Supplementary material

Supplementary methods

Exome Sequencing and Data processing

Enriched libraries were sequenced using the HiSeq platform (Illumina, USA) as paired-end 75 base reads according to manufacturer's protocol. Sequencing reads that failed quality filtering were removed using the Illumina GA Pipeline. The mean coverage of the exomes was 74x times. The descriptive exome stats are listed in Supplementary Table 1.

The Burrows-Wheeler Aligner (BWA)(Li and Durbin, 2009) was used for alignment to the human reference genome build hg19, followed by the removal of PCR duplicates using Picard (http://picard.sourceforge.net). The variant calling was performed in target+/-100bp regions. For the variant calling samtools (samtools version 0.1.17)(Li *et al.* , 2009) and GATK Unified Genotyper (GATK version 1.1-5)(McKenna *et al.* , 2010) were used. For each sample, an all-sites BCF was created with samtools mpileup then variants (SNPs and Indels) were called by bcftools [http://samtools.sourceforge.net/samtools.shtml].

Base quality recalibration and indel realignment was done with the help of GATK (DePristo *et al.* , 2011). For each exome sample, variant sites (SNPs and Indels) are called using the GATK Unified Genotyper, and marked-up with dbSNP132 rs-ids, GATK VariantFiltration applied (softfilter), including an indel mask consisting of 1000 Genomes pilot indels. Variants were assigned to quality tranches by GATK VariantRecalibrator and ApplyRecalibration. Hapmap3, Omni and dbSNP132 sites available from the Broad Institute were used as training sets for the Gaussian Mixture Model. The variants called by each of the

callers were filtered separately using vcf-filter. For each sample, the resulting gatk.vcf and mpileup.vcf files were merged using vcf-isec. GATK annotations are preferred if sites are in both call sets. The variant calls were annotated using vcf-annotate for following information:

- earliest version of dbSNP containing this call

- dbSNP 132 rsIDs

- 1000Genomes population allele frequencies

The 1000Genomes frequencies are taken from the June 2011 data release, described on the 1000 genomes site as "Genotypes for 1094 individuals for the May 2011 snp calls from the 20101123 sequence and alignment release" [http://www.1000genomes.org/data]. Additionally a number of functional scores were annotated in order to aid the filtering of variants.

Variant Filtering

We used in-house software to dynamically filter candidate variants on the basis of the autosomal recessive inheritance. Depending on the pedigree structure we looked for either homozygous or two functional heterozygous changes in the same gene. The filtering was done very stringent, we filtered following variants out: present in dbSNP132, present in 1000 genomes, synonymous and other non-coding variants apart from essential splice site changes and not present in remaining UK10K rare disease cohort (at the time of the analysis 322 exomes). All variants were checked also to be not present in the NHLBI Exome Sequencing Project (ESP) database. We reduced the number further down to the disease causing *ISPD* mutations by considering variants in the 7p21 disease locus.

Western-Blot

30 ug of proteins, extracted in sample buffer consisting of 75 mM Tris–HCl, 1% SDS, 2-mercaptoethanol, plus a cocktail of protease inhibitors (Roche), were resolved using a NuPage Pre-cast gel (4–12% Bis–Tris; Invitrogen, UK) and then transferred electrophoretically to nitrocellulose membrane (Hybond-ECL, GE Healthcare, UK). Nitrocellulose strips were blocked in 3% BSA (IgG and protease-free, Jackson Laboratories, USA) in Tris-buffered saline buffer, and then probed with anti-mouse α-DG IIH6 (Millipore UK, cat,05-593) and VIA4-1 (Leica, USA, 1:50) and anti-mouse β-DG (Vector Labs,UK) at room temperature. After washing they were incubated with the appropriate biotinylated secondary antibody followed by a HRP-streptavidin (Invitrogen). All the incubations were for 1 hour at room temperature. Membranes were visualized using chemiluminescence (ECL+Plus,GE Healthcare, UK).

Supplementary results

Case 1 is a 21 year-old female of Turkish origin. She was born preterm at 32 weeks gestational age with a birth weight of 1780 grams. She developed neonatal necrotising enterocolitis, at which time elevated CK levels above 2000 U/l were obsverved. Independent ambulation was achieved at 16 months, but she always crawled up stairs and fall frequently. At the age 2.5 years she had febrile seizures. Later at the age of 3 years she had an episode of spontaneous myoglobinuria. On examination at 3.5 years of age proximal muscle weakness with a Gowers' sign was observed. Muscle bulk was normal, and there were no contractures at that time. Deep tendon reflexes were elicitable. Cognitive development was normal for age. At the age of 7 years she had few episodes suspicious for absence seizures. She remained independently ambulant until the age of 12 years. On examination at 16 years she could only stand with assistance and had very limited arm abduction. There was evidence of generalised muscle hypertrophy including the tongue. There were contractures of both Achilles tendons but no of other joints. At the age of 19 years an echocardiogram revealed a mild decrease in cardiac function with a fractional shortening of 27%. A 24-hour electrocardiogram revealed sinus tachycardia without evidence of dysrhythmia, and treatment with Isoprolol was started. Forced vital capacity at 19 years was 85% of predicted levels and peak cough flow was 200 litres/min.

Case 2 is a 14 year old female and cousin of case 1. She is the second child of healthy, consanguineous Turkish parents. Pregnancy, birth and neonatal history were uneventful. She achieved sitting at the age of 8 months. First concerns were raised at the age of 10 months due to difficulty in bearing weight. She commando crawled at 12 months and walked at 14 months. A Gowers' sign was observed at 18 months, and CK at that time was elevated at 1800 U/l. On examination at 3.5 years she demonstrated a hyperlordotic posture and had positive Trendelenburg and Gowers' signs. Deep tendon reflexes were present. Cognitive development was normal for age. At the age of 5 years she was only able to walk 50-75 metres and was no longer able to climb stairs.

Examination at that time revealed hypertrophy of the muscles of the thighs and calves and of the tongue. Subsequently, she developed joint contractures and lost independent ambulation by the age of 12 years. At that time mildly reduced left ventricular heart function was noted, and treatment with Captopril started. Motor nerve conduction velocity of the left peroneal nerve was normal (63.3 m/s) at 13 years of age. MRI of the brain at the age of 13 years was normal.

Case 3 is a 4 year-old female and the sister of patient 2. She sat by 6 months and walked by 14 months of age. On examination at 4 years of age, she had a hyperlordotic posture and positive Trendelenburg and Gowers' signs. She had evidence of pseudohypertrophy of the calves. CK was elevated up to 9097 U/l. Heart and lung function were normal. Motor nerve conduction velocities of the peroneal nerves and sensory nerve conduction velocities of the sural nerves were normal at the age of 3.5 years. Visual evoked potentials were normal.

Case 4 is a of 7 year-old female of Scottish origin. The pregnancy, delivery and neonatal periods were uneventful. Her speech, cognitive and fine motor developments were adequate for age, and she sat independently at 8 months. First medical attention was sought by the parents who noticed an inability to bear weight at 16 months of age. CK levels were elevated up to 6000 U/l, and a muscle biopsy demonstrated dystrophic muscle. She did not crawl or bottom shuffle or pull-to-stand until the age of 3 years, at which age she could roll, come up to sitting from supine and cruise around bottom shuffling. Upper limb strength was good and she could lift toys above the head. She never acquired independent walking but has been able to use a self-propelling wheelchair. She has developed progressive hip, knee and ankle contractures. At 5.5 years she had uncomplicated squint surgery at the left eye for esotropia. Currently at 7 years of age she is non-ambulant but has antigravity muscle strength in the upper limbs. She has 90 degrees hip flexion contractures but can stand whilst holding onto objects. Her heart and lung function are normal.

Case 5 is a 10.5 year old female of Caucasian origin. First parental concerns were raised at around 6 months of age when she was noted not to be moving her legs as much as other infants of the same age. She sat at 9-10 months, stood with support at 18 months, and walked at 22 months. CK was elevated over 5000 U/l, and muscle biopsy at 1 year of age was dystrophic. A brain MRI performed at 1 year was normal. Clinical examination at 4.5 years showed subgravity neck and trunk flexion. Otherwise her muscle force was antigravity. She could jump a bit and rose from the floor with a Gowers' manoeuvre. She was normocephalic, and her cognitive, speech and fine motor development were normal for age.

Case 6 is a 8.5 year-old male of Caucasian origin. First concerns were raised at 6 months of age due to a squint and subsequently the oculomotor apraxia was diagnosed. During the following clinical work-up multiple cerebellar cysts were documented on brain MRI, and CK levels was elevated above 1500 U/l . A muscle biopsy at 16 months was dystrophic. From the developmental perspective he sat with support at 8 months and started to walk around furniture at 15 months. He was diagnosed with severe oculomotor apraxia at 6 months of age and subsequently diagnosed with severe myopia. At the age of 4 years he had axial weakness with subgravity neck flexion and proximal hip girdle power, with stronger antigravity strength in the remaining muscles . He arose from the floor with a Gowers' manoeuvre . Ophthalmological exam revealed limited abduction bilaterally with nystagmus at the extremes of gaze and an intermittent, alternating convergent squint. At his last clinical assessment at the age of 7 years he demonstrated further improvement. He walked independently with a waddling-type gait.

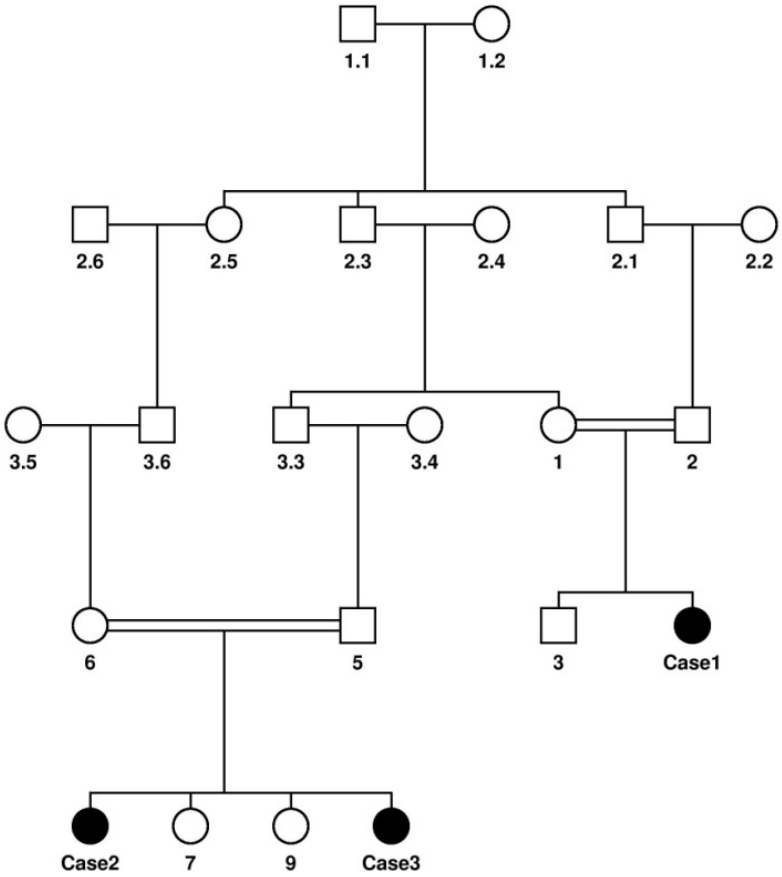
Case 7 is an 18 year-old female of Caucasian origin. Hypotonia and difficulties breastfeeding were observed during infancy. She had delayed motor milestones and started walking at 2 years of age. At the age of 3.5 years she had Gowers' sign and mild calf hypertrophy. CK levels were noted to be 40 times normal values. She lost ambulation at the age of 12 years. She is currently 18 years old and has severe contractures of the hamstrings and Achilles

tendons. She is wheelchair-dependent and has subgravity proximal arm strength and antigravity distal arm strength. She is able to write, use a keyboard, and handle a joystick of her electrical wheelchair. She has prominent hyperlaxity of shoulder joints with recurrent dislocations. A brain MRI was normal. Nocturnal hypoventilation and decreased left ventricular ejection fraction (45%) were diagnosed at age 18 years.

Case 8 is an 11 year-old female of Caucasian origin. She walked at 18 months and had always found stairs difficult, was managing one step at a time and needed to hold on the handrail. She presented at the age of 6 years with motor difficulties although more subtle motor difficulties were noted by the age of 3 years. CK at 6 years of age was 5841 IU/l. She has some mild learning difficulties and required additional support in mainstream school. Currently at 11 years of age, she remains ambulant. On examination she had a waddling-type gait and arises from the floor with a Gowers' manoeuvre. She has muscle hypertrophy of the calves and thighs and mild Achilles tendon contractures. A brain MRI performed at the 7 years of age was normal. The last echocardiogram at 9.5 years showed normal heart function.

Case 9 is a 23 year-old female of Caucasian origin. She had evidence of hypotonia and poor feeding during infancy. She sat at 6 months and started walking at 18 months. She was diagnosed with strabismus at 6 months of age and subsequently diagnosed with severe myopia. At 10 years of age she could not arise from the floor independently. Her cognitive function was formally tested and found to be at the lower end of the normal scale (IQ of 89). Currently she can walk a few steps indoors holding on, and has difficulties in turning and transferring. Swallowing difficulties with bulky food is present. Forced vital capacity was reduced at 49% predicted and polysonmography revealed desaturations. Echocardiogram showed normal heart function, and a 24h electrocardiogram revealed sinus tachycardia with a mean heart rate of 96/min.

Supplementary Figure 1: Showing the relationship of the cases 1, 2 and 3. This was family was used to map the ISPD 7p21 disease locus (Cirak *et al.* , 2009).



Supplementary Table 1:

BAIT_SET	Case 9	Case 4	Case 5	Case 6	Case 7
GENOME_SIZE	3101804739	3101804739	3101804739	3101804739	3101804739
BAIT_TERRITORY	51756122	51756122	51756122	51756122	51756122
TARGET_TERRITORY	39269754	39269754	39269754	39269754	39269754
BAIT_DESIGN_EFFICIENCY	0.758746	0.758746	0.758746	0.758746	0.758746
TOTAL_READS	118632034	112664450	108796796	70459602	111297082
PF_READS	118632034	112664450	108796796	70459602	111297082
PF_UNIQUE_READS	103940865	107043230	104776440	58926824	106476315
PCT_PF_READS	1	1	1	1	1
PCT_PF_UQ_READS	0.876162	0.950107	0.963047	0.836321	0.956686
PF_UQ_READS_ALIGNED	92877890	96833045	95098272	53116370	96505202
PCT_PF_UQ_READS_ALIGNED	0.893565	0.904616	0.90763	0.901395	0.906354
PF_UQ_BASES_ALIGNED	6908900054	7107533709	6980328089	3962056414	7080104302
ON_BAIT_BASES	4333496336	4169420130	3992004024	2307709810	4044869178
NEAR_BAIT_BASES	1380726928	1328843381	1323591040	739467735	1313286567
OFF_BAIT_BASES	1194676790	1609270198	1664733025	914878869	1721948557
ON_TARGET_BASES	3420373991	3303468842	3159460888	1828758969	3204262439
PCT_SELECTED_BASES	0.827081	0.773582	0.761511	0.76909	0.756791
PCT_OFF_BAIT	0.172919	0.226418	0.238489	0.23091	0.243209
ON_BAIT_VS_SELECTED	0.75837	0.758316	0.750999	0.757327	0.7549
MEAN_BAIT_COVERAGE	83.729155	80.558975	77.13105	44.588152	78.152478
MEAN_TARGET_COVERAGE	89.273758	86.241697	82.38732	47.957283	83.599311
PCT_USABLE_BASES_ON_BAIT	0.487052	0.493432	0.489231	0.436697	0.484573
PCT_USABLE_BASES_ON_TARGET	0.384424	0.390951	0.3872	0.346063	0.383869
FOLD_ENRICHMENT	37.590859	35.15681	34.274242	34.90706	34.238722

ZERO_CVG_TARGETS_PCT	0.032957	0.03272	0.03142	0.038844	0.031802
FOLD_80_BASE_PENALTY	3.433606	3.593404	3.295493	3.197152	3.483305
PCT_TARGET_BASES_2X	0.951657	0.949276	0.952043	0.937569	0.950645
PCT_TARGET_BASES_10X	0.882062	0.874339	0.880886	0.837206	0.875812
PCT_TARGET_BASES_20X	0.820844	0.80823	0.818189	0.724317	0.809744
PCT_TARGET_BASES_30X	0.75919	0.743913	0.754895	0.604151	0.744691
HS_LIBRARY_SIZE	177408756	415450113	541989417	72776278	463998406
HS_PENALTY_10X	7.289009	7.901674	7.400111	7.793852	7.848868
HS_PENALTY_20X	7.701841	8.087803	7.508262	9.033318	7.996178
HS_PENALTY_30X	8.173649	8.267728	7.634437	11.071551	8.161902
AT_DROPOUT	0.060934	0.053232	0.089893	0.078131	0.072486
GC_DROPOUT	21.078109	22.410855	20.27203	20.116971	21.628716
SAMPLE	UK10K_NM5061922	UK10K_NM5003379	UK10K_NM5003377	UK10K_NM5003382	UK10K_NM5003378

Supplementary Table 1: Exome metrics was calculated from the BAM files using Picard CalculateHsMetrics (http://picard.sourceforge.net/index.shtml).

BAIT_SET: The name of the bait set used in the hybrid selection.

GENOME_SIZE: The number of bases in the reference genome used for alignment.

BAIT_TERRITORY: The number of bases which have one or more baits on top of them.

TARGET_TERRITORY: The unique number of target bases in the experiment where target is usually exons etc.

BAIT_DESIGN_EFFICIENCY: Target territory / bait territory. 1 == perfectly efficient, 0.5 = half of baited bases are not target.

TOTAL_READS: The total number of reads in the SAM or BAM file examined.

PF_READS: The number of reads that pass the vendor's filter.

PF_UNIQUE_READS: The number of PF reads that are not marked as duplicates.

PCT_PF_READS: PF reads / total reads. The percent of reads passing filter.

PCT_PF_UQ_READS: PF Unique Reads / Total Reads.

PF_UQ_READS_ALIGNED: The number of PF unique reads that are aligned with mapping score > 0 to the reference genome.

PCT_PF_UQ_READS_ALIGNED: PF Reads Aligned / PF Reads.

PF_UQ_BASES_ALIGNED: The number of bases in the PF aligned reads that are mapped to a reference base. Accounts for clipping and gaps.

ON_BAIT_BASES: The number of PF aligned bases that mapped to a baited region of the genome.

NEAR_BAIT_BASES: The number of PF aligned bases that mapped to within a fixed interval of a baited region, but not on a baited region.

OFF_BAIT_BASES: The number of PF aligned bases that mapped to neither on or near a bait.

ON_TARGET_BASES: The number of PF aligned bases that mapped to a targeted region of the genome.

PCT_SELECTED_BASES: On+Near Bait Bases / PF Bases Aligned.

PCT_OFF_BAIT: The percentage of aligned PF bases that mapped neither on or near a bait.

ON_BAIT_VS_SELECTED: The percentage of on+near bait bases that are on as opposed to near.

MEAN_BAIT_COVERAGE: The mean coverage of all baits in the experiment.

MEAN_TARGET_COVERAGE: The mean coverage of targets that received at least coverage depth = 2 at one base.

PCT_USABLE_BASES_ON_BAIT: The number of aligned, de-duped, on-bait bases out of the PF bases available.

PCT_USABLE_BASES_ON_TARGET: The number of aligned, de-duped, on-target bases out of the PF bases available.

FOLD_ENRICHMENT: The fold by which the baited region has been amplified above genomic background.

ZERO_CVG_TARGETS_PCT: The number of targets that did not reach coverage=2 over any base.

FOLD_80_BASE_PENALTY: The fold over-coverage necessary to raise 80% of bases in "non-zero-cvg" targets to the mean coverage level in those targets.

PCT_TARGET_BASES_2X: The percentage of ALL target bases achieving 2X or greater coverage.

PCT_TARGET_BASES_10X: The percentage of ALL target bases achieving 10X or greater coverage.

PCT_TARGET_BASES_20X: The percentage of ALL target bases achieving 20X or greater coverage.

PCT_TARGET_BASES_30X: The percentage of ALL target bases achieving 30X or greater coverage.

HS_LIBRARY_SIZE: The estimated number of unique molecules in the selected part of the library.

HS_PENALTY_10X: The "hybrid selection penalty" incurred to get 80% of target bases to 10X. This metric should be interpreted as: if I have a design with 10 megabases of target, and want to get 10X coverage I need to sequence until PF_ALIGNED_BASES = 10^7 * 10 * HS_PENALTY_10X.

HS_PENALTY_20X: The "hybrid selection penalty" incurred to get 80% of target bases to 20X. This metric should be interpreted as: if I have a design with 10 megabases of target, and want to get 20X coverage I need to sequence until PF_ALIGNED_BASES = 10^7 * 20 * HS_PENALTY_20X.

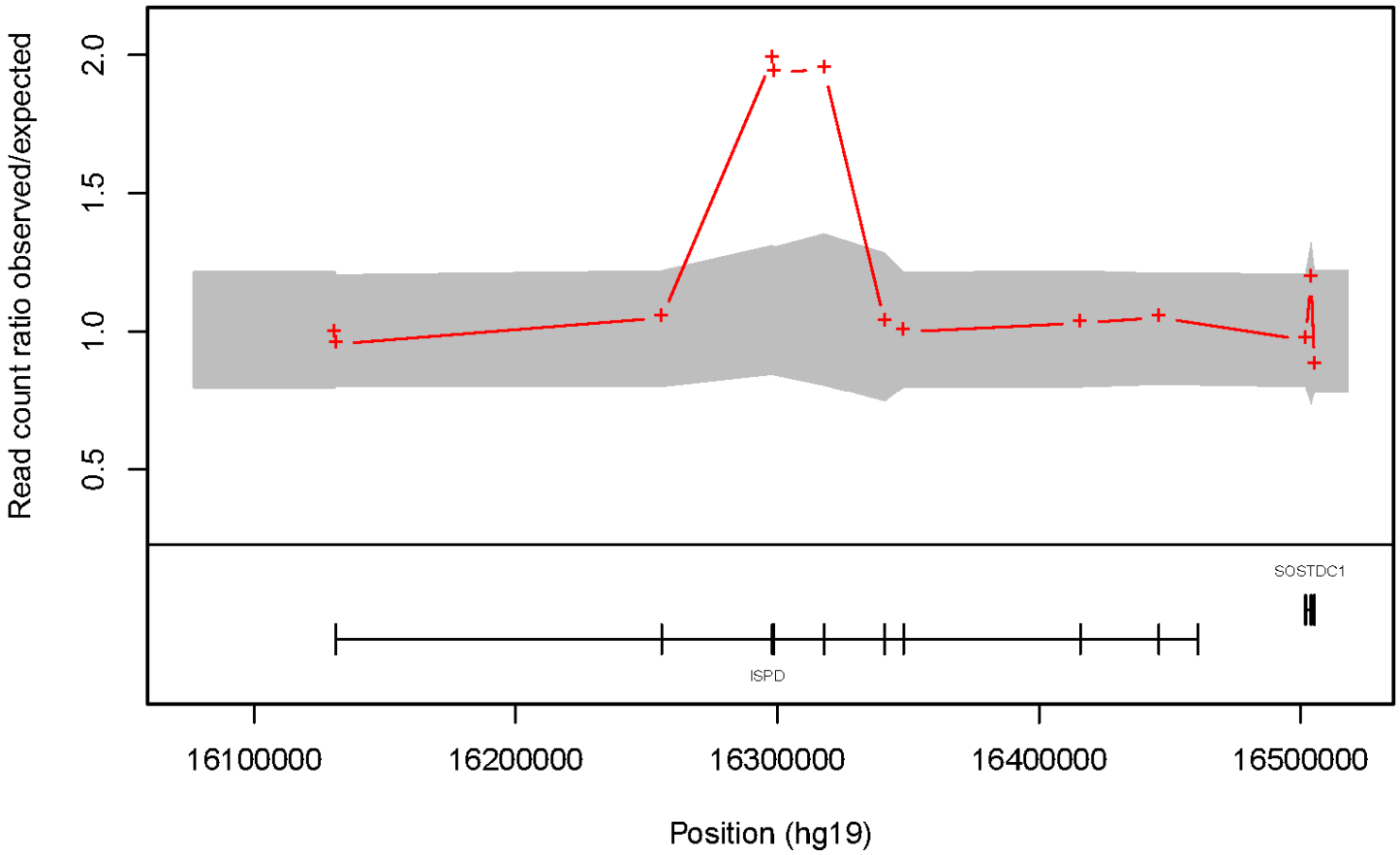
HS_PENALTY_30X: The "hybrid selection penalty" incurred to get 80% of target bases to 10X. This metric should be interpreted as: if I have a design with 10 megabases of target, and want to get 30X coverage I need to sequence until PF_ALIGNED_BASES = 10^7 * 30 * HS_PENALTY_30X.

AT_DROPOUT: A measure of how under covered <= 50% GC regions are relative to the mean. For each GC bin [0..50] we calculate a = % of target territory, and b = % of aligned reads aligned to these targets. AT DROPOUT is then abs(sum(a-b when a-b < 0)). E.g. if the value is 5% this implies that 5% of total reads that should have mapped to GC<=50% regions mapped elsewhere.

GC_DROPOUT: A measure of how under covered >= 50% GC regions are relative to the mean. For each GC bin [50..100] we calculate a = % of target territory, and b = % of aligned reads aligned to these targets. GC DROPOUT is then abs(sum(a-b when a-b < 0)). E.g. if the value is 5% this implies that 5% of total reads that should have mapped to GC>=50% regions mapped elsewhere.

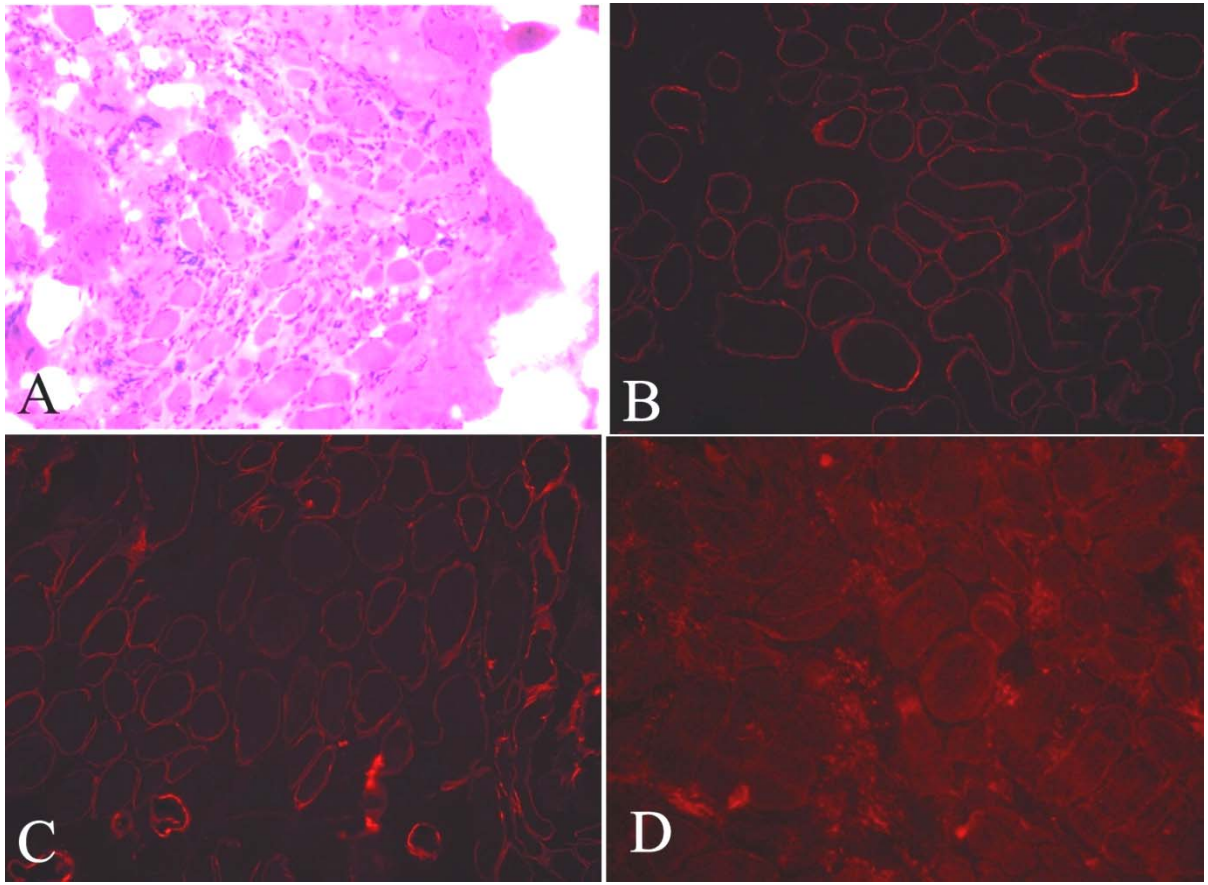
Supplementary Figure 2: Read depth CNV analysis of the exome sequence data.

For each exon and each test sample, ExomeDepth estimates the number of short sequencing reads that are expected to map to that location using additional exomes processed within the same batch. Red crosses show the ratio between the observed and expected read count for that exome sample. The grey area shows the 95% confidence interval for this read count ratio (estimated using a robust beta-binomial model).



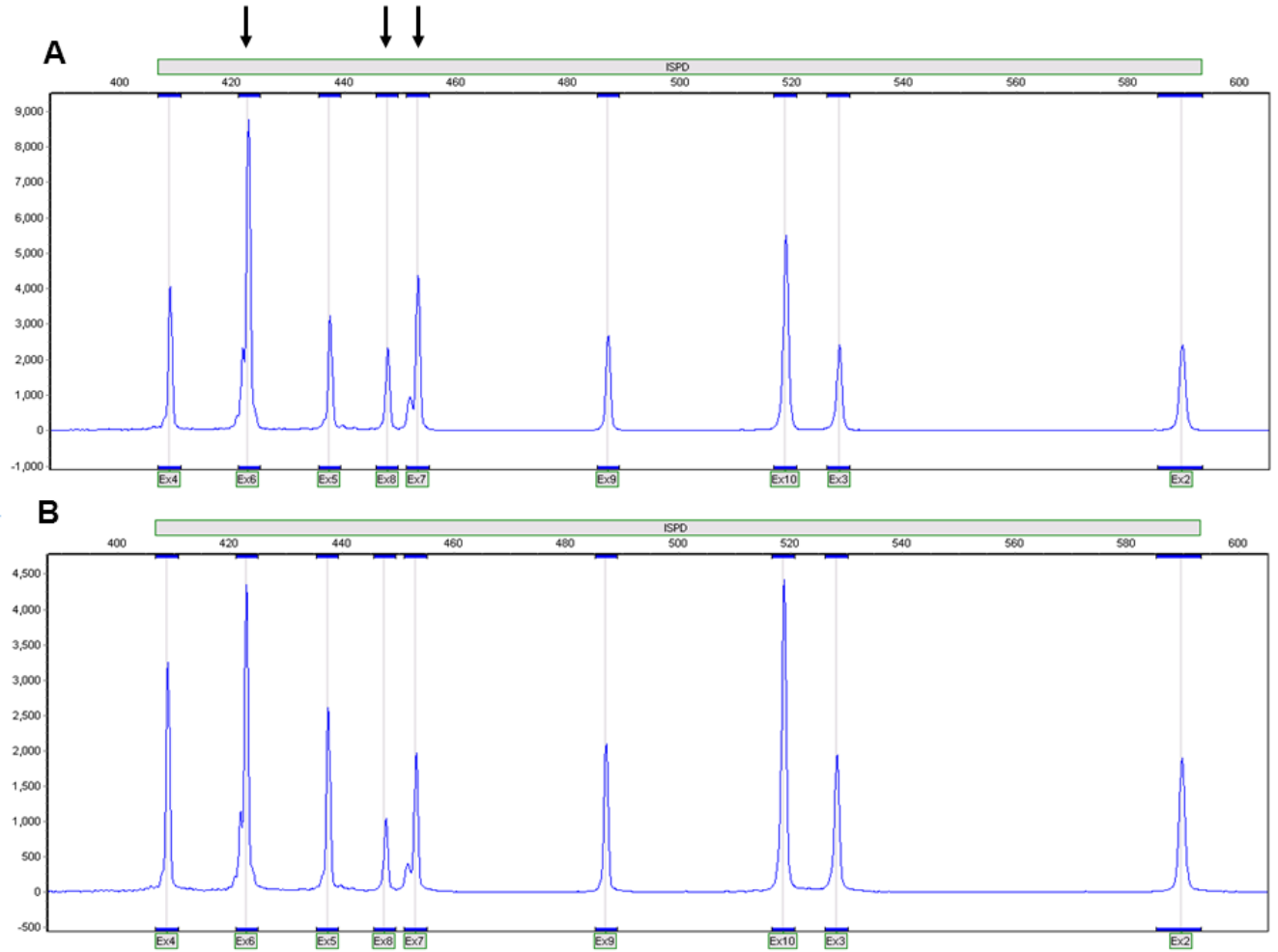
Supplementary Figure 3: Muscle biopsy images from case 1

A: Haematoxylin and Eosin staining; Immunohistochemistry B: β-dystroglycan, C: Laminin-α2 (300kDa), D: IIH6 α-dystroglycan. The muscle was processed as described earlier (Herrmann *et al.* , 2000).



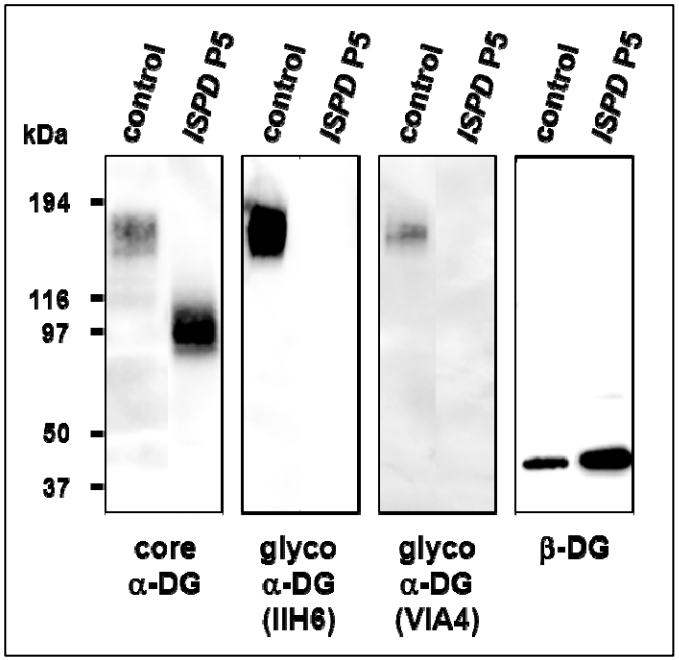
Supplementary Figure 4: **Copynumber validation**

Comparison of GeneMarker electrophretograms from Case 9 (A) versus a normal control (B) from the ISPD QF-PCR assay. The horizontal scale indicates the size of the amplicons in base pairs while the vertical scale on each profile represents the peak heights. Arrows indicate the exons that have a relative increased peak height indicative of a homozygous duplication. For example, in the normal control (B) exons 7 and 9 have similar peak heights of 1933 and 1975 respectively, while in Case 9 the exon 7 peak height of 4370 is approximately double that of exon 9 (2,666).



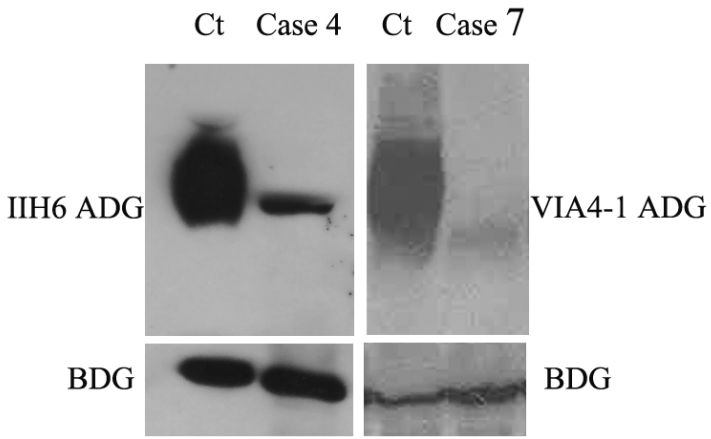
Supplementary Figure 5: WGA enriched immunoblot analysis of muscle biopsy lysate from case 5

Immunoblot analysis of WGA-enriched homogenates from control and *ISPD*-deficient patient skeletal muscle biopsy. Monoclonal antibodies (IIH6 and VIA4-1) were used to detect functional glycosylation of α-dystroglycan. α-dystroglycan from *ISPD*-deficient patient muscle biopsy shows hypoglycosylation combined with loss of α-dystroglycan functional glycosylation indicated by the lack of binding affinity to the glyco-epitope specific monoclonal antibodies IIH6 and VIA4-1.



Supplementary Figure 6: Immunoblot analysis of muscle biopsy specimen from cases 4 and 7

Western blotting analysis of muscle protein lysates from control and ISPD patients cases 4 and 7. The membrane on the left was incubated with anti α-dystroglycan IIH6 antibodies while the membrane on the right with anti α-dystroglycan VIA4-1 antibodies. Both patients showed a profound reduction in α-dystroglycan expression. The β-dystroglycan bands were normal compared to controls.



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