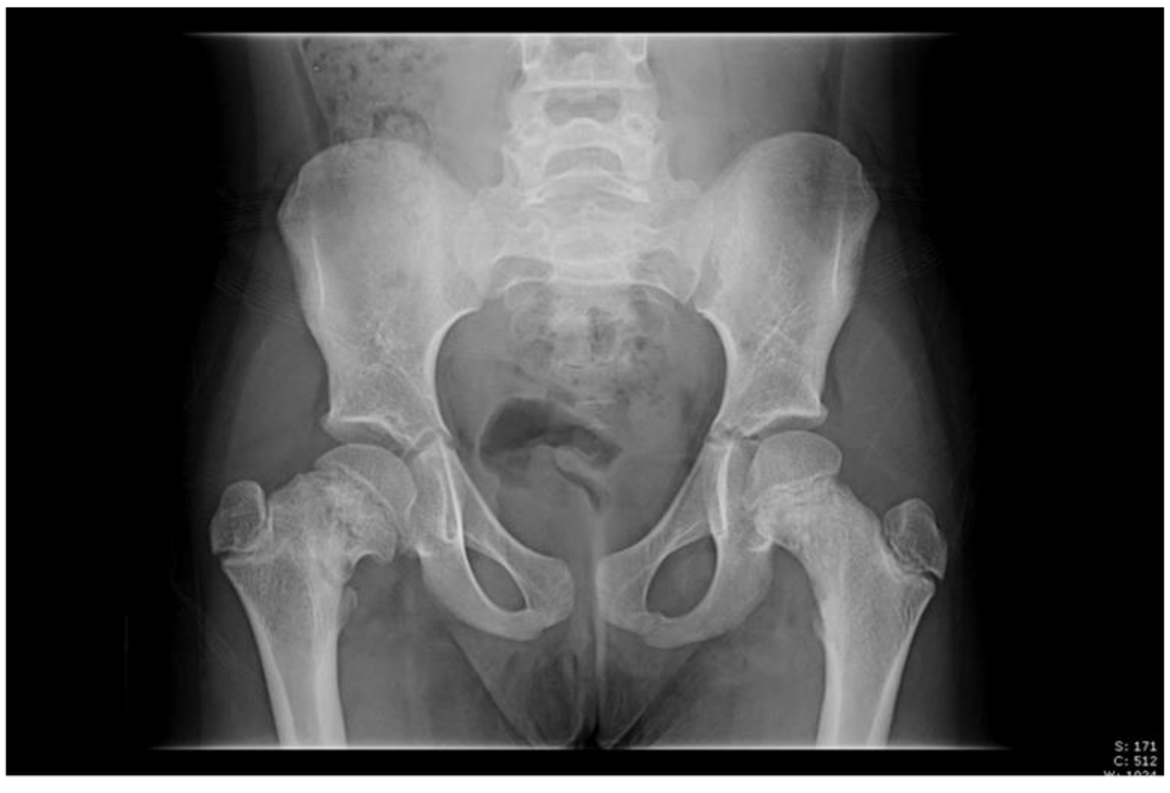

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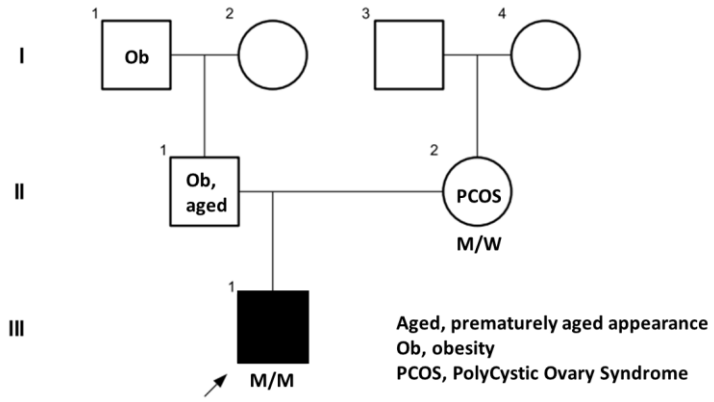
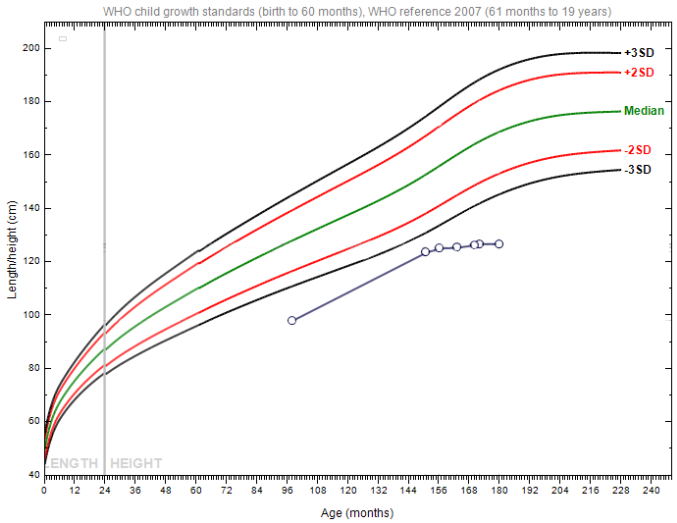
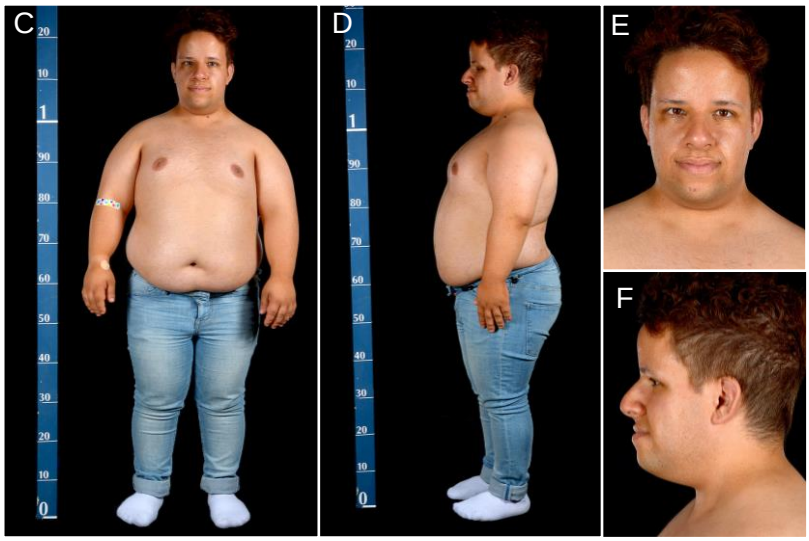

I
II
III
1
2
3
4
Ob
Ob, aged
PCOS
M/W
M/M
Aged, prematurely aged appearance
Ob, obesity
PCOS, PolyCystic Ovary Syndrome

B


WHO child growth standards (birth to 60 months), WHO reference 2007 (61 months to 19 years)
Length/height (cm)
Age (months)
+3SD
+2SD
Median
-2SD
-3SD
LENGTH
HEIGHT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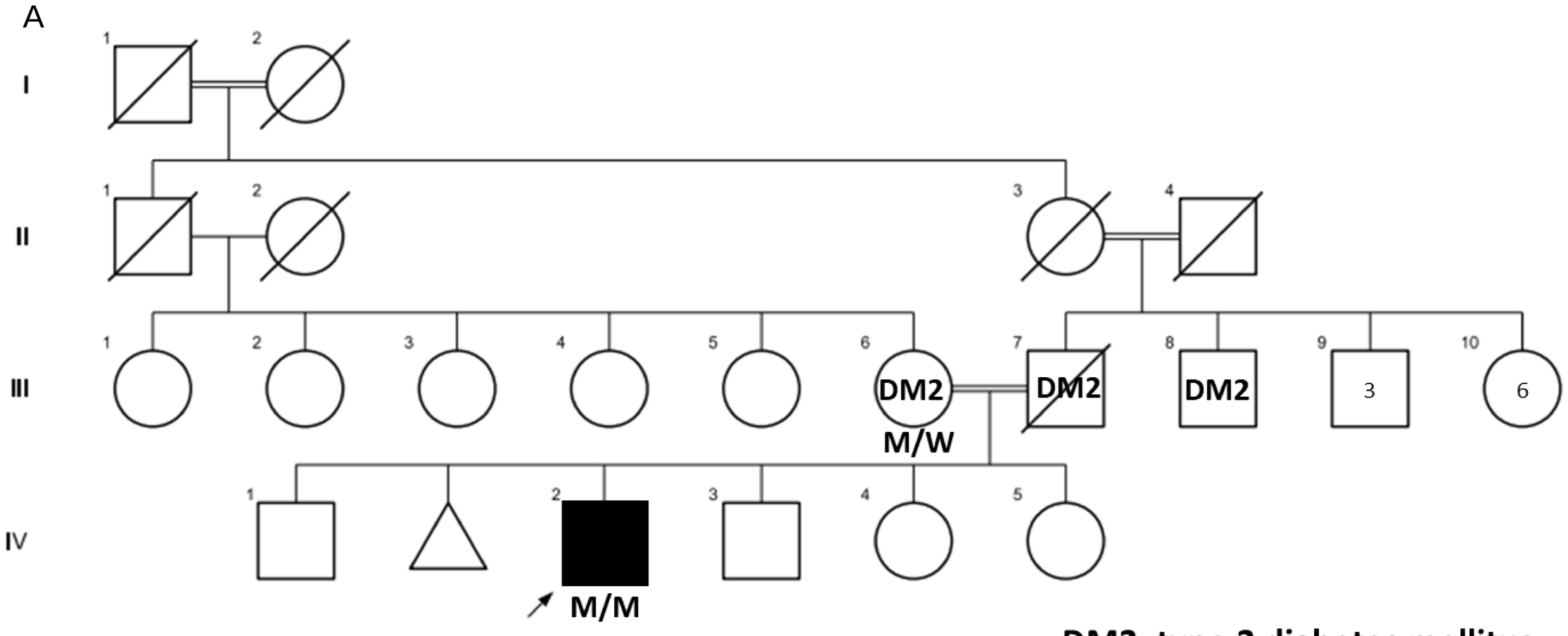
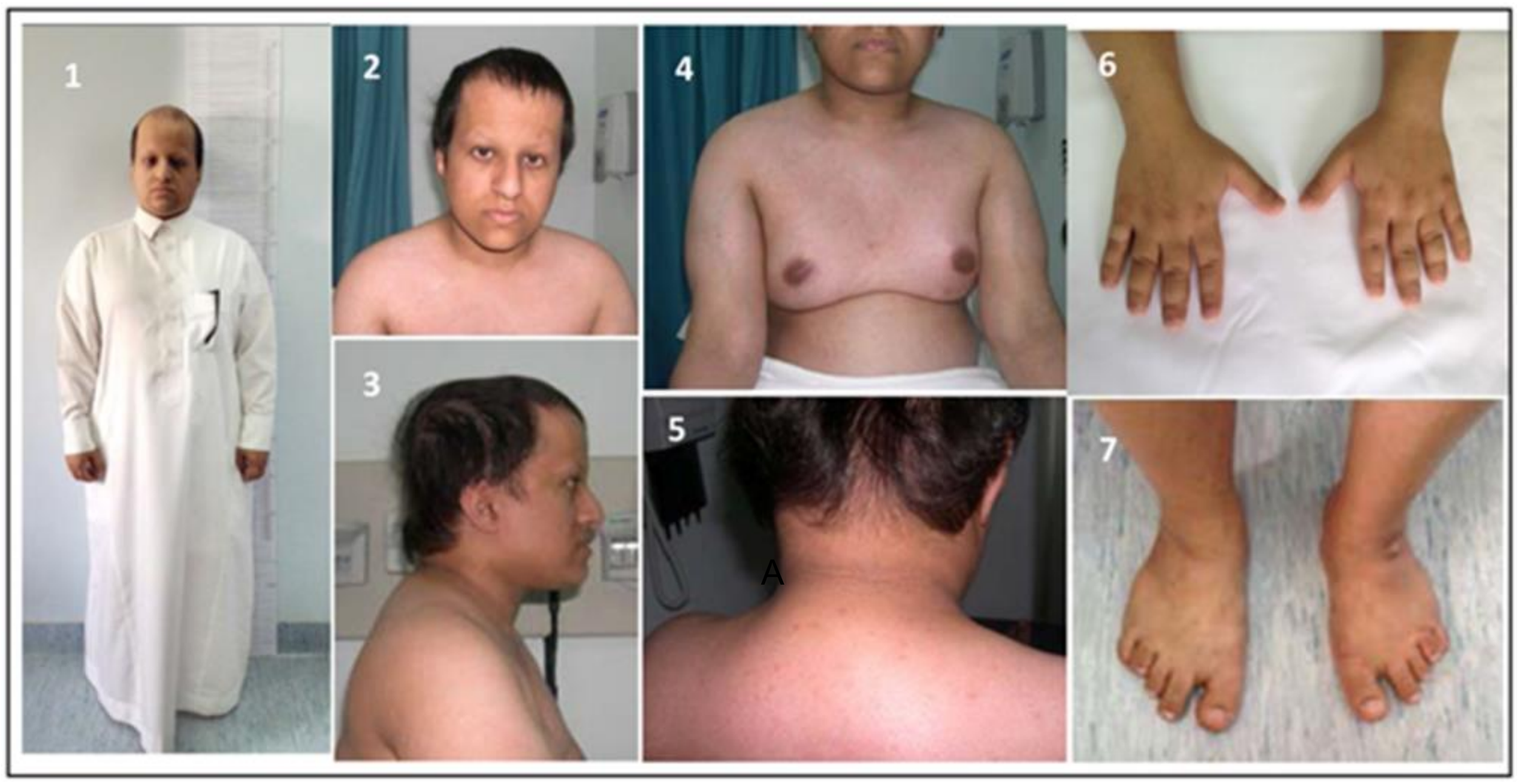


DM2, type 2 diabetes mellitus

B



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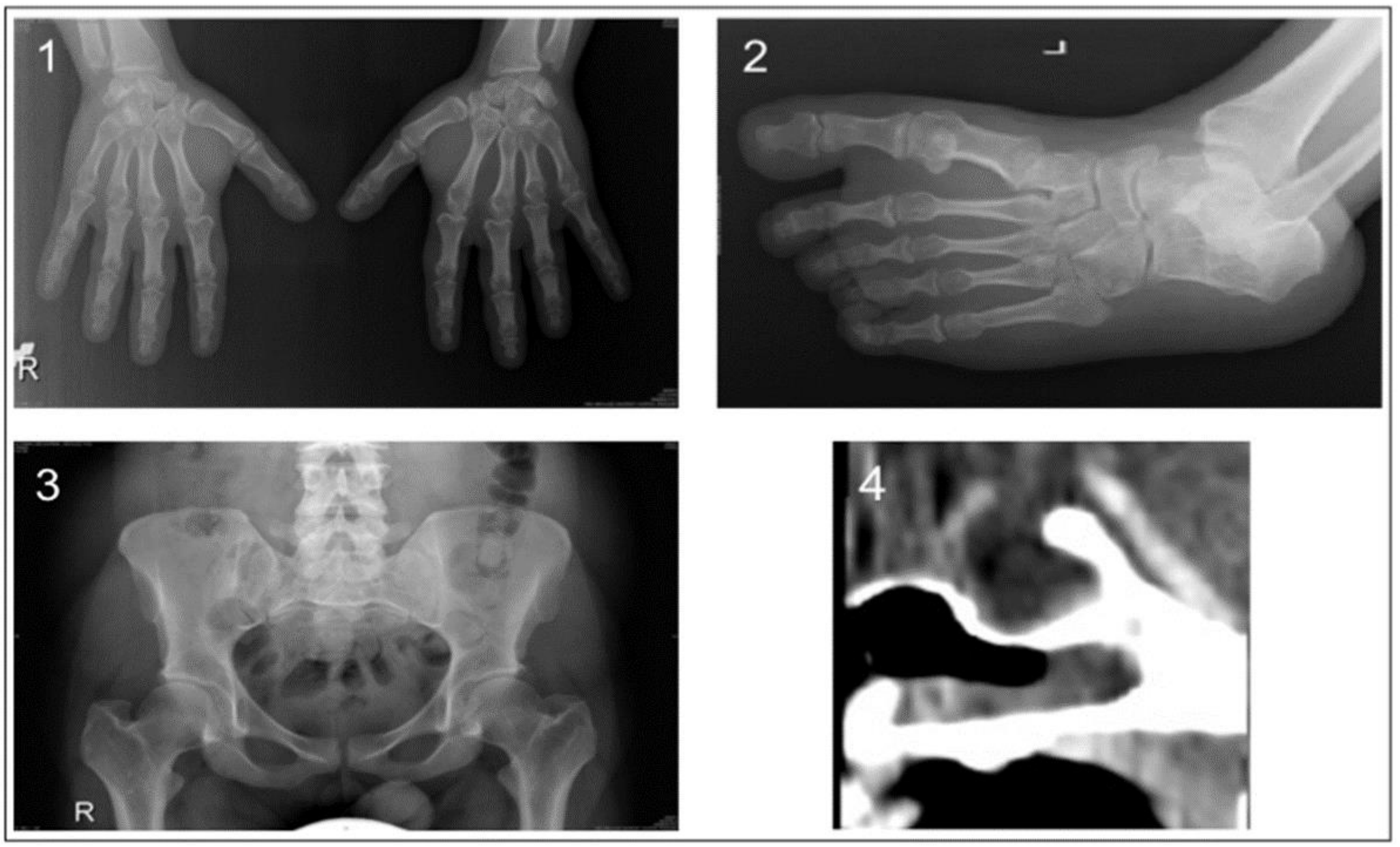


Supplementary File to the paper "Biallelic POC1A variants cause syndromic severe insulin resistance with muscle cramps"

Veronica Mericq, Isabel Huang-Doran, Dhekra Al-Naqeb, Javiera Basaure, Claudia Castiglioni, Christiaan de Bruin, Yvonne Hendriks, Enrico Bertini, Fowzan S. Alkuraya, Monique Losekoot, Khalid Al-Rubeaan, Robert K. Semple, Jan M. Wit

Supplementary Information on clinical presentations

Case 1 is a 21.5-year-old Chilean woman born to healthy parents of normal height (father -0.6 SDS, mother -1.3 SDS) (1). Birthweight at 37 weeks' gestation was 1520 g (-4.4 SDS), length 39 cm (-5.5 SDS), and occipitofrontal circumference (OFC) 31 cm (-2.4 SDS) (1). Karyotype was normal. She showed normal psychomotor development but was admitted for failure to thrive at 2 years of age, when serum IGF-I was 101 ng/mL (-0.5 SDS) and IGFBP-3 2.3 mg/L (0.6 SDS) (2).

At 8.7 years endocrinological evaluation of severe short stature and bilateral hip pain was sought. Her height was 100.5 cm (-5.1 SDS), weight 14.3 kg (-4.4 SDS), Body Mass Index (BMI) 14.2 kg/m^2 (-1.2 SDS) (1) and OFC 47.5 cm (-3.5 SDS) (3). Arm span (100 cm) minus height was close to the mean for age (4). Cognitive function was normal. She had thin, slow-growing hair, a prominent forehead, deep-set eyes, hypoplastic nostrils, smooth philtrum, thin upper lip, light skin, café au lait macules, joint hyperlaxity, and broad hands and feet with broad thumbs/big toes. Radiographs showed short phalanges, cone epiphyses of the distal phalanges, pseudo-epiphysis in the middle phalanx of the second finger and fifth finger clinodactyly and bone age was 7.9 years**.** Femoral necks were asymmetrical with abnormal remodelling, shortening and deformity. Scintigraphy showed irregular contrast in the right hip with thickened epiphyseal growth plate and no increased osteoblastic activity, consistent with prior avascular necrosis. Serum IGF-I, and plasma insulin concentrations were increased (**Supplementary Table 1**). The serum growth hormone (GH) response to clonidine (11 ng/mL) was normal. Breast development was at Tanner stage 3 at 9.3

years, consistent with plasma oestradiol, LH response to Leuprolide (**Supplementary Table 1**) and uterine size (3.9 cm). Ovaries remained small (0.6 and 1.0 mL) on ultrasonography.

At 10.8 years limbs showed greater shortening in proximal (<–4.4 SDS) than distal segments (-3.1 to -3.5 SDS). Sitting height/height ratio was normal (0.3 SDS) (5). Hands were small and wide but large in comparison to arms. Feet were small and in proportion to the legs. Three irregular café au lait macules were noted. From 10 years' old, hair became progressively dry, sparse and brittle, with increased scalp sensitivity.

Recombinant human growth hormone (rhGH) (0.05 mg/kg.d) was administered from 10.1 to 11.6 years in combination with a GnRH analogue. A small increase of height SDS (-5.5 to -5.2 SDS) was seen, but given this poor response, and development of acanthosis nigricans and hypertension (136/81mmHg at 11.8 years), rhGH treatment was discontinued. Hypertension was treated initially with enalapril. Menarche occurred at 15.3 years' old, followed by oligomenorrhoea.

At 18.7 years muscle cramps were the major complaint, affecting limbs, abdominal muscles, tongue and jaw. These had developed around the age of 2 years, and had since gradually increased in frequency and intensity, exacerbated by prolonged exercise but also present at rest, even overnight. Cramps were associated with serum creatine kinase concentrations more than ten times the upper limit of normal (**Supplementary Table 1**). Serum concentrations of calcium, phosphorus and magnesium were normal. Segmental muscle strength and muscle volumes were normal, with no osteotendinous contractures, nor muscle spasm after percussion.

At 21.5 years of age daily excruciating muscle spasms affected all skeletal muscles, lasting minutes to hours, triggered by movement and at rest. Spasms began with trunk and lower limb muscle stiffness, with co-contraction of agonist and antagonist muscles, sometimes with jerking involuntary limb movements.

Occasional mandibular and tongue spasms also occurred. Local warming tended to relieve pain. Nerve conduction studies were normal and concentric needle EMG showed a reduced recruitment pattern of motor units with polyphasic potentials of increased amplitude, indicating motor neuron involvement. Spontaneous muscle twitches, similar to fasciculations, were noted in limbs. The EMG needle triggered painful vastus lateralis spasms, leading to prolonged continuous muscle activity. Cramps subsided with amitriptyline.

Oligomenorrhoea persisted, associated with low serum oestradiol, high serum LH, biochemical hyperandrogenism and increased serum Anti-Mullerian Hormone concentration, which normalised on regular metformin (**Supplementary Table 1**). Pelvic ultrasound showed a uterine length of 5.5 cm, ovarian volumes of 12 and 4 ml, and multiple follicles of <10 mm. Adult height was 120 cm (-6.6 SDS), weight 29.6 kg, BMI 20.6 (0.3 SDS), OFC 50.0 cm (-4.0 SDS) and arm span 120 cm. Leg length was 60 cm, with a normal upper/lower segment ratio of 1.0.

Metabolic evaluation from 8.7 years old (**Supplementary Table 1**) showed progressive insulin resistance (IR), treated with metformin 850mg bid from 18.8 years, decreased to 425mg bid due to gastrointestinal symptoms. Serum triglycerides remained elevated from 11 years. Fatty liver was inferred from elevated aminotransferases and at 20.8 years, confirmed by ultrasonography. Blood pressure was well controlled on losartan 25 mg/day. Renal sonographic appearances were normal at 2 and 19.3 years, but at 21.5 years microalbuminuria and elevated blood urea nitrogen were recorded.

Case 2 is a 25-year-old man, the only child of unrelated Portuguese parents. His mother had a normal height (165 cm, 0.3 SDS) (6). His father was reported to be of short stature (162 cm, -2.1 SDS) (6), with a prematurely aged appearance, hearing impairment, obesity, and loss of dentition by 36 years. He was of normal intellectual ability.

The proband was born at 43 weeks' gestation with a birthweight of 2.45 kg [-3.2 SDS (7)]. A relatively large head and probably bony dysplasia were noted at birth, but skeletal surveys on two occasions during childhood failed to reveal a known dysplasia. Psychomotor development was normal. At 8.1 years height was 98 cm (-6.4 SDS), weight 21 kg (-1.6 SDS) and BMI 21.9 kg/m^2 (2.5 SDS) (8). Upper segment length was 54 cm [upper/lower segment ratio 1.23, equivalent to 3.5 SDS (4)] and arm span 93 cm [arm span minus height -1.3 SDS for age (9)]. Several small café au lait patches and joint hypermobility were noted. Brain MRI was normal. rhGH therapy from 9.5 to 10.5 years yielded no benefit, and was discontinued due to weight gain. Numerous dental procedures were required due to supernumerary teeth and dental caries, exacerbated by rapid jaw growth. Orthodontic assessment at age 12 revealed class III malocclusion. Nail growth was normal. Puberty onset was reportedly at 11 years old.

At 13.6 years old health was good except for muscle cramps. Height was 125.4 cm (-4.8 SDS), BMI 24.3 kg/m^2 (1.9 SDS) and OFC 53.8 cm (-1.2 SDS for age (8). Puberty was well advanced, with Tanner stage 3 genitalia and pubic hair, and testicular volumes 8 ml. Adiposity was centripetal but there was no frank lipodystrophy. Mild acanthosis nigricans was seen. There was brachydactyly and mild fifth finger clinodactyly with broad, short nails. There were scattered depigmented patches on the abdomen, and two small, irregular café au lait patches on the lower back. Muscle tone and limb reflexes were normal and no muscular hypertrophy was observed. Oral glucose tolerance testing revealed severe IR without diabetes, and reactive hypoglycaemia. Elevated serum ALT was consistent with fatty liver, and serum creatine kinase was mildly elevated (**Supplementary Table 2**). Serum calcium, phosphorus and magnesium concentrations were normal. Over the next 18 months cramps resolved, permitting vigorous activity, however acanthosis nigricans persisted.

At 22.3 years old, he was symptomatically well on no therapy but obesity had developed [height 127 cm (-7.2 SDS), weight 59.2 kg, BMI 36.7 kg/m^2]. Adiposity was centripetal with pronounced acanthosis nigricans. Arms and legs were short, but hair and nails were normal. Café au lait patches were unchanged. Biochemical evaluation demonstrated extreme fasting hyperinsulinaemia (**Supplementary Table 2**).

At 25 years old, he reported severe muscular pains, significantly worse than in teenage years. These were spasmodic, associated with paraesthesia in the fingers, and were exacerbated by cold. They were refractory to non-steroidal anti-inflammatory drugs, and limited activity, contributing to weight gain. No muscular hypertrophy was noted. He also described, for the first time, rapid, patchy hair loss occurring over several weeks in a non-androgenic distribution.

Case 3 is a 32-year-old Saudi Arab male presenting with short stature, intellectual disability, and type 2 diabetes mellitus (DM2). He was born at 39 weeks' gestation after a pregnancy complicated by intrauterine growth retardation. His parents are first cousins with 4 other healthy children. Both parents were diagnosed with DM2 at 42 years of age. At birth the proband was small for date [weight 1.8 kg (-2.8 SDS), length 45 cm (-3.0 SDS), OFC 33cm (-1.2 SDS)]. Developmental milestones were delayed from early childhood onwards. GH deficiency was suspected and rhGH therapy given from 8 years of age for 6 years, but information on serum IGF-I, GH stimulation testing and growth response is unavailable. Currently, he is semi-independent with an IQ of 68, has no secondary sexual characteristics, and has had alopecia since adolescence.

At 22 years his height was 135 cm (-5.8 SDS), weight 51.1 kg (-2.1 SDS), and BMI 28.2 kg/m^2. He had brachydactyly, posteriorly rotated, low set ears, small, broad hands and feet with hypoplastic distal phalanges and nails, partial alopecia, and centripetal adiposity. He exhibited a high forehead, hypotonia, joint hyperlaxity, brachycephaly, hypertelorism, broad upturned nose, long philtrum, short palpebral fissure, widely spaced first and second toes, and single palmar creases. Skeletal survey revealed short femoral neck and phalanges, short left third metacarpal and metatarsal bone, hypoplastic distal phalanges and nails, and short, thick long bones. He had nuchal and axillary acanthosis nigricans and fatty liver, confirmed ultrasonographically. DM2 was diagnosed and managed with Metformin, Sitagliptin and Pioglitazone. On this regimen serum insulin was slightly increased, with C-peptide and adiponectin within normal limits (**Supplementary Table 3**).

At 25-26 years, lack of secondary sexual characteristics, plasma testosterone at or below the lower limit of normal and an empty sella on imaging prompted GnRH stimulation testing, which showed a normal FSH and LH response (10) (**Supplementary Table 3**). Three-weekly testosterone ester (250 mg) injections were prescribed, but compliance has been poor. Other pituitary axes were normal.

At 26 years, muscle cramps in legs and chest on exertion and at rest were reported, with elevated serum creatinine kinase concentration of 9702 U/L (reference 25-190 U/L). No muscular hypertrophy was noted. Cramp-Fasciculation Syndrome was suggested by electromyographic findings of rare fibrillation potentials and positive sharp waves, normal motor unit action, and cramps induced by exercise. Muscle biopsy (**Supplementary Figure 1**) showed nonspecific myopathic changes suggestive of a secondary neuropathic process. These included mild focal fibrosis, increased internal nuclei, occasional lobulation and splitting together with clusters of atrophic angular fibres and hypertrophic fibres, and focally increased internal nuclei. Cytochrome oxidase staining was uneven, with scattered fibres showing subsarcolemmal mitochondrial accumulation. Myosin heavy chain immunostaining showed dominance of type II fibres. Electron microscopy revealed scattered degenerating atrophic fibres and no clear mitochondrial abnormalities. Spinal MRI was normal. Symptoms abated gradually, and serum creatinine kinase concentration decreased to 300 U/L (**Supplementary Table 3**). Serum calcium, phosphorus and magnesium concentrations were always normal.

At 29 years severe hyperglycaemia was noted with HbA1c of 12.7%, mandating insulin therapy. Non-proliferative diabetic retinopathy was found with persisting fatty liver on ultrasonography and elevated serum aminotransferase concentrations. Hypercholesterolaemia and hypertriglyceridaemia were managed with Atorvastatin 20 mg daily.

Supplementary information on genetic analyses

POC1A variants identified are described with reference to RefSeq accession number NM_015426.4.

Case 1: The index and her parents were analysed in a diagnostic setting by exome sequencing at the Laboratory for Diagnostic Genome Analysis (LDGA), Department of Clinical Genetics, Leiden University Medical Centre. Genomic DNA was extracted from peripheral blood using the Chemagic Prime instrument (PerkinElmer, Waltham, MA, USA). Exomes were enriched with the SureSelect Clinical Research Exome V2 kit (Agilent Technologies, Santa Clara, CA, USA), followed by NovaSeq 6000 System sequencing (Illumina, San Diego, CA, USA). Variant analysis used a pipeline consisting of BWA, GATK and Moon software (http://www.diploid.com/moon) using the HPO terms for severe short stature. This resulted in the homozygous *POC1A* variant and no other plausible causal mutations were identified. No pathogenic mutations were identified in 95 myopathy-related genes in the laboratory of dr. Bertini (Italy) (11).

Case 2: Microarray revealed no pathogenic copy number changes. Exome sequencing of genomic DNA and variant calling were performed as part of the UK10K Project, as described previously (12). Raw sequence data is available from the European Genome-Phenome Archive (https://www.ebi.ac.uk/ega/home; accession EGAN00001015634). Two *POC1A* variants but no other plausible causal mutations were identified and were confirmed by Sanger sequencing.

Case 3: Woodhouse-Sakati syndrome was excluded by full sequencing of C2orf37 and autozygosity analysis. Exome sequencing was then undertaken and combined with the autozygome analysis as previously described (13, 14). No candidate variants in known myopathy genes were identified.

Supplementary Table 1. Selected laboratory findings in case 1

Age (years)	8.7	9.3	9.7	11	13	14.3	18.7	19.3	20.8	21.5	Reference range
Alanine aminotransferase (U/L)		32			52	**74**	**107**	37		**82**	<55 (21.5 yrs)
Aspartate aminotransferase (U/L)		**34**			**40**	**34**	**55**	20		33	5-34
Uric acid (µmol/L)										**571**	155-357
Creatine kinase (U/L)	111	163			123	111	**1038**	138		164	26-192 (<18 yrs), 29-168 (>18 yrs)
Creatine kinase-MB (U/L)	**31**	**60**			**31**	**23**	**45**				7-25 (<18 yrs), 0-25 (>18 yrs)
Total Cholesterol (mmol/L)		3.3			4.4	4.1	4.5	3.6	4.1	4.7-4.8	<4.4 (children, adolescents) <4.9 (young adults)
HDL Cholesterol (mmol/L)					**0.75**	**0.70**					>1.2
Triglycerides (mmol/L)				**2.6**	**2.6**	**2.1**	**4.3**	**2.7**	**2.0**	**3.9-5.9**	<1.0 (10-19 yrs), <1.3 (young adults)
OGTT glucose (mmol/L)											
Baseline		4.7			**6.2**	5.4	**5.9**	**5.6**	**5.6**	5.2	<5.6
120 mins					6.2	7.3	**9.1**			**13.9**	<7.8
OGTT insulin (pmol/L)											
Baseline	45			**192**	**733**		**348**			**304**	13-85 (8.7 yrs). 23-76 (Tanner 5)
120 mins	**650**				**2177**		**>2084**			**8084**	153-486 (8.7 yrs). 153-549 (Tanner 5)
IGF-1 (nmol/L)	**45** (6-34)			**76** (4-56)		28 (22-56)	26 (25-56)			**21** (23-42)	
IGFBP-3 (mg/L)	5.2 (1.6-6.5)			6.6 (2.4-8.4)		7.0 (3.3-10)				5.7 (3.4-7.8)	
Oestradiol (pmol/L)			382				213			354, 268	<55 (prepubertal), 257-1101 (luteal)
LH (baseline/peak) (IU/L)			<0.6/14.2[1]				**22.1**			7.8	Prepubertal <0.6/<5. 2.8-14.0 (luteal)
FSH (baseline/peak) (IU/L)			3/17.7				4			2.2	Prepubertal <3. Luteal phase 1.4-5.5
Anti-Mullerian Hormone (pmol/L)										**1.6**	0.1-0.7
Testosterone (nmol/L)										**251**	37 - 197
SHBG (nmol/L)										**10**	11.7-137

[1]Baseline and peak levels (IRMA) at Leuprolide test, performed at 9.7 years. Abbreviations: FSH = Follicle-stimulating hormone; LH = luteinising hormone.

Laboratory results outside of the reference range are printed in **bold** print. OGTT = 75g oral glucose tolerance test .

Supplementary Table 2. Selected laboratory findings in case 2

Age (years)	**13.3**	**22.3**	**Reference range**
Alanine aminotransferase (U/L)	**60**	35	7-40
Total creatine kinase (U/L)	**1075**		42-163
Total cholesterol (mmol/L)	3.0	4.4	<4.4 to <4.9
LDL cholesterol (mmol/L)	1.8	0.29	<2.9 to <3.1
HDL cholesterol (mmol/L)	**0.96**	**0.83**	>1.2
Triglyceride (mmol/L)	0.6	**2.8**	<1.0 (10-19 yrs) <1.3 (18-21 yrs)
IGF-1 (nmol/L)	59.4		11.5-75.0
Testosterone (nmol/L)	14.0		8.0-32
Haemoglobin A1c (mmol/mol)	33		<42
OGTT glucose (mmol/L) *0, 30, 60, 90, 120, 150, 180 mins*	4.0, 7.3, 6.7, 6.7, 6.8, 6.0, 2.7		Baseline <5.6
OGTT insulin (pmol/L) *0, 30, 60, 90, 120, 150, 180 mins*	N/A, 2450, 2490, 2420, 3460, 2210, 410	**947**[1]	15-73

[1]Fasting level only at 22.3 years.

Abbreviations: NA = not available; OGTT = 75g oral glucose tolerance test.

Laboratory results outside of the reference range are printed in **bold** print.

Supplementary Table 3. Selected laboratory findings in case 3

Age (years)	25	26	27	28	29	30	31	32	Reference range
Alanine aminotransferase (U/L)		**102**	**44**	**59**	**71**	**42**	39	29	5-41
Aspartate aminotransferase (U/L)		**87**	28	30	30	23	26	16	12-37
Total creatine kinase (U/L)		**9702**	**307**	NA	**427**	**215**	**602**		25-190
Creatine kinase MB (U/L)		**122.1**							7-25
Total cholesterol (mmol/L)			**5.9**	**5.5**	**6.2**	**5.9**	**5.6**	**6.8**	<4.9
LDL cholesterol (mmol/L)			**4.3**	**3.8**	**4.3**	**3.6**	**3.7**	**3.5**	<3.1
HDL cholesterol (mmol/L)			1.2	**0.8**	**0.9**	**0.8**	**0.9**	**0.8**	>1.2
Triglycerides (mmol/L)			0.8	**2.0**	**2.5**	**3.1**	**2.1**	**5.5**	<1.3
Free T3 (pmol/L)			5.8				5.5		4.4-6.8
Free T4 (pmol/L)			17.0		17.1	16.7	18	17.8	12-22
Thyroid stimulating hormone (mIU/L)			1.6		1.7	2.2	1.8	2.1	2-5
Haemoglobin A1c (mmol/mol)			39	**64**	**82**	**96**	**71**	**95**	<42
Fasting capillary blood glucose (mmol/L)[1]						**15.7**			3.9-5.8
Insulin (pmol/L)[2]			**186**						15-73
C-peptide (pmol/L)			824						379-901
Adiponectin (µg/mL)			5.7						4-20[4]
Testosterone (nmol/L)	**6.1**	**9.5**	10.7			**8.0**	**6.7**		9.9-27.8
GnRH test: FSH (IU/L)[3]									
Baseline		3.3	4.4						0.7-7.2
Stimulated		7.9							0.5-10.5
GnRH test: LH (IU/L)[3]									
Baseline		7.5	5.1						1.8-8.4
Stimulated		38.9							7.4-54.2

[1]Patient was following by home glucose monitoring for blood sugar control. [2]On metformin 500mg twice daily, sitagliptin 100mg once daily and pioglitazone 15mg once daily. [3]Maximum of concentrations at 30, 60 and 90 minutes after injection of GnRH. Reference range from Bang et al, 2017 (10) [4]For males with BMI 25-30kg/m^2.

Abbreviations: FSH = Follicle-stimulating hormone; LH = luteinising hormone.

Laboratory results outside of the reference range are printed in **bold** print.

Supplementary Table 4. *POC1A* variants detected in this study

Nucleotide change (NM_015426.4)	Protein change	gnomAD (v2.1.1) MAF*	SIFT**	PolyPhen**	CADD score (Phred)	ClinVar	ACMG/AMP (Intervar)	Reference
c.649C>T	p.(Arg217Trp)	0.0028%	Not tolerated (p = 1.00)	Probably damaging (score 1.000; sensitivity 0.00; specificity 1.00)	25.5	Not present	VUS	13
c.370G>A	p.(Asp124Asn)	Not present	Not tolerated (p = 1.00)	Probably damaging (score 1.000; sensitivity 0.00; specificity: 1.00)	29.9	LP	LP	Not published
c.241C>T	p.(Arg81*)	0.0032%	-	-	37	1x P; 1x LP	P	3, 10, 29

*MAF = minor allele frequency; **Prediction of amino acid substitution.

Abbreviations: LP, Likely pathogenic; P, Pathogenic: VUS, variant of uncertain significance.

Supplementary Table 5. Clinical assessment parameters for reported cases with insulin resistance[a]

	Cases 1-3[b]	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
First author and Date	**Shalev *et al*, 2012**	**Chen *et al*, 2015**	**Giorgio *et al*, 2017**	**Majore *et al*, 2020**	**Present report**	**Present report**	**Present report**
Number of cases	3 out of 9	1	1	1	1	1	1
Ethnicity	Arab	Italian	Italian	Italian	Chilean	Portuguese	Arab
Height SDS	-7; -7; NR	-4.1	-4	-2.4	-7.2	-5.8	-5.8
IR/DM2	DM2; DM2; DM2	IR	IR/DM2	IR	IR	IR	IR/DM2
Age at diagnosis of DM2 or IR/gender	20/M; 24/M; 29/M	12.7/F	14/F	15/F	8/F	13/M	22/M
Hypertension	NR	No	NR	NR	+	NR	-
Hypertriglyceridaemia	+; +; +	+	+	+	+	+	-
Decreased HDL-chol	+, +, +	+			+	+	+
Centripetal adiposity	NR	+/-	+	+	-	+	+
Acanthosis nigricans (age noted)	NR	+ (8.5 yrs)	+ (7-8 yrs)	+ (13 yrs)	+ (11 yrs)	+ (13 yrs)	+ (<22 yrs)
Fatty liver	NR	+	+	+	+	+	+
PCOS	NA	+	irregular menses	+	+	NA	NA
Testicular failure	+; +; NR	NR	NA	NA	NA	-	+

[a]For genetic details, please see Supplementary Table 4. [b]The first 2 cases were reported by Shalev et al (2012). A third affected individual from this family (A-III-2) developed DM2 after publication. Data on serum lipids were kindly provided by Dr. Stavit Shalev.

Abbreviations: DM2, diabetes mellitus type 2; F, female; HDL-chol, HDL-cholesterol; IR, insulin resistance; M, male; NA, not applicable; NR, not reported; PCOS, polycystic ovary syndrome; +, present; -, absent

Supplementary Table 6. Anthropometric data in reported cases with SOFT syndrome

cDNA (NM-015426.4	Exon	Protein	N	Age, (sex)	Birth weight SDS	Birth length SDS	Birth OFC SDS	Height SDS	OFC SDS	Weight SDS	Reference
Cases without severe insulin resistance											
c.512T>C (Fam 1)	5	p.(Leu171Pro)	5	30 M@	-0.3*			-7.0	-3.0		(15, 16)
				23 F	0.5*	0.4*	2.7*	-6.0	-3.0		
				33 F				-9.0	-4.0		
				14 M@	-0.5*	-1.2*		-6.0	-4.0		
				0.75 M	-0.3*	-1.9*		-6.0	-2.5		
(Fam 2)			3	24 M				-7.0	-3.5		
				2.8 M	-0.3*	-0.8*	2.2*	-7.0	-1.7#		
				9 F	0.4*	-1.0*	0.3*	-8.0	-2.5		
c.241C>T (Fam 1)	3	p.(Arg81*)	3	6.0 F	-3.9	-4.7	-2.2	-6.7	-2.3	-5.0	(17)
				1.9 F	-3.8	-5.8	-2.2	-7.1		-6.3	
				0.3 M	-2.3	-3.0	-0.3^	-5.1	0.2^	-3.2	
(Fam 2)			1	6.0 M	-4.1			-7.1	-6.4	-6.3	
(Fam 3)			1	2.7 M	-6.6			-7.1	-3.3	-5.9	
c.358A>G	4	p.(Thr120Ala)	2	9/11.5 F	-4.0			-2.2	-0.3/-0.7&	-0.7/-1.3&	(18)
				6.5/8 M	-3.2			-5.0	-0.7/-1.3&	-3.1	
c.254del	3	p.(Leu85Alafs*22)	1	13.5 M	-4.0	-5.3	-1.2	-4.3			(19)
c.515G>A	5	p.(Trp172*)	1	1.1 M	-2.9	-4.5	-0.1	-7.2	-1.7	-4.8	
c.239C>T/ c.241C>T	3 3	p.(Ser80Phe)/ p.(Arg81*)	1	8.5 M	-4.3	-4.1		-6.7	-2.3	-6.0	(20)
c.491G>A	5	p.(Ser164Asn)	1	6.5 F	-3.1	-1.8	-1.6	-4.6	-0.3#	-4.0	(21)
c.649C>T	6	p.(Arg217Trp)	1	6.7 F	-2.2	-2.4	-0.8	-3.5	-1.4	-1.8	(22)
c.275+2T>G	Intr3	p.?	1	8.7 M	-3.0	-2.8	-0.2	-4.5	-4.1		(23)
c.64G>T (Fam 1)	2	p.(Val22Phe)	5	7.8 M	-3.2	-5.7	-2.7	-6.4	-6.0	-7.7	(24)
				2.0 F	-3.4	-3.7	-3.0	-6.3	-3.0	-11.7	
				3.8 M	-3.1	-4.4	-1.4	-6.5	-2.0	-6.9	
				3.8 M	-3.2	-4.4	-2.2	-7.5	-5.4#	-12.2	
				5.5 M	-2.7	-4.0	-1.4	-5.1	-6.0#	-6.2	
(Fam 2)			2	4.5 M	-3.6*	-5.0*	-0.4*	-5.5#	-1.4#	-7.2#	
				3.6 M	-1.9*	-3.7*	0.1*	-5.2#	-1.5#	-7.0#	
Mean (SD)			N=28	8.9 (19M,9F)	-2.7 (1.7)	-3.3(1.7)	-0.8 (1.5)	-6.1 (1.4)	-2.8 (1.8)	-5.9 (2.9)	

(range)				(0.3-30)	(-6.6;0.5)	(-5.8;0.4)	(-3.0;2.7)	(-9.0;-2.2)	(-6.4;0.2)	(-12.2;-1.3)	
Cases with severe insulin resistance											
c.1048del	10	p.(Gln350Argfs*4)	1	21.3 F	-3.1			-4.1			(12)
c.1048dup	10	p.(Gln350Profs*12	1	42 F				-4.0			(25)
c.884del/ c.1048del	9/10	p.(Val295Glyfs*59)/ p.(Gln350Argfs*4)	1	30 F	-1.6			-2.4			(26)
c.649C>T	6	p.(Arg217Trp)	1	8.8/22 F	-3.7	-4.3	-1.6	-5.3/-7.2	-4.7	-5.9	This report
c.370G>A/ c.649C>T	4/6	p. (Asp124Asn)/ p. (Arg217Trp)	1	32 M	-2.8	-3.0	-1.3^	-5.8	-1.2		This report
c.241C>T	3	p.(Arg81*)	1	32 M				-5.8		-2.1	This report
Mean (SD) (range)			N=6	29.8 (7.6) (21;42)	-2.8 (0.9) (-3.7;-1.6)	-3.7 (-4.3;-3.0)	-1.5 (-1.6;-1.3)	-4.9 (1.7) (-7.2;-2.4)	-3.0 (-4.7;-1.2)	-4.0 (-5.9;-2.1)	

@These patients developed diabetes mellitus type 2 at 20 and 26 years, respectively

*SDS of birth length, weight and OFC was calculated based on Swedish reference (7)

#SDS of these measures was calculated using Dutch references (27)

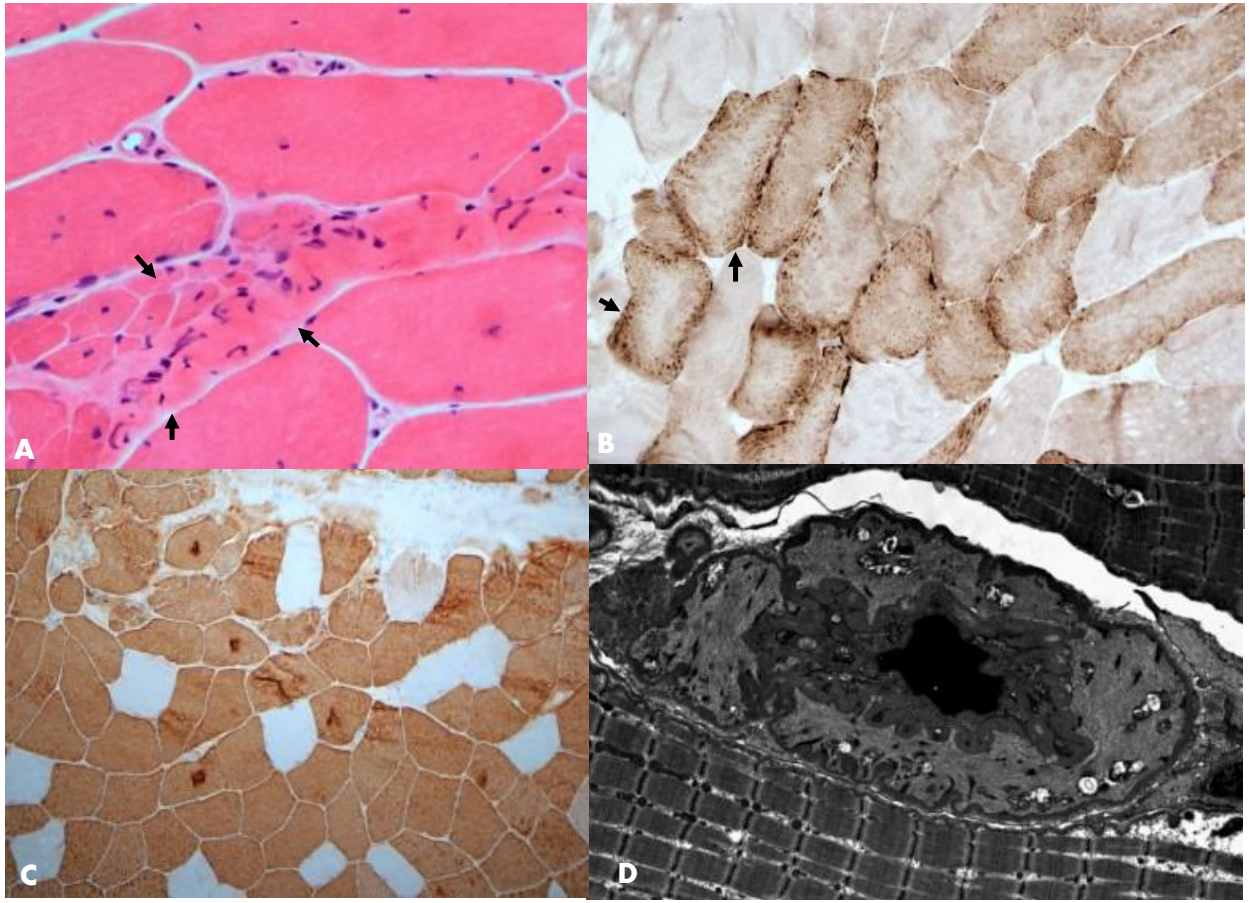
^Estimated based on percentile position

&The values at the oldest reported ages were used for calculating mean and SD

Other SDS values are copied from the original papers.

Abbreviations: F, female; M, male; OFC, occipitofrontal circumference; SDS, standard deviation score.

Supplementary Figure 1.



Muscle biopsy of patient 3. A: Haematoxylin and eosin staining reveals focal myopathic features, including variation in fibre size. Angular atrophic and hypertrophic fibres, focal prominent perimysial components and focal clumps of increased internal nuclei (black arrows) (X400). B: Cytochrome oxidase shows scattered fibres with subsarcolemmal mitochondrial accumulation (black arrows) (X200). C: Immunostaining for the fast class of myosin heavy chain highlights predominance of type II fibres (X100). D: Electron microscopy confirms nuclear abnormalities of the scattered degenerating atrophic angular fibres with nuclear clumps observed at light microscopy (X6000).

Supplementary Figure 2

DeepGestalt of the face of patients with SOFT syndrome.

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