Case of autosomal-recessive spinal muscular atrophy with respiratory distress type 1 caused by compound heterozygous mutations in immunoglobulin-binding protein 2 gene: expansion in clinical features

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Background
The etiological factors for early-onset infantile hypotonia with respiratory distress are variable. Spinal muscle atrophy with respiratory-distress type 1 (SMARD1) is usually presented with early-onset severe hypotonia and respiratory insufficiency that may require mechanical ventilation.

Patients and methods
Herein, we report on an Egyptian male infant who was born to nonconsanguineous parents, presented at the age of 2 months with acute onset of respiratory distress and severe hypotonia and required mechanical ventilatory support. As an expansion to the typical SMARD1 clinical features, hepatomegaly, elevated liver transaminases, and subdural hygroma were identified. Additionally, computed tomography chest showed pulmonary consolidation without evidence of diaphragmatic paralysis. The patient was mechanically ventilated and fed by nasogastric tube. There were multiple trials of extubation, which failed and tracheostomy was done. The patient died at the age of 11-month old. Whole-exome sequencing was done for the index patient and followed by variant filtration. Parental segregation was done to evaluate the phase of the detected variants.

Results
Whole-exome sequencing revealed two heterozygous variants in the immunoglobulin-binding protein 2 (*IGHMBP2*) gene, c.138 T>A and c.1616C>T, a pathogenic variant, and another of uncertain significance, respectively. In addition, a variant of uncertain significance was identified in *CHRND* gene (c.389 A>T). Biallelic *IGHMBP2* variants are causative for SMARD1 and axonal Charcot–Marie–Tooth disease type 2S. Segregation study and clinical presentation prioritize the compound heterozygous variants in *IGHMBP2* gene (c.138 T>A) and (c.1616C>T) as the causing disease molecular pathology.

Conclusion
Both SMARD1 and congenital myasthenic syndromes are possible genetic diagnoses for this patient. However, the clinical phenotype was more compatible with SMARD1. Nevertheless, the additional manifestations such as microcephaly, hepatomegaly, hypothyroidism, and neuroimaging were not featured in SMARD1.

Keywords:
autosomal recessive, immunoglobulin-binding protein 2 gene, spinal muscle atrophy with respiratory-distress type 1, whole-exome sequencing

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Background

Hypotonia is a sign of a number of the nervous-system disorders that can affect brain, brain stem, spinal cord, peripheral nerves, neuromuscular junction, and muscle (Leyenaar *et al.*, 2005).

The etiological factors for early-onset infantile hypotonia with respiratory compromise are variable. Congenital myopathies, congenital muscular dystrophies, congenital myasthenic syndromes, and congenital myotonic dystrophy can be presented with early-onset severe hypotonia and severe respiratory insufficiency that may require mechanical ventilation (Lingappa *et al.*, 2016). Nonetheless, there are a number of clinical features and potential genetic factors that can be utilized for differential diagnosis (Porro *et al.*, 2014).

Spinal muscular atrophy (SMA) is one of the common autosomal-recessive genetic disorders. Its incidence in livebirths is estimated to be 1 in 6000 to 1 in 10 000 and has carrier frequency of 1/40–1/60

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(D'Amico *et al.*, 2011). It is a neuromuscular disorder that is mainly caused by homozygous mutations of the survival motor neuron 1 (SMN1) (D'Amico *et al.*, 2011). The prevalence of SMA in Egypt is estimated to be higher than the worldwide frequency and this may be due to high consanguinity rate (Shawky and El-Sayed, 2011).

In about 1% of SMA cases with a negative genetic confirmation of the involvement of SMN genes, mutations in the gene encoding immunoglobulin-binding protein 2 (*IGHMBP2*) were detected, the rare form among the group of SMA disorders (Grohmann *et al.*, 2001; Porro *et al.*, 2014). *IGHMBP2* and *SMN* genes have shared important functions for maintaining the motor neuron integrity, including pre messenger RNA (mRNA) processing and transcription activation (Grohmann *et al.*, 2001; de Planell-Saguer *et al.*, 2009).

The spinal muscle atrophy with respiratory-distress type-1 (SMARD1) disease can be differentiated from SMA by the involvement of the symmetrical distal muscular atrophy and respiratory distress due to diaphragmatic palsy as well as the sensory and autonomic nervous-system impairment (Messina *et al.*, 2012; Tomaselli *et al.*, 2018). Sometimes, there was variability in the SMARD1 clinical severity and features even within the same family members with the same mutations (Joseph *et al.*, 2009).

The *IGHMBP2* gene is located on chromosome 11q13.3, has 15 exons, and encodes the immunoglobulin mu-binding protein 2 (993 amino acids) (Grohmann *et al.*, 1999). The IGHMBP2 protein consists of four domains: an ATPase domain, a single-stranded nucleic acid-binding R3H domain, a DEXDc domain, and an AN1-type zinc-finger motif (Grohmann *et al.*, 2004). IGHMBP2 has been defined according to sequence homology, as a member of the helicase superfamily 1 (Lim *et al.*, 2012). It is an ATP-dependent 5'–3' DNA/RNA helicase and can unwind both duplexes. It is mainly found in the cytoplasm, and it was suggested to have a function in RNA processing due to the presence of an RNA helicase domain and a single-stranded nucleic acid-binding domain (de Planell-Saguer *et al.*, 2009). As well as, it interacts with a unique set of small RNAs that includes $tRNA^{Tyr}$, and with other proteins, that are required for tRNA transcription and ribosome biogenesis and function. Therefore, all that support IGHMBP2 role in the transcription activation, pre-mRNA splicing complexes, and translation may be a component of the translational machinery, which can genetically suppress motor neuron degeneration (Kaindl *et al.*, 2008; de Planell-Saguer *et al.*, 2009; Lim *et al.*, 2012). Intriguingly, mutations in *IGHMBP2* gene cause two definite phenotypes: SMARD1 [also defined as distal hereditary motor neuropathy type VI (dHMN6 or HMN6)] (OMIM #604320) (Grohmann *et al.*, 2001) and Charcot–Marie–Tooth disease type 2 S (CMT2S) (OMIM # 616155) (Cottenie *et al.*, 2014). *IGHMBP2* belongs to a group of genes causing both of CMT and dHMN/dSMA, with a comparable function that is important for the regulation of pre-mRNA processing and transcription (Porro *et al.*, 2014).

In SMARD1, diaphragmatic paralysis and distal muscular atrophy result from the degeneration of alpha motor neurons of the spinal cord. In few records, sensory and autonomic nerves are affected too (Tomaselli *et al.*, 2018). The hallmark of the disease is that it starts in infancy and causes early death due to respiratory distress, however, few cases with milder phenotypes (later onset and survival until 15–20 years of age) have been documented (Grohmann *et al.*, 1999; Grohmann *et al.*, 2001). In contrast, CMT2S is manifested as an axonal neuropathy with slowly progressive, distal–predominant muscle weakness and sensory loss with preserved respiratory function (Cottenie *et al.*, 2014; Schottmann *et al.*, 2015a, 2015b). As yet, SMARD1 or CMT2S patients cannot be differentiated genetically. As well, the relationship between the mutation effect at the protein level and clinical severity is still not fully elucidated (Cottenie *et al.*, 2014, Schottmann *et al.*, 2015a, 2015b). Lately, another gene *LAS1L* has been reported to be associated with the SMARD phenotype. Both *LAS1L* and *IGHMBP2* genes have a role in the ribosome biogenesis (Hachiya *et al.*, 2005; Butterfield *et al.*, 2014). Another gene *REEP1* has been associated with SMARD1 phenotype (Schottmann *et al.*, 2015a, 2015b). These newly proposed genes have to be examined in SMARD1 *IGHMBP2* mutation-negative patients.

The *IGHMBP2* gene is expressed in all body tissues with high rates in the testis. As well, it is expressed in developing and adult human brain, with high levels in the cerebellum (Cottenie *et al.*, 2014). According to Human Genome Mutation Database (HGMD), a total of 190 variants were detected and reported in *IGHMBP2*, including 148 missense or nonsense, 17 splicing mutations and 30 indels, and structural and rearrangement mutations. Mainly, *IGHMBP2* mutations cause SMARD1 according to the HGMD (August, 2021). Most patients have compound heterozygous or homozygous mutations, but some cases are caused by chromosomal rearrangements at the IGHMBP2 locus. Most of the detected mutations were distributed over the gene length, but mainly on the protein domain that contains DEAD-box helicases (Grohmann *et al.*, 2003; Guenther *et al.*, 2004).

In the current report, we report on the first Egyptian case with SMARD1 using whole-exome sequencing (WES).

Patients and methods

Clinical description

A male Egyptian infant aged 4 months was the offspring of a nonconsanguineous marriage with a previous history of two abortions. Unfortunately, no clinical records or investigations were done for the dead fetuses. The mother had a history of numbness of toes and recurrent stumbling. The index case was born full term with irrelevant antenatal history. He was delivered by cesarean section with immediate first cry and birth weight was 3.5 kg. The baby was active with good suckling power for the first 2 months of life. At the age of 2 months, the patient developed vomiting with aspiration, acute-onset respiratory distress, and cyanosis that required prolonged mechanical ventilation. Protocols were approved by the Medical Research Ethics Committee at Faculty of Medicine, Tanta University, Egypt (ethical committee reference number is not available). Informed consents were signed by the patient parents and all studied family members.

On examination, his weight and head circumference were below the third centile and the length was on the fifth centile. The patient had mild dysmorphic features such as hairy high forehead, synophrys, long eye lashes, broad depressed nasal root, short upturned nose, and mild retromicrognathia. Hepatomegaly was detected, about 4 cm below the costal margin. Neurologically, the infant was in frog-leg position, hypotonic with areflexia and bilateral contractures of the ankle joints. The muscle mass was decreased with firm consistency. He had head lag with complete paralysis of the extremities with muscle-power grade 0. Weak cry with poor suckling and recurrent aspiration was recorded. The extraocular muscle showed normal movement with no evidence of ptosis or facial weakness. He developed tongue fasciculations late in the course of the disease. The parents refused to do nerve or muscle biopsy. For persistent poor oral feeding, he required nasogastric tube. He experienced failure of repeated attempts of extubation, so tracheostomy was done when he was 4-month old. The patient died because of pneumonia when he was 11-month old.

Laboratory investigations and imaging studies

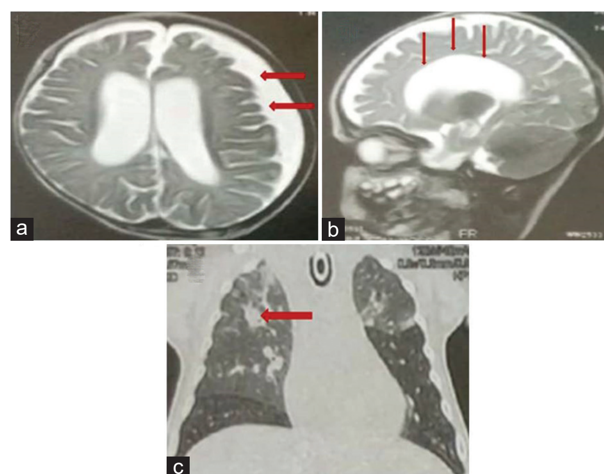
The laboratory investigations revealed elevated liver enzymes (SGPT: 110–148 U/l with normal reference range up to 37 U/l, SGOT: 103–153 U/l with normal reference range up to 31 U/l). Renal functions were normal. The level of thyroid-stimulating hormone was 18.211 μIU/ml (normal reference range: 0.87–6.15). The level of FT3 was 3.71 pg/ml (normal reference range: 2.6–4.4) and that of FT4 was 1.31 ng/dl (normal reference range: 0.9–1.99). Thyroid-scan study was normal. After thyroxin replacement, thyroid function normalized.

Metabolic workup, including plasma amino acid analysis, free carnitine and acylcarnitine profile, and lactate and pyruvate levels, showed normal ranges. The CPK was 63 U/l (normal reference range: 41–330).

The patient had normal echocardiography. Pelviabdominal ultrasonography revealed hepatomegaly with liver span 7 cm. The MRI study of the brain showed a well-defined left-parietal subdural hygroma measuring 1×6×9 cm (Fig. 1a), exerting mild mass effect in the form of buckling of the underlying sulci with prominent ventricular system and extraaxial cerebrospinal fluid spaces indicating central and cortical atrophic changes and thin corpus callosum (Fig. 1b). The chest computed tomography showed patches of consolidation (Fig. 1c) with normal diaphragm. Nerve-conduction velocity confirmed the presence of marked severe peripheral polyneuropathy with complete denervated and fibrosed muscles. Tongue fasciculations were identified late in the course of the disease.

Blood karyotyping was done and showed normal results. As well as, SMA molecular diagnostic testing was done using real-time and *SMN1* gene sequencing and showed normal results.

Figure 1



Remarkable clinical features of the index case. (a) T2-weighted MRI of the brain showing subdural hygroma (arrows). (b) T2-weighted MRI of the brain showing thin corpus callosum (arrows) and brain atrophy. (c) CT chest with angiography showing patches of consolidation (arrow). CT, computed tomography.

Genomic analysis

DNA extraction

Five milliliters of blood samples were collected from each of the affected infant and his parents. The genomic DNA was extracted using QIAamp DNA Blood Mini Kit as recommended by the manufacturers. The concentration of the extracted DNA was determined using the NanoDrop spectrophotometer 2000 (NanoDrop Technologies, Montchanin, Delaware, USA) at 260/280 nm.

Whole-exome analysis

WES was carried out for the molecular diagnosis of the index case. Agilent SureSelect Human All ExonV5 kit was used for enrichment of the coding regions and then paired-end sequencing (125-bp reads) using HiSeq PE Cluster Kit v4 and HiSeq SBS kit v4 on HiSeq. 2500 instrument was done. The resultant reads were aligned to the human genome reference (GRCh37/hg19) using alignment software BWA (Li and Durbin, 2009). The haplotype caller GATK 3.7 (Van der Auwera *et al.*, 2013) has been used for variant calling. The VCF file of all the detected variants was annotated using ANNOVAR software (Wang *et al.*, 2010). The annotated VCF file was analyzed and filtered using PhenoDB platform (Hamosh *et al.*, 2013) according to different suggested inheritance patterns.

Confirmation of the detected mutations using Sanger sequencing

The last filtrated single-nucleotide variants were confirmed and segregated using the proband and his parent DNA samples using specific PCR primers, which were designed to amplify the target regions containing the identified single-nucleotide variants. The PCR products were amplified using Taq DNA polymerase, recombinant 5 U/μl. The amplified PCR product was examined using gel electrophoresis, purified, and amplified using The BigDye Terminator v3.1 Cycle Sequencing Kit and sequenced on a 3500 genetic analyzer.

In silico functional analysis

The effect of the mutation on the gene function was assessed by checking the SNP database (dbSNP, 2021) and Clinvar databases, and using a number of different programs and algorithms, including PolyPhen (Adzhubei *et al.*, 2010), SIFT (Ng and Henikoff, 2003), Mutationtaster (Schwarz *et al.*, 2014), and PhD-SNPg (Capriotti and Fariselli, 2017). The Varsome platform was used to help in the evaluation of the detected-variant effect and pathogenicity using guidelines of the American College of Medical Genetics and Genomics, Association for Molecular Pathology (ACMG-AMP) (Kopanos *et al.*, 2019).

Results

The average coverage of the WES was about 151×. The resulting variants were filtered according to different proposed inheritance patterns. A number of variants were selected since they were relevant to the clinical features.

Three variants were selected for further evaluation and studying, including a heterozygous missense variant in exon 5 of *CHRND* gene (NM_000751.1:c.389 A>T p.(Asn130Ile)), in addition to two heterozygous variants in the *IGHMBP2* gene [one nonsense (stop gain) in exon 2 (NM_002180.2:c.138 T>A p.(Cys46*)) and one missense in exon 11 (NM_002180.2:c.1616C>T p.(Ser539Leu))] (Table 1).

The detected variants were assessed by checking the dbSNP and Clinvar databases. The *CHRND* variant c.389 A>T p.(Asn130Ile) (rs1553574327) causes an amino acid change from Asn to Ile at position 130. It is classified as a variant of uncertain significance. The *IGHMBP2* truncating variant c.138 T>A p.(Cys46*) (rs372000714) creates a premature stop codon. According to HGMD professional 2021, this variant has previously been described as disease causing for SMARD1 (Grohmann *et al.*, 2003; HGMD, 2021), as well as CMT2S (Cottenie *et al.*, 2014). ClinVar lists this variant as pathogenic (clinical testing, variation ID: 162194).

The second *IGHMBP2* variant c.1616C>T p.(Ser539Leu) (rs879253887) causes an amino acid change from serine to leukine at position 539. ClinVar lists this variant as uncertain and likely pathogenic (clinical testing, variation ID: 245629). Thus, it is classified as a variant of uncertain significance.

All detected variants were checked using databases of gnomAD, 1000 genomes project, and different prioritizing and variant-scoring tools to predict the effect of the variant (Table 1).

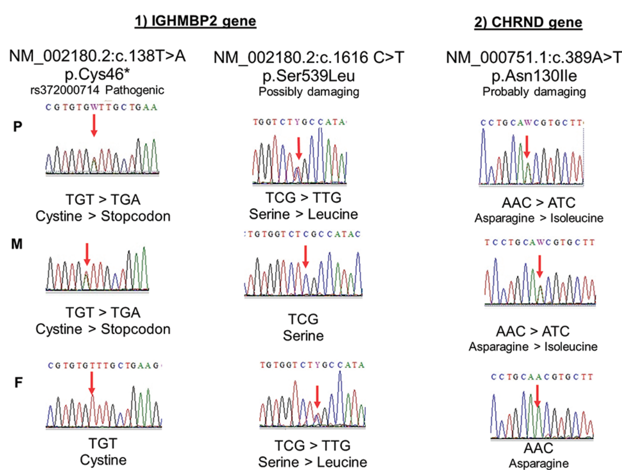
Parental carrier testing was done to define the phase of the detected variants. Following the segregation study, the mother has two heterozygous variants, the *IGHMBP2* variant c.138 T>A p.(Cys46*) and the *CHRND* variant c.389 A>T p.(Asn130Ile) (Fig. 2). The father has a heterozygous IGHMBP2 variant c.1616C>T p.(Ser539Leu) (Fig. 2). The validation of the WES results using Sanger sequencing shows complete cosegregation of the *IGHMBP2* variants,

Table 1 Summary of the in-silico predication of the detected whole-exome sequencing variant effects

Variants	Zygosity	1000 genomes	gnomAD	SIFT	PhyloP	PhastCons	Polyphen2
CHRND:c. 389 A>T p.Asn130Ile	Heterozygote	Not detected	Not detected	Pathogenic	Conserved 2.953	Conserved 1.00	Probably damaging 1.00
IGHMBP2:c.138 T>A p.(Cys46*)	Heterozygote	Not detected	0.000016	NA	Conserved 4.17	Conserved 1.00	NA
IGHMBP2:c.1616C>T p.(Ser539Leu)	Heterozygote	Not detected	0.0000040	Deleterious	0.803 1	1.00	Possibly damaging

Sorting intolerance from tolerant (SIFT) predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids [score ranges from 0.0 (deleterious) to 1.0 (tolerated)]. The variant with the score 0.0–0.05 is considered deleterious. PhastCons and PhyloP scores (MutationTaster) rely on the grade of conservation of a given nucleotide (a negative sign indicates faster-than expected evolution, while positive values imply conservation). Polyphen2 (Polymorphism Phenotyping v2) predicts the possible impact of amino acid substitutions on the stability and function of human proteins using structural and comparative evolutionary considerations [score ranges from 0.0 (tolerated) to 1.0 (deleterious)]. IGHMBP2, immunoglobulin-binding protein 2; NA, not applicable.

Figure 2



The results of segregation study using Sanger sequencing. (1) Chromatograms of *IGHMBP2* variant-sequencing results: (a) c.138 T>A p.(Cys46*), (b) c.1616C>T p.(Ser539Leu). (2) Chromatograms of *CHRND* variant-sequencing results: (a) c.389 A>T p.(Asn130Ile). P, proband; M, mother; F, father. IGHMBP2, immunoglobulin-binding protein 2.

either c.138 T>A or c.1616C>T mutations with the disease phenotype in this family. Therefore, *CHRND* variant has been considered an accidental finding and the family was informed.

Discussion

SMARD1 is a severe, rare autosomal-recessive disease with infantile onset and high mortality with no effective treatment other than symptomatic care (Kim *et al.*, 2019). It is characterized by profound hypotonia and weakness with absent reflexes, and abnormal finger-fat pads. It is marked by the presence of progressive respiratory distress with diaphragmatic paralysis and the respiratory failure, which is manifested between 6 weeks and 6 months along with diaphragmatic eventration. Sometimes, it leads to premature birth (Kaindl *et al.*, 2008; Eckart *et al.*, 2012). The present patient exhibited some of the typical features of the disease. These included the profound hypotonia with areflexia, recurrent aspiration, and progressive respiratory distress that required mechanical ventilation. Some additional features are not typically present in SMARD1 like hypothyroidism and microcephaly, which have been reported as atypical features (Chiu *et al.*, 2018). Hepatomegaly has been noticed in the current case with elevated liver enzymes and subdural hygroma and was not reported before to the best of our knowledge. On the other hand, chest radiograph and computed tomography chest did not show eventration of the diaphragm, which is typically present in almost all cases of SMARD1 (Grohmann *et al.*, 2001). Also, we identified in our case tongue fasciculations late in the course of the disease.

The WES study for the index case revealed that the patient was heterozygous for *CHRND* variant c.389 A>T, p. (Asn130Ile), maternally inherited by segregation analysis. Pathogenic *CHRND* variants are causative for autosomal-dominant congenital slow-channel myasthenic syndrome 3A and autosomal-recessive congenital myasthenic syndrome type 3C associated with acetylcholine-receptor deficiency. However, despite the overlapping features between the two disorders, our case had no ptosis. Moreover, the mother had the same variant. Therefore, this variant was excluded as the major disease-causing mutation, but it can be hypothesized as a modifier agent for the disease severity.

Two heterozygous variants were identified in the *IGHMBP2* gene. The *IGHMBP2* variant c.138 T>A, p.(Cys46*) is known to be a pathogenic variant causing SMARD1 (20). The *IGHMBP2* variant c.1616C>T, p.(Ser539Leu) reporting by clinvar has conflicting interpretations of pathogenicity, either as likely pathogenic or of unknown significance. However, it was associated with SMARD1 in six individuals; their results were submitted to Clinvar database by Pediatrics-Neurology Children Center, Children's Hospital, Toulouse, France (Clinvar accession VCV000245629.2). They submitted the variant as

likely pathogenic as it is located in the DNA helicase domain of *IGHMBP2*. The DNA helicase domain is the main functional domain of the protein IGHMBP2, where there is the ATP-binding site (region 2A) (Lim *et al.*, 2012). The amino acid Ser539 is essential for stabilizing the RecA-like fold by the interaction with Val580 and this interaction is essential for the stabilization of domain 2A (Cottenie *et al.*, 2014). The conflict about the pathogenicity of c.1616C>T relies on the poor conservation of its flanking region, However, the Mutationtaster results showed a deleterious effect of the mutation on the protein structure due to the conservation of a given C nucleotide at position 1616 (the direct PhyLop and Phastcons scores are 5.588 and 1, respectively, and the flanking PhyLop scores are 0.803 and −0.546, as well as flanking Phastcons scores are 1 and 0.895). The *IGHMBP2* variant c.1616C>T was detected in two other individuals with the same clinical condition submitted to Clinvar by GeneDx (Accession: SCV000292588.10) and Invitae (Accession: SCV001417951.1) as of uncertain significance due to the evolutionary conservation conflict. According to Sun and Yu (2019), the final assumption of the deleteriousness of the variant using evolutionary computational predictions, should be treated with caution.

Finally, by the application of the ACGM guidelines of the variant classification (Richards *et al.*, 2015) and using Varsome (a variant knowledge community, data aggregator, and variant data discovery tool) (32), *IGHMBP2* variant c.1616C>T, p.(Ser539Leu) is proposed to be pathogenic. Fulfilling the ACGM criteria for a pathogenic variant (Table 2) included moderate evidences for pathogenicity, such as PM2, PM3, as well as supporting evidences (PP2 and PP3) and finally a strong pathogenicity evidence PS4. The variation was prevalent in the diseased population (about nine cases) in comparison with the control (Richards *et al.*, 2015).

The pathogenic mechanism of the *IGHMBP2* mutations on the protein function is still unclear and questionable and even could not be assessed by the reduction of mRNA. But it was suggested to be related to the translation process of *IGHMBP2* (Guenther *et al.*, 2009). The variant pathogenicity should be assessed by functional analysis of protein levels, which is indispensible and cannot be compensated by computational analysis.

The disease severity was suggested to be related to the reduction of IGHMBP2 enzymatic activity (Litvinenko *et al.*, 2014), however, this assumption was contradicted by interfamilial variability of the disease severity (Joseph *et al.*, 2009). In our opinion, the difference in the genetic makeup of the patients may be the cause of the variability in disease severity, even within the same family, and this was suggested by a number of recent studies (Kammenga, 2017; Chen *et al.*, 2016).

Table 2 ACMG criteria fulfilled by studying the immunoglobulin-binding protein 2 variants c.1616C>T p.(Ser539Leu) and supporting its pathogenicity

	Evidence	Meaning
Moderate	PM2	Absent from in Exome Sequencing Projects (1000 Genomes Project, or Exome Aggregation Consortium)
	PM3	Detected in trans with another pathogenic variant and frame shifting variant IGHMBP2: c.138 T>A p.(Cys46*), which was co-segregated within index case family
Supporting	PP2	Missense variants in IGHMBP2 gene has a low rate of benign missense variation, that 40 out of 65 non-VUS missense variants in gene IGHMBP2 are pathogenic (61.5%) (79 out of 476 clinically reported variants in gene IGHMBP2 are pathogenic=16.6% which is more than threshold of 12.0%)
	PP3	Multiple lines of computational evidence support a deleterious effect on the gene (11 pathogenic predictions from DANN, DEOGEN2, EIGEN, FATHMM-MKL, M-CAP, MVP, Mutation Assessor, MutationTaster, PrimateAI, REVEL and SIFT vs no benign predictions)
Strong	PS4	The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls (Variation ID: 245629)

IGHMBP2, immunoglobulin-binding protein 2; PM, moderate evidence of pathogenicity; PP, supporting evidence of pathogenicity criteria; PS, strong evidence of pathogenicity.

Conclusion

We present the first Egyptian case with SMARD1 with expansion of the clinical features. Molecular diagnosis was identified by WES and confirmed by Sanger sequencing of two compound heterozygous mutations in *IGHMBP2* (*IGHMBP2*: c.138 T>A, *IGHMBP2*: c.1616C>T). SMARD1 should be considered in cases with early respiratory insufficiency or near-miss sudden infant-death syndrome even with atypical manifestations like hepatomegaly and hypothyroidism. The current study highlights the importance of cooperation of bioinformaticians, molecular scientists, and clinicians for reaching diagnosis of cases with uncharacteristic presentations.

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the clinical evaluation, the write-up, and the revision. A.I.H. participated in the clinical evaluation of patients in the ICU unit. R.K. and H.D. designed and wrote and revised the paper. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and approved the paper.

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Conflicts of interest

There are no conflicts of interest.

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