



Genes Associated with Coma or Recurrent Coma and Role of Next Generation Sequencing in Diagnosis of Disease-Causing Genes

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ABSTRACT

Coma is a state of prolonged unconsciousness. Some coma cases result from inherited disorders such as fatty-acid β -oxidation disorder, acute intermittent porphyria (due to mutations in genes *CPT1*, *CPTII* and *ACADM*), urea cycle defects (due to mutation in *OTC* gene), organic acidurias, mitochondrial diseases and familial hemiplegic migraine (due to mutations in *CACNA1A*, *ATP1A2* and *SCN1A*). The evaluation of familial cases of coma or sporadic coma can be performed using next generation sequencing (NGS), a high-throughput sequencing technique that can sequence an entire genome in a single reaction. This technique has been widely applied in the genetic diagnosis of diseases. In this review, we describe some genes associated with coma or recurrent coma and discuss the role of NGS in detection of these genes.

Keywords: [Coma](#), [High-Throughput Nucleotide Sequencing](#), [Genes](#).

INTRODUCTION

Coma is a deep state of unconsciousness lasting more than six hours in which a person cannot be awakened. In this condition, patients are unable to respond to stimulators such as sound, light and pain (1). Coma can be caused by different disorders including central nervous system diseases, metabolic disorders, hypothermia, hypoxia, hypoglycemia and acute neurologic disorders such as strokes (2).

Several studies have indicated that coma or recurrent coma could be associated with some inborn errors of metabolism such as fatty-acid β -oxidation disorders (3), acute intermittent porphyria (4), urea cycle defects (5), organic acidurias (6), mitochondrial diseases (7) and familial hemiplegic migraine (FHM)(8-10). In recent decades, some cases of episodic coma have been reported worldwide. In the past, Sanger sequencing was used to evaluate possible relationship of genes with coma. However, the method falls short to survey many genes simultaneously and to explore new genes associated with the condition. Therefore, new genetic technologies such as next generation sequencing (NGS) have been developed to facilitate the evaluation of genetic disorders and even unknown inherited diseases. In this review, we discuss genes that are linked to coma and the role of NGS in diagnosing this disorder.

Different types of coma or recurrent coma

Metabolic disorders: Recurrent episodes of coma are usually related to metabolic disorders. Inborn errors of metabolism often result from mutations in genes that code for enzymes involved in the metabolism of carbohydrates, fatty acids and proteins. The worldwide prevalence of inborn errors of metabolism has been estimated to be 1 in 2,500 live births (11, 12). Most metabolic disorders show an autosomal recessive pattern, but some may be due to autosomal dominant and X-linked inheritance (13-15). The followings are the cases of inborn errors of metabolism associated with coma:

Ornithine transcarboxylase deficiency

This disorder is caused by mutations in *OTC* gene located on the X chromosome. Symptoms of disease include hyperammonemia, lethargy, confusion, nausea, vomiting, bizarre behavior and coma (16, 17). In 1984, Oizumi et al. reported a case of coma caused by ornithine transcarbamylase

deficiency associated with hyperammonemia (5). Zubeda Sheikh et al. reported a case of recurrent coma associated with refractory epilepticus in a man with previous history of hospitalization due to coma. An extensive workup revealed ornithine transcarboxylase deficiency as the diagnosis

Lesch-Nyhan syndrome (LNS): Lesch-Nyhan syndrome is an X-linked recessive disorder caused by a deficiency in the hypoxanthine-guanine phosphoribosyl transferase enzyme, which leads to high production of uric acid. The resulting hyperuricemia lead to neurological and behavioral abnormalities such as self-mutilation (18, 19). In 1991, Bryan et al. introduced a patient with Lesch-Nyhan syndrome who presented with episodic coma. The authors suggested that this problem may be related to a defect in the cellular energy metabolism in purine-depleted cells due to deficiency in the purine salvage pathway, and consequently the disruption of adenosine triphosphate synthesis (20).

Acute intermittent porphyria (AIP): This disorder results from mutations in the hydroxymethylbilane synthase gene. This rare metabolic disorder arise from porphobilinogen deaminase deficiency, an enzyme involved in heme biosynthesis. Common symptoms of AIP are abdominal pain, vomiting, constipation, muscle weakness as well as neurological complaints such as peripheral polyneuropathy, lethargy and altered consciousness ranging from somnolence to coma (4).

Maple syrup urine disease: Maple syrup urine disease (MSUD) is an autosomal recessive metabolic disorder caused by mutations in the *BCKDHA*, *BCKDHB*, *DBT* and *DLD* genes, which encode the E1 α , E1 β , E2 and E3 subunits of the branched chain α ketoacid dehydrogenase (BCKAD) complex, respectively (21). The clinical manifestations depends on the BCKAD residual activity. In early infancy, this condition can be characterized by poor feeding, vomiting, lethargy and developmental delay. If untreated, brain damage can lead to seizure, coma and death (22).

Mitochondrial diseases: Coma can also occur in cases of fatty acid β -oxidation disorders (FAODs). This group of genetic metabolic disorders is caused by defects in β -oxidation enzymes involved in fatty acid oxidation (23). Newborns with

FAOD usually manifest hypoketotic hypoglycemia, metabolic acidosis, hepatic failure, cardiomyopathy and seizures. The most prevalent fatty acid oxidation disorder is medium chain acyl-CoA dehydrogenase deficiency. The symptoms include lethargy, nausea or vomiting, hypoglycemia, hepatomegaly, seizures and repeated episodes of hypoketotic, hypoglycemic coma (3). In 2006, Roomets et al. reported a case of deep coma without hypoglycemia because of carnitine palmitoyltransferase I deficiency (24). Coma also has been reported in a case of carnitine palmitoyltransferase II deficiency (25).

Leukodystrophies: Leukodystrophies are described as a group of inherited disorders that affect the central nervous system and the peripheral nerves. Leukodystrophies caused by mutations in different genes have been reported in forms of the following disorders: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), adult-onset autosomal dominant leukodystrophy, Pelizaeus-Merzbacher disease, Sjogren-Larsson syndrome, Canavan disease and etc., all of which result in a range of neurological disorders (26). CADASIL is caused by mutations in the *NOTCH3* gene located on chromosome 19. It is characterized by repeated strokes, dementia and migraine known as CADASIL coma (27). Eswaradass et al. reported a case of CADASIL coma in a male with heterozygous mutation in the *NOTCH3* gene (28).

Monogenetic migraine coma: Recurrent coma can occur due to familial hemiplegic migraine (FHM), a rare monogenetic migraine with aura characterized by typical attacks associated with transient motor deficit, visual signs and speech impairment. To date, three main genes including *CACNA1A*, *ATP1A2* and *SCN1A* have been reported to be involved in etiology of FMH1, FMH2 and FMH3, respectively. The *CACNA1A* gene is located on chromosome 19p13 and encodes the $\alpha 1$ subunit of the P/Q-type of *high-voltage-activated* Ca^{2+} channels. The gene is abundantly expressed in the cerebellum, hippocampus and cortex of the mammalian brain (29). The *ATP1A2* gene located on chromosome 1 (1q23) codes for a catalytic subunit of sodium/potassium ATPase. The *SCN1A* gene, located on chromosome 2q24,

encodes a transmembrane alpha subunit of the brain sodium channel (29).

Hepatic coma: Hepatic coma refers to a set of neuropsychiatric conditions such as confusion, asterix and coma that occur during liver failure. It can have exogenous and endogenous causes (30). Metabolic related to fatty liver disease (MAFLD) previously known as *nonalcoholic fatty liver disease* (NAFLD) is the most common liver disease, which involves fat accumulation in hepatocytes, leading to obesity and metabolic syndrome (31). Non-alcoholic steatohepatitis (NASH) is the critical stage of NAFLD (32, 33) that may be asymptomatic at first but lead to jaundice, blood clots and *coma as the disease progresses*. Many genetic alterations including mutation in the *PNPLA3* gene are thought to be associated with NAFLD and NASH (34).

NGS: This method enables sequencing of an organism's genome in a single reaction (35). It has been widely applied in the diagnosis of genetic diseases. Principally, the NGS technique is similar to conventional capillary electrophoresis sequencing, but it can simultaneously sequence thousands of DNA fragments from a *single sample*. The NGS involves four basic steps: Library preparation: DNA is randomly fragmented by various methods. *These fragments are* modified with *adaptor* sequences to both ends of each DNA fragment.: Cluster generation: the prepared library is loaded into a flow cell to generate library clusters. Sequencing: the captured libraries are sequenced by the *sequencing* platforms and short reads with various lengths are produced (Figure 1) (36).

Data analysis: reads generated through NGS are mapped to a reference genome using bioinformatics tools (Figure 2). Variant calling is performed using bioinformatics software such as Genome Analysis Tool Kit (GATK). All found variants are checked with databases including dbSNP, 1000 Genomes Project, ESP 6500 Exome Project, and ExAC v0.2, ExAC Browser, OMIM and ClinVar for evaluating pathogenicity of the variants. In silico tools such as SIFT, PolyPhen-2, CADD and Mutation Taster are also used.

NGS types

Genomics: *Whole genome sequencing (WGS)*

It is a process through which the complete genome of an organism *including chromosomal DNA and* the mitochondrial

DNA are sequenced at a single run. The method is mostly applied for sequencing human genomes (37).

Whole exome sequencing (WES) : Exome sequencing is a technique for *sequencing* all *coding regions of genome* named *exome*. In WES, all *exons and splicing sites* of the genome are captured and subsequently sequenced. In humans, the exome contains less than two percent of the genome; however, it contains the majority of disease-related variants. Therefore, WES can be considered as a cost-effective method for identifying specific variants in a wide range of issues including genetic disorders, population genetics and cancer investigations (Figure3) (38, 39).

De novo sequencing: It is related to *sequencing* and construction of a novel *genome* because there is no reference genome sequence to align the short reads generated by NGS. In this process, sequence reads are assembled to generate contigs for creating a new reference genome (40).

Targeted sequencing: In targeted sequencing, a collection of specific regions of the genome can be extracted and sequenced, enabling studying individual genes. It results in higher coverage levels than WGS, which allows detection of very rare variants. Different types of targeted sequencing panels have been used in cancer studies (41), metabolic disorders (42) and epileptic disorders (43).

Transcriptomic sequencing: This technique enables sequencing of total RNA (RNA-seq). First, RNA samples are converted to cDNAs, and then library preparation and sequencing are carried out. RNA-seq can be used for sequencing mRNAs, small RNAs, noncoding RNAs or microRNAs (44).

Epigenomics: *Epigenetics* is mostly related to changes that modify gene activity and expression via mechanisms other than DNA sequence changes. These

molecular *mechanisms* include DNA methylation, small RNA-mediated regulation, DNA-protein interactions and histone modification (36).

Role of NGS in diagnosis of coma or recurrent coma: Whole exome sequencing and *targeted gene sequencing panels* are widely applied for evaluation of genetic disorders including metabolic diseases, neurometabolic disorders and mitochondrial disorders. Thus, we can screen genes involved in coma or recurrent coma by using NGS methods.

Coma associated with FHM

A five-gene targeted NGS panel containing the three FHM genes (*CACNA1A*, *ATPIA2* and *SCN1A*), two genes involved in migraine-related disorders (*NOTCH3* and the *KCNK18*) and the *KCNK18* gene has been designed for evaluation of genes associated with recurrent coma in FHM (45, 46) (Table1).

Coma associated with metabolic disorders.

Coma can occur in neonates due to metabolic intoxication syndrome. A *metabolic gene panel* can be used to explore the condition. There are gene panels (for example: <https://www.centogene.com/diagnostics/ngs-panels/metabolic-disorders>) that can be used for evaluation of over 1,250 metabolic disease genes.

Fatty acid oxidation disorder gene panel: Table 2 shows some of the genes associated with the fatty acid oxidation disorder (available at <https://www.cd-genomics.com/diseasepanel/custom-fatty-acid-oxidation-disorder-panel.html>).

Coma with unknown causes : Although, NGS has been extensively applied in diagnosis of diseases, it could play a significant role in genetic evaluation of rare disorders and exploring novel genes associated with diseases.

Table 1- The targeted NGS 5-gene panel for FHM

Gene	Method
<i>CACNA1A</i> (FHM1)	Sequence analysis
<i>ATPIA2</i> (FHM2)	Gene-targeted deletion/duplication analysis
	Sequence analysis
	Sequence analysis
<i>SCN1A</i> (FHM3)	Gene-targeted deletion/duplication analysis
<i>NOTCH3</i>	Gene-targeted
<i>KCNK18</i>	Gene-targeted

Table 2- Custom fatty acid oxidation disorder panel

<i>ACAD8</i>	<i>ACAD9</i>	<i>ACADM</i>
<i>ACADS</i>	<i>ACADVL</i>	<i>CPT1A</i>
<i>CPT2</i>	<i>ETFA</i>	<i>ETFB</i>
<i>ETFDH</i>	<i>GLUD1</i>	<i>HADH</i>
<i>HADHA</i>	<i>HADHB</i>	<i>HMGCL</i>
<i>HMGCS2</i>	<i>HSD17B10</i>	<i>LPINI</i>
<i>MLYCD</i>	<i>PPARG</i>	<i>SLC22A5</i>
<i>SLC25A20</i>	<i>TAZ</i>	

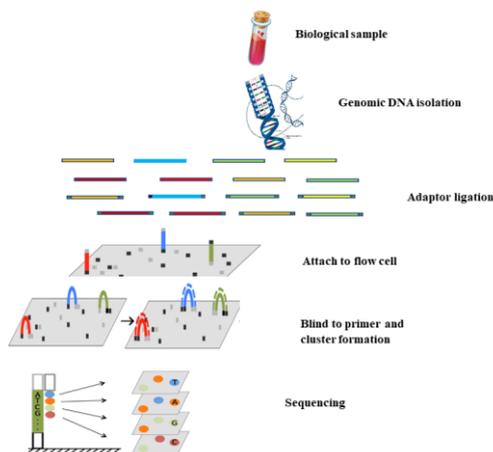


Figure 1-The steps of DNA extraction, fragmentation, amplification and sequencing in NGS

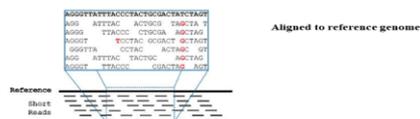


Figure 2- Mapping and alignment of short reads generated by NGS with reference genome.

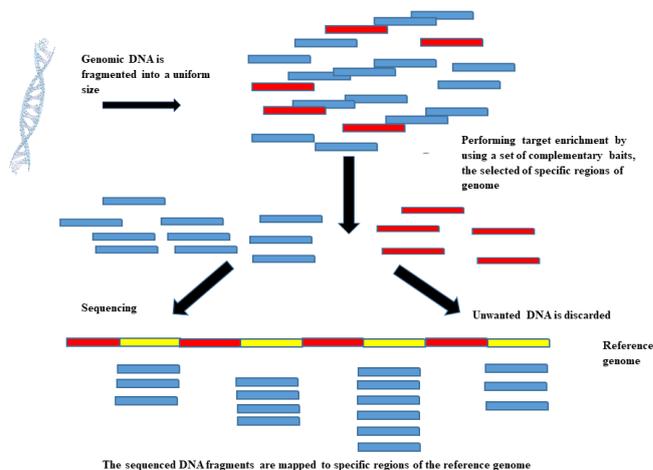


Figure 3- The steps of whole exome sequencing in which all coding regions of genome are captured using a set baits, sequenced and then aligning with the reference genome

DISCUSSION

Coma is referred to a *state* of prolonged *unconsciousness*. Coma or recurrent coma can occur because of inherited conditions including FHM as well as metabolic and mitochondrial disorders. Evidence suggest that some genes including *OTC*, *CPT I*, *CPTII*, *ACADM*, *CACNA1A*, *ATPIA2* and *SCN1A* may be associated with the above mentioned conditions. Sanger sequencing was the method of choice for evaluation of disease-related genes (47). However, in cases of coma or recurrent coma with unknown genetic origin, sequencing of genes is more difficult and time consuming. Therefore, NGS has been recently introduced as a more efficient technique for evaluating disease-related genes. The technique allows simultaneous analysis of several genes. On the other hand, WES has contributed greatly to quicker diagnosis of metabolic and neurogenetic disorders in clinical settings. In a previous study, WES was used to explore coronary artery disease-associated genes in an Iranian family (48). Thus, this new method can be utilized for screening familial cases of coma or sporadic coma and identifying unknown genes related to this condition. In this regard, Maksemous et al. used targeted NGS multigene panel to screen 172 individuals with suspected hemiplegic migraine for diseases-causing genes and causative variants. The targeted NGS 5-gene panel include three FHM genes (*CACNA1A*, *ATPIA2* and *SCN1A*) as well as two migraine-related genes (*NOTCH3* and *KCNK18*) (49).

CONCLUSION

We described the general concepts of coma or recurrent coma and some associated genes. Recent evidence suggests that NGS and WES could be used as efficient tools for detecting some types inherited coma. Since most coma cases are related to metabolic disorders, it is recommended to first screen for inborn errors of metabolism using WES and/or targeted gene sequencing panels, and then identify genes associated with coma or recurrent coma.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding publication of this article.

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