To what extent does Acyl-CoA dehydrogenase short chain gene Affect the risk of heart related diseases

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Abstract

The acyl-CoA dehydrogenase short chain is the genes which are found in the mitochondria of the cells, expressed in various tissues in the body. The enzymes which produced from these genes have a role to catalyze the foremost step of the mitochondrial fatty acid beta-oxidation pathway which is an important process in making the FADH2[A] and NADH[B], for the cellular respiration. Lacking ACADS[c] genes might lead to the cells unavailable to produce ATPs in the mitochondria, and as these genes are also found in the cardiac tissues of the human body, this review papers will assess the extent in which the ACADs[C] genes affect the risk of developing heart disease.
Keywords : The acyl-CoA dehydrogenase short chain, mitochondria, heart disease

1 Introduction and Background

At present, there are about 610,000 people who die of heart disease in the United States every year which is 1 in every 4 deaths. While categorized with ethnic groups, the non-Hispanic black and non-Hispanic white has the highest percentage of death for 23.8%. There are several factors contributing to this unpredictable incidence including both biological and environmental factors. The environmental factors including diet, lifestyle, daily habits, smoking and more. However, there is almost no argument raised about the biological influence on heart related disease, which makes up who we are as well as the genes which affect heart diseases. There are about 24,000 genes inside our body with six discovered genes found to have an effect on heart related disease in 2007 which includes ACADS[C] genes. In May, 1989, Naito E *et al.* J discovered the ACADS[C] genes which is approved by the HGNC (HUGO Gene Nomenclature Committee). It was not until people were more concerned with their risk of heart disease, that this gene became important. The ACADS[C] gene is found mostly in duodenum of the human body, however is also found in a significant number in the heart of humans. ACADS[C] is found to have an impact on decreasing the amount of fat digested inside the body, accordingly, fat is a main factor in contributing to heart disease. This literature review aims to investigate deeper into the significance of ACADS[C] gene and to evaluate the types of heart disease which might be associated with ACADS[C] gene, in order to benefit the population and to give support to further treatments on heart disease.

2 The discovery and importance of ACADS[C] genes

The ACADS or acyl-CoA dehydrogenase short chain is also known as SCADS[D] which are commonly used by scientists. It is the protein coding type of gene which could be discovered in human (*Homo sapiens*) Moreover, this gene is expressed in overall, 27 tissues inside a human body, in the area which requires high amount of ATP in order to functions.

with six of these tissues contain high frequency of this gene (high RPKM[E] value) including; Duodenum (34.4 RPKM[E]), fat (33.7 RPKM[E]), small intestine (30.0 RPKM[E]), liver (29.3 RPKM[E]), colon (27.7 RPKM[E]) and heart (9.8 RPKM[E]). According to the research, the $ACADS_3$ gene main function is to encode a tetrameric mitochondrial flavoprotein which is the protein utilized in the mitochondria for the cellular respiration, and is also a member of the acyl-CoA dehydrogenase family, fig [1]. The enzymes produced have a role to catalyse the foremost step of the mitochondrial fatty acid beta-oxidation pathway which is an important process in making the FADH2[A] and NADH[B] in the aerobic respiraton. In biochemistry, the mitochondrial fatty acid beta-oxidation pathway is the fatty acid molecules are broken down or oxidized, providing a major source of ATP[F] which is the primary form of energy carried by all forms of living organisms, and is also the most important for heart and skeletal muscle to function and maintain the body movement. Therefore, deficiency or mutation of ACADS[C] genes might possibly affect the availability of ATP[F] for the body to function properly, as the beta-oxidtion pathway is limited by the losses of enzymes and so the anaerobic respiration and aerobic respiration cannot happens which then possibly lead to the deficiency of ATPs and so the cells would not have enough ATPs to be able to function appropriately.

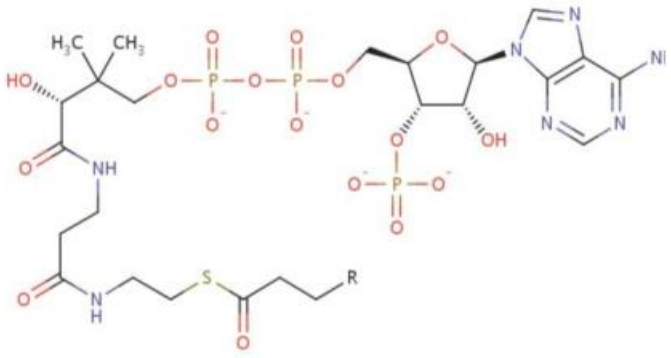

Fig [1]

3 The ACADS[C] deficiency and diagnosis

The mutation or strange orientation of this gene is associated with short-chain acyl-CoA dehydrogenase (ACADS) deficiency. The deficiency of ACADS[C] genes caused the autosomal recessive metabolic disorder of fatty acid beta-oxidation pathway. This is likely to prevent the body from converting a particular type of fats into energy during the cellular respiration, significantly in the periods without food or the periods without glucose available in the body. Essentially, all children identified through newborn screening have been healthy. Therefore, some reported symptoms are likely to be coincidental. However, the several symptoms and evidence of SCADs[D] deficiency may arise during childhood and can include vomiting, low blood sugar, a lack of energy, poor feeding, and unable to gain weight and growth rate is altered as the results of the losses of ATPs available for body to functions. Other features of this disorder include hypotonia which is a state of low muscle tone, seizures, delayed in development, and a small head size (microcephaly). These symptoms of ACADS[C] deficiency may be triggered when the children do not have enough food, empty atomach and when suffered by the diseases including viral infections. This disorder is sometimes incorrectly diagnosed for Reye syndrome, which is a conditions that can develop in children after they have been infected by the virues and is recovering from it such as the chicken pox. In some populations with ACADS[C] deficiency, the symptoms and evidence do not appear since childhood but more likely to be first appeared in adulthood or in the period of maturity. These individuals are more likely to have problems related to certain kind of muscle weakness and neural connections in the nervous system. Each member of the family experiences different severity in this conditions. Some individuals who diagnosed with ACADS[C] deficiency based on laboratory testing or by using the medical equipment to diagnosed, never develop any symptoms of the condition. This ACAD[C] deficiency conditions are thought to affect approximately 1 in 35,000 to 50,000 newborns, according to the U.S national library of medicine.

4 The case study of ACADS3 deficiency

There are some relevant reports and case studies on this ACADS[C] deficiency. First of all, the report of Tein et al. (2008) reported 10 children of Ashkenazi Jewsih descent with variable phenotypic expression of ACADS[C] deficiency. The common clinical features showed up during the study included hypotonia, developmental delay, speech delay lethargy, feeding difficulties as well as myopathy. Muscle biopsy was performed in 3 patients and showed 2 with histologic features of multiminicore myopathy and 1 with lipid storage disease. Laboratory abnormalities included ethylmalonic aciduria (autosomal recessive metabolic disorder that prevent the functions of normal amino acid metabolism) and methylsuccinic aciduria, as well as increased serum acyl carnitines . Secondly, Turnbull et al. (1984) reported the case of a 53 year old woman who presented with lipid storage myopathy and low concentration of carnitine in skeletal muscle. The 53 year old women suffered with impared fatty acid oxidation in muscle was found to be caused by deficiency of short chain acyl- CoA dehydrogenase activity in the mitochondria. Turnbull et al. suggested that the muscle carnitine deficiency was secondary to this enzyme deficiency. However, Bhala et al (1995) proposed that 'the case of Turnbull et al (1984) was not a primary case of ACADS[C] deficiency but rather a case of riboflavin-responsive multiple acyl- CoA dehydrogenase deficiency'. While, Pedersen et al. (2008) showed that a clinical variation among 114 patients with ACADS[C] deficiency ranging from 0 to 60 years. There are 25% of the patients showed the clinical symptoms on the first day of life, of these symptoms more than half was identified within the first year of life and the least with only four patients, the symptoms was found more than ten years of age. There are significant symptoms showed up in the participants includings developmental delay, seizure, speech delay, failure to thrive and hypothonia. The symptoms in which the patients most suffered with is developmental delay with the hypotonia while there are also 7% of the patients experienced and reported suffered with growth retardation, dysmorohic figure and cardiomyopathy which increased the risk of developing the heart diseases in a later life. Most interestingly, there were four patients reported not facing any symptoms. However, the number of 114 patients can not represent the whole population, also have no generalizability.

5 Heart disease and ACADS[C] genes relation

As the lack of ACADS[C] genes in the body caused the muscles to weaken, as well as heart muscle as a results of being unable to synthesise enzymes necessary for the cellular respiration. The incident might be one of the small factors which could lead to heart disease. First of all, cardiomyopathy is a condition which refers to diseases of the heart muscle. These diseases have many causes, signals and symptoms, the way to cure and the medical complications involved. In cardiomyopathy, the heart muscle becomes enlarged, thick, or inflexible. In rare cases, cardiac muscle is replaced with scar tissue in which prevent the heart muscles to get the sufficient energy from cellular respiration as the blood hardly flow through those scar tissues. As cardiomyopathy worsens, the heart becomes weaker. It's less able to pump blood through the body and maintain a normal heart's electrical rhythm and can lead to a heart failure or irregular heartbeats known as arrhythmias. As a consequences, heart failure can cause fluid to build up in the lungs, ankles, feet, legs, or abdomen which then lead to the more complicated medical complications such as heart valve problems. Some people who have cardiomyopathy have no signals or symptoms and need no medicine. For other people, the disease develops quickly, symptoms are severe, and major complications might occur and the risks are very high that it could lead to death. While one factor that can cause the cardiomyopathy include the family history of cardiomyopathy, according to the national heart, lung and blood institute of USA. As the research suggested that the cardiomyopathy may have caused by the lack of ACADS[C] genes in the body. Also the cardiovascular disease is a general term for conditions affecting the heart or blood vessels. It's usually involved with a build-up of fatty deposits inside the arteries, referred to as atherosclerosis and an increased the risk of blood clots. It can also be related with damage to arteries in organs such as the brain, heart, kidneys and eyes. "Each of these conditions raises the risks of cardiovascular disease by about 10%. But if you have a number of them, it adds up," explains Dr. Pradeep Natarajan, director of preventive medicine at -Harvard-affiliated Massachusetts General Hospital. He and his colleagues recently developed a genetic risk score using 57 of these variants to identify people with a high genetic risk of heart disease. Then, they determined the genetic risk scores of

nearly 9,500 people who had taken part in several different studies to test the effects of cholesterol-lowering statins. About one in five of them had a high score, which translates to a 60% higher risk of coronary artery disease than the average person. The high-risk people were also more likely to have early evidence of dangerous plaque in their heart and neck arteries. This result is consistent with the incident of $ACADS_3$ deficiency which the experiment suggested that the lack of ACADS[C] genes may have caused the heart disease in two categories of cardiomyopathy and cardiovascular disease.

6 Conclusion

In conclusion, ACADS[C] genes are associated with the process of ATP[F] production which required for the body in order to function properly. It is found mostly in duodenum of humans while it is found moderately in the heart muscle of humans. The research suggested that the lack of ACADS[C] genes (ACADS[C] deficiency) is could possibly cause seizure. Nevertheless, there are also the incident of heart disease such as cardiomyopathy caused. The deduction arose from the research and experiment, suggested that as the ACADS[C] involved with ATP[C] production, when there is a lack of this genes, the heart muscle might not have enough energy to function properly. Therefore, the cardiomyopathy might develop causing the lower blood pressure in the vessel and the lack of oxygen throughout the body of the patients. However, as there is a very low amount of paper and research on this gene, there is no generalizability and reliability. Also, the ACADS[C] genes can cause effects throughout the body from the nervous system. So, the ACADS[C] genes can be one of the small factors that involved in causing heart disease, while there is also another genes that could also contributed to the heart disease, with environmental factor that should also be taken into consideration. And if there is further evaluation of ACADS[C] genes, the gene therapy can also be used in order to treat this condition and lowered the risk of heart disease effectively.

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Appendix

A. *The full form of FADH2 is Flavin adenine dinucleotide and the detailed description is a redox cofactor which is produced during the Citric acid cycle and used during the last part of respiration in the electron transport chain.*
B. *The full form of NADH is Nicotinamide adenine dinucleotide. Its important role is to involve in cellular respiration as an electron acceptor.*
C. *The full form of ACADS gene is Acyl-CoA Dehydrogenase Short chain gene.*
D. *The full form of SCAD gene is Short-chain acyl-CoA dehydrogenase, which is the same gene as ACADS*
E. *RPKM stands for Reads Per Kilobase Million and is a normalized unit of transcript expression.*
F. *ATP stands for Adenosine Triphosphate, it is a molecule that carries energy within cells.*