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Research paper

Reveal genes functionally associated with ACADS by a network study

Yulong Chen, Zhiguang Su *

Molecular Medicine Research Center, West China Hospital, State Key Laboratory of Biotherapy, Sichuan University, Chengdu, China

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ABSTRACT

Establishing a systematic network is aimed at finding essential human gene–gene/gene–disease pathway by means of network inter-connecting patterns and functional annotation analysis. In the present study, we have analyzed functional gene interactions of short-chain acyl-coenzyme A dehydrogenase gene (ACADS). ACADS plays a vital role in free fatty acid β-oxidation and regulates energy homeostasis. Modules of highly interconnected genes in disease-specific ACADS network are derived by integrating gene function and protein interaction data. Among the 8 genes in ACADS web retrieved from both STRING and GeneMANIA, ACADS is effectively conjoined with 4 genes including HAHDA, HADHB, ECHS1 and ACAT1. The functional analysis is done via ontological briefing and candidate disease identification. We observed that the highly efficient-interlinked genes connected with ACADS are HAHDA, HADHB, ECHS1 and ACAT1. Interestingly, the ontological aspect of genes in the ACADS network reveals that ACADS, HAHDA and HADHB play equally vital roles in fatty acid metabolism. The gene ACAT1 together with ACADS indulges in ketone metabolism. Our computational gene web analysis also predicts potential candidate disease recognition, thus indicating the involvement of ACADS, HAHDA, HADHB, ECHS1 and ACAT1 not only with lipid metabolism but also with infant death syndrome, skeletal myopathy, acute hepatic encephalopathy, Reye-like syndrome, episodic ketosis, and metabolic acidosis. The current study presents a comprehensible layout of ACADS network, its functional strategies and candidate disease approach associated with ACADS network.

1. Introduction

The activity of genes is regulated by proteins and their interactions (Jacob and Monod, 1961). Proteins interact with each other in a variety of functional complexes, regulatory interactions, and metabolic pathways. These interactions can be presented as a meaningful set of genetic functions when they are conceptualized as gene networks, which have been put-upon to find novel candidate genes, based on the assumption that neighbors of a disease-causing gene in a network are more likely to cause either the same or a similar disease (Franke et al., 2006). Gene network describes which genes are closely connected within a given pathway, it represents precise information than lists of genes or pathways. Hence, gene network has the potential to detect more elusive signals, such as local disturbances within known pathways, as well as within pathways that have not yet been described. Recently, gene network analysis has been used to describe the relationship among genes and various phenotypes (Calvano et al., 2005; Segal et al., 2005; Jiang et al., 2008; Anitha et al., 2014).

Gene networks can be constructed by ensembling previously reported interactions in the literature and various databases like the database of interacting proteins (DIP) (Xenarios et al., 2000), the biomolecular interaction network database (BIND) (Alfarano et al., 2005), the BioGRID (Chatr-Aryamontri et al., 2013), human protein reference database (HPRD) (Keshava Prasad et al., 2009), and IntAct (Kerrien et al., 2012). Network study provides unified information originating from multiple studies and to identify key components in a system (Hayasaka et al., 2011).

Fatty acid catabolism, also known as β-oxidation, represents an important energy source for the body during times of fasting and metabolic stress. The degradation of free fatty acids after releasing from adipose tissue is a reaction of four cyclic steps that takes place in mitochondria and peroxisomes. The acyl-CoA dehydrogenase (ACAD) is a family of enzymes that catalyze the α,β-dehydrogenation of acyl-CoA esters, which is the first and rate-limiting step of the mitochondrial β-oxidation cycle. In the human genome, five of the eleven members of ACAD family are involved in β-oxidation of fatty acids (Swigonova et al., 2009). Patients have been identified with inherited disorders of

Abbreviations: ACADS, short-chain acyl-coenzyme A dehydrogenase; *ACAD*, acyl-CoA dehydrogenase; *HADHA*, hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase α; *HADHB*, hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase β; *ACAA2*, acetyl-CoA acyltransferase 2; *ACAT1*, acetyl-CoA acetyltransferase 1; *ECH1*, enoyl CoA hydratase short chain 1; *ACAA1*, acetyl-CoA acyltransferase 1; *EHHADH*, enoyl-CoA, hydratase/3-hydroxyacyl CoA dehydrogenase; *GCDH*, glutaryl-CoA dehydrogenase; KEGG, kyoto encyclopedia of genes and genomes; DIP, database of interacting proteins; STRING, search tool for retrieval of interacting genes/protein; BIND, biomolecular interaction network database; MINT, molecular INTeraction database; HPRD, human protein reference database.

* Corresponding author at: Molecular Medicine Research Center, West China Hospital, Sichuan University, 1 Keyuan 4th Road, Gaopeng Street, Chengdu 610041, China.
E-mail address: zhiguang.su@scu.edu.cn (Z. Su).

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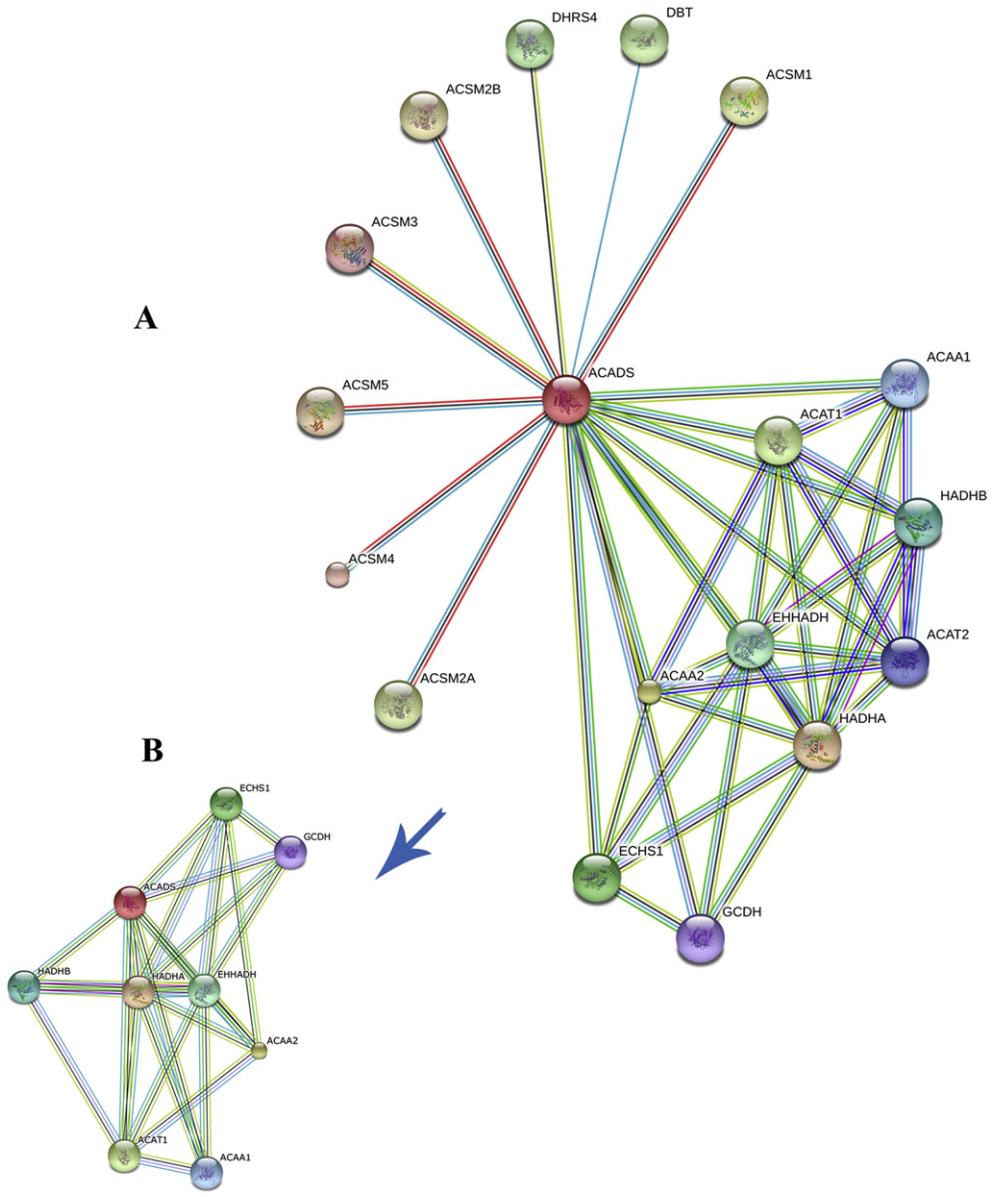

Fig. 1. ACADS network obtained from STRING9.1. (A) Represents twenty linked genes in ACADS network. (B) Represents filtered eight common genes (HADHA, HADHB, EHHADH, ACAA2, ACAT1, ECHS1 and GCDH) associated in ACADS network.

mitochondrial β-oxidation with ACADS deficiencies, e.g. the medium-chain acyl-CoA dehydrogenase deficiency is characterized by fasting-induced disease episodes of hypoketotic-hypoglycemia, metabolic acidosis, hyperammonemia, and fatty liver (Roe and Ding, 2001). Short-chain-3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency results into hyperinsulinism, suggesting that a novel link between fatty acid oxidation and insulin secretion may explain hyperinsulinism in these patients (Eaton et al., 2003). Mice deficiency of very long-chain ACAD and medium- and short-chain L-3-hydroxyacyl-CoA dehydrogenase exhibit reduced glucose and body weight and elevated levels of insulin (Zhang et al., 2010; Schulz et al., 2011), similar to children with SCHAD deficiency.

The short-chain ACAD (ACADS) is most active with hexanoyl- and butyryl-CoA as substrates. Absence of ACADS in human caused an accumulation of the byproducts of butyryl-CoA butyryl, including butyrylcarnitine, butyrylglycine, and ethylmalonic acid (EMA) in the blood, urine and cells (Jethva et al., 2008). The *ACADS* gene spans approximately 14.2 kb with ten exons. It is located on chromosome 12q22, which has been linked to a susceptibility locus for metabolic syndrome (Corydon et al., 1997). More than 40 mutations involved in the structure of *ACADS* gene have been found to cause ACADS deficiency. Almost all of these mutations change single protein building blocks in the ACADS enzyme. These mutations prevent the enzyme from properly metabolizing short-chain fatty acid. As a result, fats could not be converted into energy, which can lead to the characteristic signs and symptoms of this disorder, including lack of energy lethargy, hypoglycemia, hypotonia, and weakness (Corydon et al., 1997). Mouse deficiency of ACADS activity fairly faithfully reproduces the biochemical phenotype of the human disease with plasma accumulation of butyrylcarnitine and urinary EMA excretion (Wood et al., 1989).

It has been recognized that dysfunction of fatty acid metabolism is a multi-factorial syndrome but there are no gene network studies to depict the relationship and interactions among the predisposing factors that result in fatty acid dysfunction. Hence we attempted to construct a gene network with ACADS as a central node as ACADS is considered to be a major gene involved in fatty acid catabolism. Our results will be helpful for researchers in the field of metabolisms of lipid and ketone body and related disorders.