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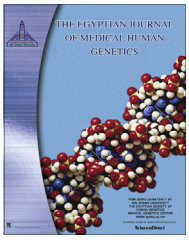

CASE REPORT

Screening of a clinically and biochemically diagnosed SOD patient using exome sequencing: A case report with a mutations/variations analysis approach

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KEYWORDS

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Abstract *Background:* Sulfite oxidase deficiency (SOD) is a rare neurometabolic inherited disorder causing severe delay in developmental stages and premature death. The disease follows an autosomal recessive pattern of inheritance and causes deficiency in the activity of sulfite oxidase, an enzyme that normally catalyzes conversion of sulfite to sulfate.

Aim of the study: SOD is an underdiagnosed disorder and its diagnosis can be difficult in young infants as early clinical features and neuroimaging changes may imitate some common diseases. Since the prognosis of the disease is poor, using exome sequencing as a powerful and efficient strategy for identifying the genes underlying rare mendelian disorders can provide important knowledge about early diagnosis, disease mechanisms, biological pathways, and potential therapeutic targets.

Patients and methods: In this study, a case who was a newborn infant boy with suspected SOD and his healthy parents were recruited for exome sequencing. The first laboratory reports of the patient were positive urine sulfite, elevated urinary thiosulfate, and high levels of plasma lactate and pyruvate. The patient also presented some symptoms such as intractable seizures, abnormal tone, feeding difficulties, profound mental retardation, abnormal respiratory drive, aspiration pneumonia, microcephaly, and dislocated ocular lenses. The genomic DNA of the patient and

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his parents was extracted from peripheral blood lymphocytes as targets for exome sequencing, performed by Axeq Technologies (Amsterdam, the Netherlands).

Results: The results showed no single predominate mutation in the *SUOX* gene as one of the candidate genes involved in the catabolism of sulfur-containing amino acids. The same results obtained in the molybdenum cofactor biosynthetic genes (*MOCS1*, *MOCS2*, and *GEPH* genes). Instead, the results revealed that causal variations are present in genes underlying in different biochemical pathways among which the sulfur metabolism, signaling and signal transduction, and transcription pathways are of higher importance.

Conclusion: In this study, several classes of genes were introduced as candidate genes involved in SOD. However, further studies are necessary to examine the reported genes in more details on how these genes may relate to each other and contribute to the pathology of SOD disease.

1. Introduction

Sulfite oxidase deficiency (SOD) is an inherited disease which causes neurometabolic abnormalities due to changes in sulfated amino acid metabolism and leading to early death [1]. Two forms of SOD are distinguished and referred to as molybdenum cofactor deficiency and isolated sulfite oxidase deficiency [2]. They have cumulatively been identified in fewer than one hundred cases, and isolated sulfite oxidase deficiency seems to be much less common [2,3]. Although patients with molybdenum cofactor deficiency manifest xanthinuria, clinical symptoms are similar in both forms [4]. Sulfite oxidase is a soluble homo-dimer enzyme with a molecular mass of 101–110 kDa located in the inter-membrane space of mitochondria [5,6]. This enzyme transfers electrons from sulfite into the electron transport chain by means of cytochrome c [7]. In fact, sulfite oxidase is responsible for oxidizing toxic sulfites to nontoxic sulfates in the final step of the metabolism pathway of the sulfur amino acids including methionine and cysteine [5]. Since sulfite oxidase enzyme is generally deficient as a result of a defect in a gene coding for sulfite oxidase or coding for its cofactor [8], two other metabolites sulfocysteine and thiosulfate are formed in alternative metabolic pathways [9]. The sulfite oxidase gene (*SUOX*) is mostly expressed in liver, kidney, skeletal muscle, heart, placenta, and the cerebral cortex [10]. This gene is located on chromosome 12 in the region of q13.2, and its coding sequence contains only one intron. The product of the gene is a protein named molybdohemoprotein (sulfite oxidase) with 466 amino acids [3]. Its cofactor, molybdenum, is a truncated protein normally synthesized by a complex pathway that requires the products of at least four different genes (*MOCS1*, *MOCS2*, *MOCS3*, and *GEPH*). Based on the recent researches, causative mutations have been identified in *MOCS1*, *MOCS2*, and *GEPH*, and a total of 32 different disease-causing mutations have been detected in molybdenum cofactor-deficient patients and their relatives [11]. As a rare disease, SOD and its genetic variants can be investigated through new and promising technologies such as exome sequencing (ES). ES is a powerful new tool for gene discovery in medical genetic research [12]. The first study to determine if it was possible to identify causal genetic variants using ES was carried out in 2009 for detection of the Freeman–Sheldon Syndrome (FSS) (OMIM 193700) [13]. This experiment helped to confirm that ES can be used to identify causal variants of rare genetic disorders, especially unknown causal genes for rare Mendelian diseases. Therefore, ES can be applied to locate pathogenic genes in such disorders that previously have not been possible to study due to limitations in traditional methods. The aim of present study was to recruit this new method as the state-of-the-art diagnostic tool for identifying genes involved in a patient with suspected SOD.

2. Clinical report

The age of onset for SOD disorder is typically after the first month of life (10-week to 15-month). In this report, a 5-month-old boy, born after a normal pregnancy and delivery was selected as the case. The parents of this case were maternal first-cousins (mother age: 22 and father age: 28). Since enzymatic proof of diagnosis may take several months and may require invasive studies, diagnosis of SOD was carried out based on the presence or absence of physical findings and characteristic metabolites. The "classic presentation" of the patient included intractable seizures and abnormal tone (particularly opisthotonus). Feeding difficulties were present shortly after birth, and some problems including poor feeding that requires a gastrostomy tube, vomiting, and gastroesophageal reflux was observed in first weeks of life. The infant had profound mental retardation, abnormal respiratory drive, aspiration pneumonia, microcephaly, and dislocated ocular lenses. A positive sulfite dipstick finding of very fresh urine was highly suggestive of SOD. An elevated urinary thiosulfate level was also essentially diagnostic of SOD. Plasma lactate and pyruvate levels were significantly elevated, although these findings are nonspecific. (Besides, other recently-reported specific chemicals like S-sulfocysteine and xanthine were not detected in urine [14,15]). No medical treatments that improve neurologic outcome are known, particularly for those with neonatal presentation of SOD (except in one case with Molybdenum cofactor deficiency [16]); however, this patient showed some clinical benefit from a cysteine-restricted and methionine-restricted diet.

3. Materials and methods

Genomic DNA was extracted using ZR DNA purification kit (Zymoresearch, USA) from the blood of the affected person and his unaffected parents and consequently was prepared for Illumina sequencing library performed by Axeq Technologies (Axeq Europe, the Netherlands). Since in the first step of analysis, we could not confirm previously reported

mutation in SOD candidate genes, the sequencing libraries were enriched for desired targets using Illumina Exome Enrichment protocol. Subsequently, captured libraries were sequenced using Illumina HiSeq 2000 Sequencer (Figs. 1 and 2).

4. Results

In current study, mutations in the *SUOX* gene and the genes identified as the components of the molybdenum cofactor (*MOCS1*, *MOCS2*, and *GEPH* genes) were found not to have any single predominate mutation. The results obtained through the data analysis of the mentioned case and his family are presented in Supplementary material Table 1. This table includes information about investigated reads, target regions and target genotypes, as well as the number of coding SNPs, synonymous SNPs, nonsynonymous SNPs, Indels, and coding Indels. The application of general filter and custom filter data analysis process provided the required information on the studied genes. The general filter supplied knowledge on variations, changes, regions, and SNPs. The custom filter, on the other hand, detailed more data about different variants causing SOD (Supplementary material Table 2). Variants extracted by custom filter were categorized as 52 Simple Recessive (illustrated in Table 1), 33 Compound Heterozygote (presented in Table 2), and 118 De novo (data are not shown). Since De novo variants were not worthwhile to mention, only Simple Recessive and Compound Heterozygote mutations were deeply deliberated and discussed to explore the real causing ones in relation to SOD.

5. Discussion

Since the first description of SOD in 1967, several cases have been identified mostly with severe neurological abnormalities, refractory seizures imitating hypoxic-ischemic encephalopathy, and early death [5,17]. The identification of SOD is somehow dubious as it does not have a simple diagnostic test [9]. Therefore, this inherited disease could easily be missed based on routine screening [18]. However, several molecular investigations have been done so far, which enable accurate diagnosis of disease. For example, in 1996 a point mutation in *SUOX* was reported in an SOD patient resulting in a truncated protein which missed the molybdenum-binding site [19]. In 1997, four variants in the coding sequence of cloned human sulfite oxidase (Arg160Gln, Ala208Asp, Ser370Tyr, and Gly473Asp) including two point mutations near the sulfate binding site and two point mutations within the domain mediating dimerization were characterized [5]. Subsequently, in 1999, two point mutations namely 623C3A and 1109C3A were found in *SUOX* gene leading to A208D and S370Y substitutions, respectively, in which both residues are critical for sulfite oxidase activity [18]. Afterward, twelve novel mutations in the *SUOX* gene in SOD patients were detected in 2002. These mutations consisted of two frame-shift mutations, a 4-basepair deletion (562del4), a 1-basepair insertion (113insC), nonsense mutations causing Y343X and Q364X substitutions, and eight missense mutations generating substitutions of a single amino acid [3]. Additionally, a unique 4-basepair deletion in a homozygous state was detected in

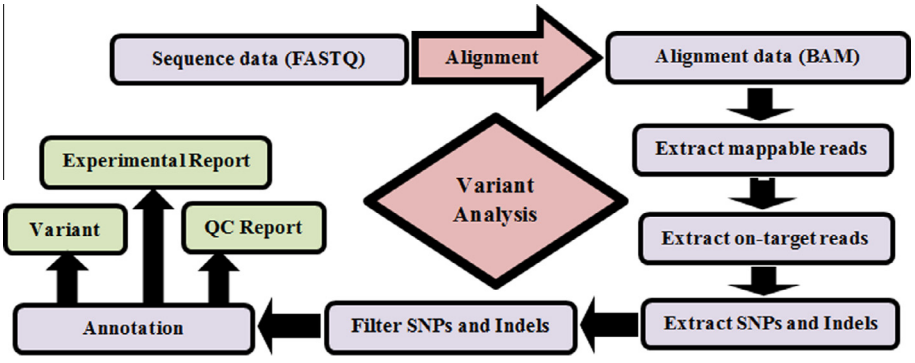

Figure 1 The analysis procedure of data achieved by ES.

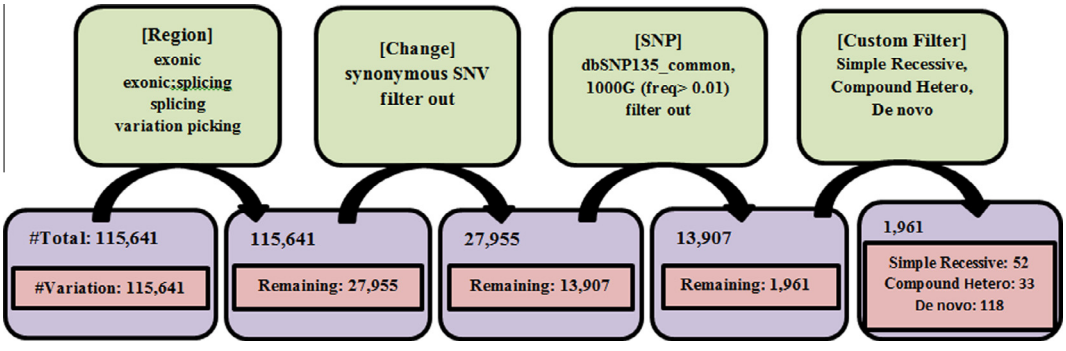

Figure 2 Classification procedure of data analysis after implementing ES.

Table 1 Simple recessive variants identified by ES.

Chromosome	Father	Mother	Patient	Region	Gene	Change
Chr1:113257782		C > T het	C > T hom	Exonic	PPM1J	nonsynonymous_SNV
Chr1:120469147	T > C het	T > C het	T > C hom	Exonic	NOTCH2	nonsynonymous_SNV
Chr1:203455861	A > G het	A > G het	A > G hom	Exonic	PRELP	nonsynonymous_SNV
Chr1:212981105	T > C het	T > C het	T > C hom	Exonic	TATDN3	nonsynonymous_SNV
Chr1:214507610	G > T het	G > T het	G > T hom	Exonic	SMYD2	nonsynonymous_SNV
Chr1:217975157	C > T het	C > T het	C > T hom	Exonic	SPATA17	stopgain_SNV
Chr1:231362783	G > A het	G > A het	G > A hom	Exonic	C1orf131	nonsynonymous_SNV
Chr2:166810195	- > CGCTCACC het		- > CGCTCACC hom	Exonic; splicing	TTC21B;TTC21B	frameshift_insertion
Chr2:169713209	G > A het	G > A het	G > A hom	Exonic	NOSTRIN	nonsynonymous_SNV
Chr2:187559049		- > GCA het	-.GCA hom	Exonic	FAM171B	nonframeshift_insertion
Chr2:223504402	G > A het	G > A het	G > A hom	Exonic	FARSB	nonsynonymous_SNV
Chr4:41015833	A > G het	A > G het	A > G hom	Exonic	APBB2	nonsynonymous_SNV
Chr5:74021853	ACTCAA > - het	ACTCAA > - het	ACTCAA > - hom	Exonic	GFM2	nonframeshift_deletion
Chr5:74032599	G > A het	G > A het	G > A hom	Exonic	GFM2	nonsynonymous_SNV
Chr5:79616278	A > G het	A > G het	A > G hom	Exonic	SPZ1	nonsynonymous_SNV
Chr5:139931628	- > GT het	- > GT het	- > GT hom	Exonic	SRA1	frameshift_insertion
Chr6:99323489	- > GA het	- > GA het	- > GA hom	Exonic	FBXL4	frameshift_insertion
Chr7:100637839	C > G het	C > G het	C > G hom	Exonic	MUC12	nonsynonymous_SNV
Chr7:100645525	A > C het		A > C hom	Exonic	MUC12	nonsynonymous_SNV
Chr7:131241054		- > GCGA CG het	- > GCGACG hom	Exonic	PODXL	nonframeshift_insertion
Chr7:143417083	T > C het	T > C het	T > C hom	Exonic	FAM115C	nonsynonymous_SNV
Chr7:158664076	AAG > - het	AAG > - het	AAG > - hom	Exonic	WDR60	nonframeshift_deletion
Chr8:18257703	C > T het	C > T het	C > T hom	Exonic	NAT2	nonsynonymous_SNV
Chr9:103340627	G > A het	G > A het	G > A hom	Exonic	MURC	nonsynonymous_SNV
Chr9:107367666	CG > - het	CG > - het	CG > - hom	Exonic	OR13C2	frameshift_deletion
Chr10:124352012	C > T het	C > T het	C > T hom	Exonic	DMBT1	nonsynonymous_SNV
Chr11:124750455		GGAGTC > - het	GGAGTC > - hom	Exonic	ROBO3	nonframeshift_deletion
Chr12:6777111	CTG > - het	CTG > - het	CTG > - hom	Exonic	ZNF384	nonframeshift_deletion
Chr12:102131655	T > C het	T > C het	T > C hom	Exonic	SYCP3	nonsynonymous_SNV
Chr12:102160048	A > G het	A > G het	A > G hom	Exonic	GNPTAB	nonsynonymous_SNV
Chr12:103248932	C > T het	C > T het	C > T hom	Exonic	PAH	nonsynonymous_SNV
Chr12:107155117	C > T het	C > T het	C > T hom	Exonic	RFX4	nonsynonymous_SNV
Chr12:110206380	G > A het	G > A het	G > A hom	Exonic	C12orf34	nonsynonymous_SNV
Chr12:113346579	A > C het	A > C het	A > C hom	Exonic; splicing	OAS1	nonsynonymous_SNV
Chr12:123214166	G > A het	G > A het	G > A hom	Exonic	HCAR1	nonsynonymous_SNV
Chr12:123351773	G > A het	G > A het	G > > A hom	Exonic	VPS37B	nonsynonymous_SNV
Chr12:129100757	C > G het	C > G het	C > G hom	Exonic	TMEM132C	nonsynonymous_SNV
Chr14:23240726	- > GCA het	- > GCA het	- > GCA hom	Exonic	OXA1L	nonframeshift_insertion
Chr14:23548797	- > ACGTGA het	- > ACGTGA het	- > ACGTGA hom	Exonic	ACIN1	nonframeshift_insertion
Chr15:21071460	C > T het		C > T hom	Exonic	POTEB	nonsynonymous_SNV
Chr15:82637110		C > T het	C > T hom	Exonic	GOLGA6L10	nonsynonymous_SNV
Chr16:71981420		- > TGTT het	- > TGTT hom	Exonic	PKD1L3	unknown
Chr16:81242150	TT > - het	TT > - het	TT > - hom	Exonic	PKD1L2	frameshift_deletion
Chr17:18064722	C > T het	C > T het	C > T hom	Exonic	MYO15A	nonsynonymous_SNV
Chr17:19566768	C > T het	C > T het	C > T hom	Exonic	ALDH3A2	nonsynonymous_SNV
Chr17:29226507	C > T het	C > T het	C > T hom	Exonic	TEFM	nonsynonymous_SNV
Chr19:52803674	TG > - het	TG > - het	TG > - hom	Exonic	ZNF480	frameshift_deletion
ChrX:70367609		C > T het	C > T hom	Exonic	NLGN3	nonsynonymous_SNV
ChrX:114424132		G > A het	G > A hom	Exonic	RBMXL3	nonsynonymous_SNV
ChrX:135474448		GAT > - het	GAT > - hom	Exonic	GPR112	nonframeshift_deletion
ChrX:149680832		C > T het	C > T hom	Exonic	MAMLD1	nonsynonymous_SNV
ChrX:151935412		T > C het	T > C hom	Exonic	MAGEA3	nonsynonymous_SNV

the cDNA of *SUOX* gene in a newborn affected with SOD [20]. In 2005, mutation analysis of *SUOX* showed a novel 4-basepair deletion in a patient whose parents were found to be heterozygous carriers of the deletion [1]. In other studies, a homozygous nonsense mutation of the *SUOX* gene in the patient was identified by a genome wide microarray analysis [21]. The present study was actually a breakthrough in diagnosis of a variety of genetic elements involved in the pathogenesis of SOD (a patient with suspected SOD) because of applying ES as a useful tool for detecting disease-causing mutations. Although we did not find any mutations in *SUOX*, *MOCS1*, *MOCS2*, and *GEPH* genes, the child was confirmed to be an SOD case because of having biochemical and clinical signs of the disease. Thus, other genetic variants

Table 2 Compound Heterozygote variants identified by ES.

Chromosome	Father	Mother	Patient	Region	Gene	Change
Chr1:161967990	G > A het		G > A het	Exonic	OLFML2B	nonsynonymous_SNV
Chr2:161970046		A > G het	A > G het	Exonic	OLFML2B	nonsynonymous_SNV
Chr1:170129665	T > G het		T > G het	Exonic	METTL11B	nonsynonymous_SNV
Chr1:170136876		T > C het	T > C het	Exonic	METTL11B	nonsynonymous_SNV
Chr3:19389225			T > A het	Exonic	KCNH8	nonsynonymous_SNV
Chr3:19559510	G > C het		G > C het	Exonic	KCNH8	nonsynonymous_SNV
Chr4:8951859		G > A hom	G > A het	Exonic	LOC650293	Stopgain_SNV
Chr4:8951918	C > T het		C > T het	Exonic	LOC650293	nonsynonymous_SNV
Chr8:2005572	G > A het		G > A het	Exonic	MYOM2	nonsynonymous_SNV
Chr8:2020542		C > T het	C > T het	Exonic	MYOM2	nonsynonymous_SNV
Chr8:110455184			C > T het	Exonic	PKHD1L1	nonsynonymous_SNV
Chr8:110492352	C > T het	C > T het	C > T het	Exonic	PKHD1L1	nonsynonymous_SNV
Chr10:76735758	G > A het		G > A het	Exonic	KAT6B	nonsynonymous_SNV
Chr10:76781927			GAA > - het	Exonic	KAT6B	nonframeshift_deletion
Chr11:66359172	C > T het		C > T het	Exonic	CCDC87	nonsynonymous_SNV
Chr11:66360206		C > T het	C > T het	Exonic	CCDC87	nonsynonymous_SNV
Chr11:89819403			G > C het	Exonic	UBTFL1	nonsynonymous_SNV
Chr11:89819889		- > T het	- > T het	Exonic	UBTFL1	frameshift_insertion
Chr12:112688164			T > C het	Exonic	C12orf51	nonsynonymous_SNV
Chr12:112688167	A > C het		A > C het	Exonic	C12orf51	nonsynonymous_SNV
Chr16:72821644			C > T het	Exonic	ZFHX3	nonsynonymous_SNV
Chr16:72822581	CTGCTG > - het	CTGCTG > - het	CTGCTG > - het	Exonic	ZFHX3	nonframeshift_deletion
Chr18:14105193	C > T het		C > T het	Exonic	ZNF519	nonsynonymous_SNV
Chr18:14106282		T > G het	T > G het	Exonic	ZNF519	nonsynonymous_SNV
Chr18:28972226	C > A het		C > A het	Exonic	DSG4	nonsynonymous_SNV
Chr18:28993231		T > G het	T > G het	Exonic	DSG4	nonsynonymous_SNV
Chr19:40900200	CTC > - het			Exonic	PRX	nonframeshift_deletion
Chr19:40901647			A > G het	Exonic	PRX	nonsynonymous_SNV
Chr19:40902713		G > A het	G > A het	Exonic	PRX	nonsynonymous_SNV
Chr19:42596244	C > A het		C > A het	Exonic	POU2F2	nonsynonymous_SNV
Chr19:42596347			G > T het	Exonic	POU2F2	nonsynonymous_SNV
Chr19:51960988	T > A het		T > A het	Exonic	SIGLEC8	nonsynonymous_SNV
Chr19:51961638			GCA > - het	Exonic	SIGLEC8	nonframeshift_deletion

had to be regarded as possible causative genetic factors leading to our suspected SOD case. The results obtained in this study showed that the variations can be classified via the custom filter to different genes groups partaking in about 10 pathways among which the sulfur metabolism (e.g. *DMBT1*, *PRELP*, and *PAH*), signaling and signal transduction (e.g. *MUC12*, *MURC*, *HCAR1*, *NLGN3*, *ROBO3*, *ZFHX3*, *APBB2*, *SPZ1*, *SRA1*, and *WDR60*), membrane and trans-membrane proteins (e.g. *FAM171B*, *NOTCH2*, *GPR112*, *HCAR1*, *MYO15A*, *PKD1L2*, *TMEM132C*, *PRX*, *PKD1L3*, and *ROBO3*), and transcription (e.g. *MAMLD1*, *RBMXL3*, *RFX4*, *ZNF384*, *ZNF480*, *KAT6B*, *POU2F2*, *PRX*, *ZFHX3*, *ZNF519*, *TEFM*, and *SPZ1*) pathways are of higher importance (www.kegg.jp, www.genecards.org). The results confirmed that there are some genes more correlated than the others to the sulfur metabolism and sulfur relay system pathways and SOD disease, and probably they can be considered as candidate genes underlying manifestation of SOD symptoms. Among them, *DMBT1* and *PRELP* in sulfur metabolism pathway, and *MUC12*, *MURC*, *HCAR1*, *NLGN3*, *ROBO3*, *SPZ1*, and *SRA1* in signaling and signal transduction pathways can be candidate genes in succeeding molecular diagnostic tests. However, future studies are necessary to examine how these genes may relate to each other and contribute to the pathogenesis of SOD disease.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejmhg.2015.06.003.

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