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RESEARCH ARTICLE

FAMILIAL HYPERCHOLESTEROLEMIA: A CASE REPORT FROM A COMPLEX INDIAN FAMILY

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Abstract

Familial hypercholesterolemia (FH) is an autosomal dominant genetic disorder with a very high prevalence of almost 1 in 200-500 people. Genetic testings have commonly revealed mutations in genes namely LDLR, APOB, and PCSK9. In order to provide better management and minimize the risk of premature Coronary heart disease (CHD) in the affected people, early identification of FH in patients and screening of their first-degree relatives is recommended. In this paper, we present a rare case of a complicatedly related Indian family with a homozygous LDLR mutation detected in three members. The case study re-emphasizes the importance of screening for genetic mutations in patients with Hypercholesterolemia and also their immediate family members for better management, improving the quality of life, and increasing the life span.

Introduction:-

Familial hypercholesterolemia (FH), a multi-gene disorder is affecting about 1 in 200-500 individuals (Brautbar et al 2015; Rader et al 2003; Goldberg et al 2011). This syndrome is characterized by an increased level of total cholesterol and low-density lipoprotein (LDL) cholesterol. The presence of cholesterol-rich fat deposits called xanthomas and corneal arcus are the characteristic clinical features observed in some severe cases. Increased lipid levels predispose an individual to an increased risk for atherosclerosis and coronary heart disease (CHD) (Simon Broom's Register Group; 1991, Al-Rasadi et al. 2014). One of the oldest and most widely accepted criteria used for diagnosis of FH is Simon Broome's criteria which involves the presence of total cholesterol levels >7.5 mMol/L or LDL cholesterol >4.9 mMol/L, presence of tendon xanthomas, corneal arcus and family history of high cholesterol or premature coronary heart disease or well diagnosed FH (Austin et al. 2004a; Marks et al. 2003; Tada, Takamura, Kawashiri 2021). Although many more models have been proposed for the diagnosis of FH, they are all based on the cutoff of LDL cholesterol levels. But owing to the variability observed in different populations in the values of the LDL levels cautions needs to be exercised while making the diagnosis. Besides, it also has to be remembered that children in adolescence may not always present with features like xanthomas and corneal arcus (Tada H, Takamura M, Kawashiri M 2021).

Although several reports have indicated an autosomal dominant mode of inheritance of FH, linkage analysis and clinical findings have also suggested a rare autosomal recessive mode of inheritance caused by mutations in the

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LDLRAP1 gene (Soutar et al. 2003; Henderson et al. 2016). The genetic etiology of this disorder is well established and is majorly contributed by mutations in genes associated with lipid metabolism like LDL receptor gene (LDLR), Apoprotein B (APOB), and proprotein convertase subtilisin/Kexin type 9 (PCSK9) (Marais A, 2004, Austin et al. 2004b). The prevalence of individuals with FH carrying homozygous mutations in these genes is one in a million while the heterozygous mutations are found in almost 1 in 500 individuals. Lipid levels in these subjects are increased in a gene dosage-dependent manner (Soutar, Naoumova 2007). The average age of onset of the symptoms of CHD in subjects carrying heterozygous mutations in these genes is 55 years for men and around 60 years for women. Homozygous mutations on the other hand are much more deleterious, leading to the risk of both atherosclerosis and CHD at a very early age in childhood (Nordestgaard et al. 2013; Reiner 2015).

Almost 70-80 percent of the genetic variations associated with FH are contributed by mutations in the LDLR gene. Nearly 1700 mutations have been reported in LDLR gene, which is further divided into five subclasses depending upon the impact on the phenotypes shown (Leigh et al. 2017). On the other hand, mutations in APOB and PCSK9 genes which are involved in the binding of LDL to its receptors and its internalization respectively, contribute to approximately 5% of the subjects presented with FH (Garg A and Simha V, 2007 and Paththinige et al. 2017). Moreover, co-existing mutations (double heterozygotes) of LDLR, APOB and PCSK9 have also been reported (Marina et al. 2014).

In this article, we present a case study of 2 patients (ES and SS) who are indirectly related and visited our outpatient department with clinical symptoms of classic hyperlipidemia, along with a strong family history of FH. Genetic testing was advised to them with the intent to confirm the diagnosis.

The aim of the present study was: 1) To identify mutations in genes implicated in familial hypercholesterolemia in these two patients along with their family members who were distantly related (the Maternal Aunt of ES was married to the maternal cousin brother of SS). 2) To compare and analyze their similarities and differences in their clinical presentation.

Material And Methods:-

An 8 year old boy (ES) originally from Tamil Nadu, India presented with Xanthomas all over the body (Fig. 1a) to the pediatric cardiac OPD of our hospital. His younger sibling, a known case of hypercholesterolemia had passed away due to triple vessels coronary artery disease at the age of 7 years, just a few days before the patient had visited us. The lipid profile of the patient and immediate family members revealed that their total cholesterol as well as LDL cholesterol levels were exceedingly high.

The patient ES was referred to our genetic laboratory for sequencing of a panel of genes implicated in FH. Although FH has a well-established genetic etiology, multiple genes have been shown to be able to cause the condition. Targeted next generation sequencing (NGS) is the best and most cost-effective option to study all the genes simultaneously in the fastest manner. As we did not have an in-house NGS assay for FH, NGS assay for FH was performed on ES at an outsourced laboratory using a panel that included following genes: LDLR, PCSK9, APOE, SREBF2, LDLRAP1, CETP, APOA1, APOA5, APOC2, APOC3, GPIHBP1, LPL, LIPC, ABCA1, ABCG5, ABCG8, and SLCO1B1. Results analysis revealed the presence of homozygous missense substitution mutation c.268G>T in exon 3(p.D90Y; ENST00000557933) in the LDLR gene. Mutation nomenclature is based on HGVS 2016 update recommendations (Den Dunnen JT, Dalgleish R, Maglott DR et al 2016).

After detection of the causative mutation in the proband, other immediate members of the family which included the youngest sibling and parents were also tested for the same mutation using Sanger's Sequencing.

Targeted sanger resequencing for screening of the detected variant in the family members was carried out in the cytogenetic and molecular biology laboratory of our hospital using ABI 3500 capillary electrophoresis system.

At the same time, another distant relative of the patient (SS) from the same community (21 years/Male), was admitted to our hospital with complaints of heaviness in the chest and chest discomfort. He was also diagnosed to have hyperlipidemia with supravalvular aortic stenosis. He presented with corneal arcus in both eyes (Fig 1b), but no Xanthomas on the body. Lipid profile analysis revealed very high levels of total cholesterol and LDL cholesterol. Since both ES and SS had a strong family history of hypercholesterolemia and were distantly related, we decided to

screen the second patient (SS) also for the same mutation who was found to be positive for the same homozygous missense substitution mutation c.268G>T in exon 3(p.D90Y; ENST00000557933) in the LDLR gene as ES.

Family member screening for mutation analysis of c.268G>T in Exon 3 of the LDLR gene using Sanger sequencing could be tested in the parents and the younger sibling of ES. From the SS family, only he and his mother could be tested for the mutation as his sister was not willing to be checked for the mutation.

LDL cholesterol, Total cholesterol and Triglycerides studies of the probands and their relatives were carried out in the biochemistry dept of our hospital.

Results:-

NGS analysis revealed a homozygous missense mutation in the proband (ES), c.268G>T; CHR 19:11213417 in exon 3 of LDLR gene leading to substitution of amino acid Aspartic acid to Tyrosine at codon 90 (p.D90Y; ENST00000557933). Family members of ES i.e. parents as well as the younger sibling were also tested for the same mutation. Both mothers, as well as the father, were found to bear a single copy of the mutation (heterozygous c.268G>T mutation) while the younger sibling of ES was also found to have the same homozygous c.268G>T mutation. The mutation analysis of the deceased older sibling of index case 1(ES) was unfortunately not possible.

Lipid profile was assessed for the proband along with his family members (Fig. 2 and Fig2a). Lipid levels in ES showed exceedingly high levels of total cholesterol (537 mg/dl) as well as LDL cholesterol (496 mg/dl) whereas serum triglyceride levels were within the normal range (67 mg/dl). The 2 year old, the youngest sibling of ES was also assessed for lipid levels and was found to have high total cholesterol levels of (688 mg/dl) and high LDL cholesterol levels (635 mg/dl), however his serum triglyceride levels were in the normal range (121 mg/dl). Serum lipid levels for ES's father were also found to be high, with total cholesterol levels of 304 mg/dl and LDL cholesterol levels of 237.4 mg/dl. Again, his serum triglyceride levels were in the normal range (141.9 mg/dl). In contrast, and to our surprise, the lipid levels of the ES's mother were in the normal range with total cholesterol levels of 194.9 mg/dl, LDL cholesterol levels of 132.77 mg/dl and triglyceride levels of 113 mg/dl.

Values of lipid levels in the younger sibling of ES who had presented with multiple xanthomas and coronary heart disease and had died at the age of 7 years were unavailable.

In the second case, SS, 22 year old male, was referred to the hospital with hyperlipidemia, corneal arcus and complaint of chest discomfort. His angiography had shown changes suggestive of CAD. Clinical signs of hypercholesterolemia were observed with total cholesterol levels of 505mg/dl and LDL cholesterol levels of 462 mg/dl (Fig. 2a). His triglyceride levels were again within the normal range (78 mg/dl).

To our surprise, the patient's pedigree analysis showed that SS was a distant relative of the 1st proband ES (Maternal Aunt of ES was married to maternal cousin brother of SS) (Fig. 3). Similar to ES, SS also had a history of heart diseases in the family suggested by the death of his father at the age of 50 due to heart attack. Information regarding the lipid levels or the mutation status of his father was not available. In view of strong genetic background in the first proband ES for hypercholesterolemia, we assessed SS for confirmation of the same mutation. Strikingly, he was also found to have the same homozygous missense mutation (c.268G>T; CHR 19:11213417 in exon 3 of LDLR gene leading to substitution of amino acid Aspartic acid to Tyrosine at codon 90 [p.D90Y; ENST00000557933]) that was present in SS.

The mother of SS was also tested for this mutation and was also found to carry a single copy of the mutation (heterozygous status). Unlike SS, although his mother had no clinical symptoms of hypercholesterolemia but when her lipid profile was checked we observed that she had high levels of total cholesterol (386 mg/dl) and LDL cholesterol levels (294 mg/dl) but her triglyceride levels were also normal (91 mg/dl), similar to other members of the family (Fig 2a).

Mutation and biochemical studies could not be assessed for SS's sister as she did not agree to testing.

A dose-dependent increase in the levels of LDL cholesterol and total cholesterol has also been noted in our patients (Fig 2b). In homozygous patients (ES, Younger brother of ES and SS) with two copies of the affected gene showed LDL cholesterol in the range of 537-688 mg/dl. Their total cholesterol was in the range of 496-635mg/dl. In

heterozygous relatives (Parents of ES and mother of SS) having 1 copy of the affected gene, LDL cholesterol was in the range of 132-294 and total cholesterol was in the range of 194-386 mg/dl.

An interesting thing to note here is that although the mother of ES was carrying one copy of the affected gene, her LDL and total cholesterol levels were not increased.

Discussion:-

FH is a deleterious cardiovascular condition of increased cholesterol and lipid levels with a well-established genetic etiology. Autosomal dominant heterozygous mutations in lipid metabolizing genes are found to be present in 1 in 500 cases. Homozygous mutations on the other hand are very rare and are found to be affecting one in million people worldwide (Cuchel M, Bruckert E, Ginsberg H.N et al, 2014). In the present study, two distantly related proband cases of homozygous familial hypercholesterolemia along with their family members with high total cholesterol and LDL cholesterol levels are discussed. The association of LDL cholesterol levels with a mutation in exon 3 of the LDLR gene in a gene dosage-dependent manner is described (Fig. 2). Index case ES along with his family members; particularly, the younger sibling and father presented with high total cholesterol and LDL cholesterol levels ES and his brother showed the presence of the mutation c.268G>T (p.D90Y) in exon 3 of LDLR gene in the homozygous state whereas his father was heterozygous for the same mutation. It was surprising that the mother of ES, although bearing above mentioned heterozygous mutation in the LDLR gene similar to the father, did not show any clinical or biochemical signs of hypercholesterolemia whereas on the other hand the mother of SS with the same mutation in the heterozygous state had increased level of cholesterol and LDL cholesterol. It is well documented that hypercholesterolemia is a condition with multigenetic etiology and gene epistasis can be instrumental in generating differential phenotypes in affected pedigrees (Al-Allaf FA et al 2010). It has been long observed that Fibroblast culture studies in compound heterozygous patients with mutations in the LDLR gene produce abnormal LDLR receptors (Tolleshaug H et al 1982). A Study on the spectrum of LDLR mutations and their genotype-phenotype correlation has been reported (Mollaki V et al 2014). At the same time, studies using linkage analysis strongly suggest the possibility of genes that can potentially ameliorate the accelerating levels of cholesterol or LDL and modify the clinical presentation of the condition in different members of the same families with hypercholesterolemia (Wang et al. 2011; Bertolini et al. 2017). Besides, mutations in APOB and APOE genes have also been reported to contribute for the suppression of phenotypes of hypercholesterolemia (Moyer AM and Baudhuin LM 2015). Apo E polymorphism studies have revealed variability in the lipid traits like total cholesterol and LDL cholesterol (Ferrières J et al 1994). Unequal lipid levels in some of the family members with the same mutations also support the same hypothesis. Extensive studies regarding such gene-gene interaction in non-hyperlipidemic cases despite the strong genetic background of FH and/or presence of causative mutations of FH are strongly warranted to understand the exact genetic component underlying these effects. We would like to state that the candidate gene screening done by us did not include all the genes that are associated with the etiopathology of the disease. Also, within the panel of genes covered in the NGS only targeted mutations were screened. Thus, we could not rule out the possibility of the presence of any other co-existing mutations in these same genes which could lead to this phenotype. A previous study by Alves AC et al, (2014) has shown that mutations outside the LDL binding region of the LDL gene do exist and they can play a crucial role in disease presentation (Alves et al. 2014).

The index case (Proband 2, SS) from the second family which was referred to us, had the presentation of symptoms at a later age (21 years when he was referred to us) as compared to affected individuals from family 1, although he carried the same mutation in homozygous status. The patient had clinical as well as biochemical signs of hypercholesterolemia including corneal arcus (Fig. 1b) along with elevated total cholesterol and LDL levels. The patient's father was known to have a history of coronary heart disease followed by death due to a heart attack. Any data regarding the lipid levels or diagnosis of FH in father of index case 2 was not available for comparative analysis. Mother of Index case 2 (SS), carrying a single copy of the same mutation also showed high levels of cholesterol similar to the Father of ES (Proband 1). Detailed family history of this proband indicated that the patient was a distant relative of the previous family although their lineage was not the same. ES's maternal aunt was married to SS's maternal aunt's son. As both the families belonged to the same ethnic background and presented 3 individuals carrying the same rare homozygous mutation, associated with a rare genetic condition present in their families, it could be a common mutation in their community. Earlier reports of the high prevalence of consanguineous marriages in South Indian communities can perhaps explain such founder's effect and transmission of the same mutations over generations (Bhaskar et al, 2012). The possibility of many other individuals serving as carriers by bearing heterozygous mutation cannot be ruled out. It would be worth noting here that in the first of the

only two submitters of this mutation in the Clin Var database, this mutation has been reported in a South African of Indian origin. (Rubinsztein et al. 1993).

As expected, our data also showed a gene dose-dependent increase in the levels of total cholesterol as well as LDL cholesterol (Fig. 2a). Total cholesterol levels were significantly higher in individuals bearing the homozygous mutation (505-688mg/dl) as compared to heterozygous mutation (194-386 mg/dl)(Fig. 2a). LDL cholesterol levels also showed a similar trend. The range of values for LDL Cholesterol for the homozygous variant was 462-635mg/dl and for the heterozygous variant was 132-294 mg/dl.

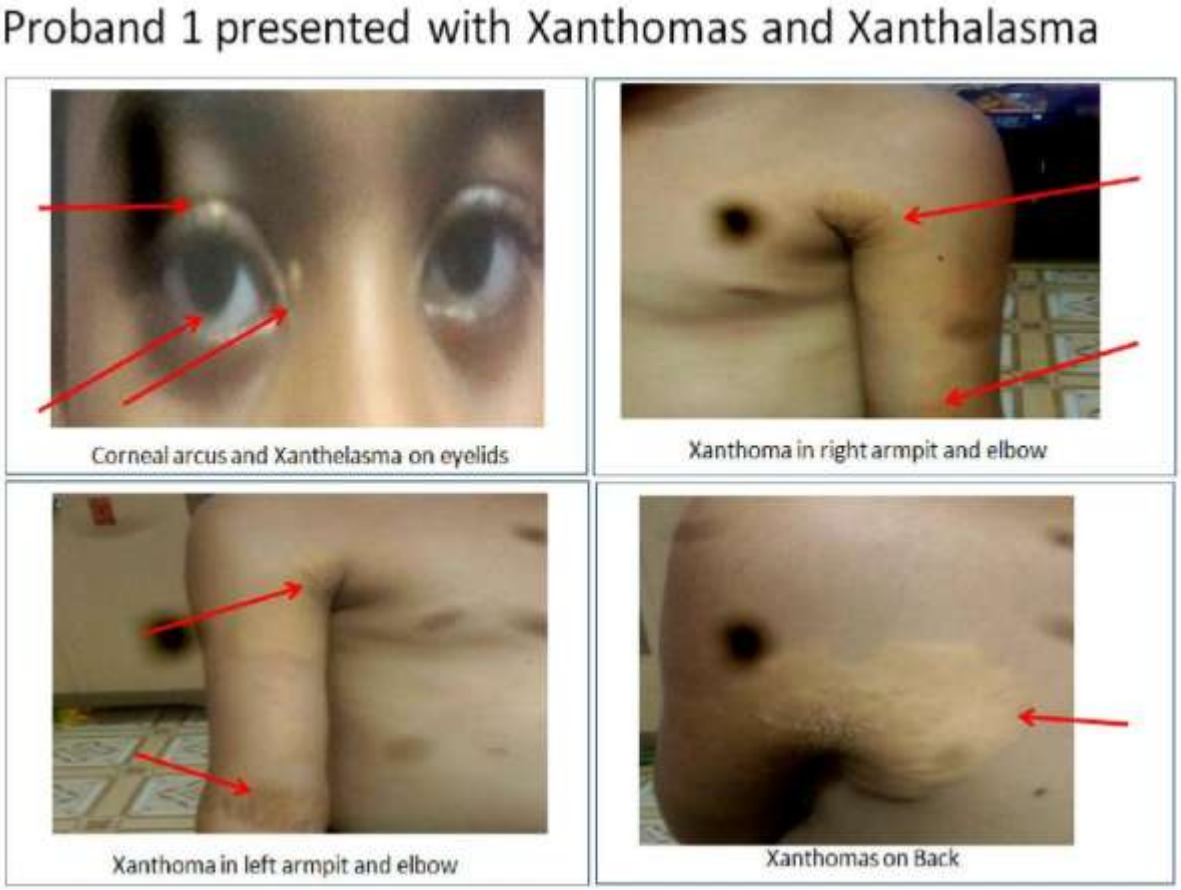
Current management guidelines emphasize on reduction of LDL levels and standard therapy is statins and although they are effective in the large majority of cases but sometimes they fail to achieve their target of LDL levels (Hovingh G. Kees et al 2013). Various new therapies have come up in recent times for the management of patients with hypercholesterolemia. Although combination lipid-lowering therapy is a conventional treatment option for these patients but recently, with LDLR-independent medications available, invasive procedures like lipoprotein apheresis and liver transplant can be avoided. At the same time new Drugs like evinacumab have also brought great hopes for these patients. Thus, timely diagnosis and understanding of the genetic aspects of the same will not only save lives and increase the lifespan but also improve the quality of lives of many affected patients (German C 2022).

Conclusion:-

This study highlights the importance of conscious and proactive genetic screening for Hypercholesterolemia, especially in communities that practice consanguineous marriages, to identify the condition, guide them and manage them effectively. Besides, linkage study analysis among affected family members with the variable clinical presentation may also provide insight into the epistatic behavior of the genes involved in lipid metabolism. This can further lead to the better management of patients affected with hypercholesterolemia.

Figure Legends

Fig. 1a and 1b:- Clinical presentation of Proband 1 (ES) and Proband 2 (SS).



1a) Proband 1 (ES):- (i) Corneal arcus and Xanthelasma on eyelids (ii) Xanthoma in right armpit and elbow (iii) Xanthoma in left armpit and elbow (iv) Xanthomas on back.

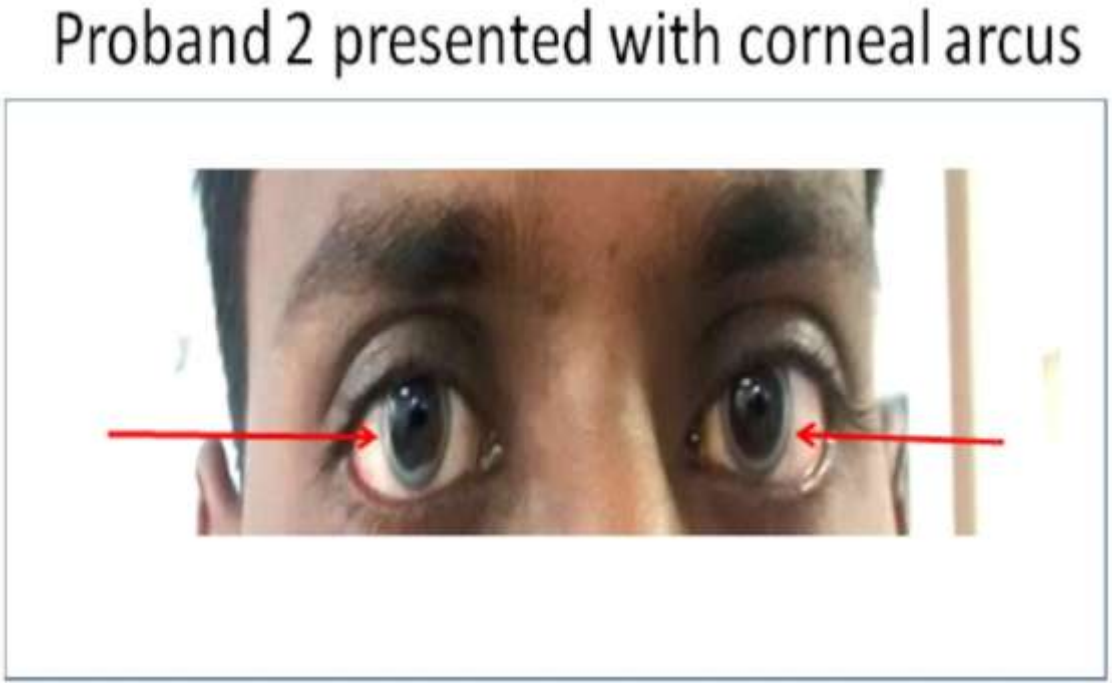
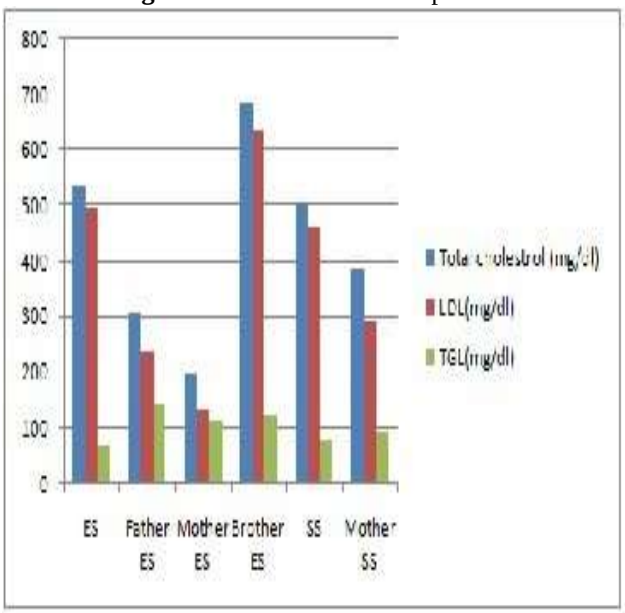


Fig 1b) Proband 2 (SS): Corneal arcus

Fig. 2a and b:- Biochemical profiles of Proband 1(ES) and Proband 2 (SS) and their relatives.



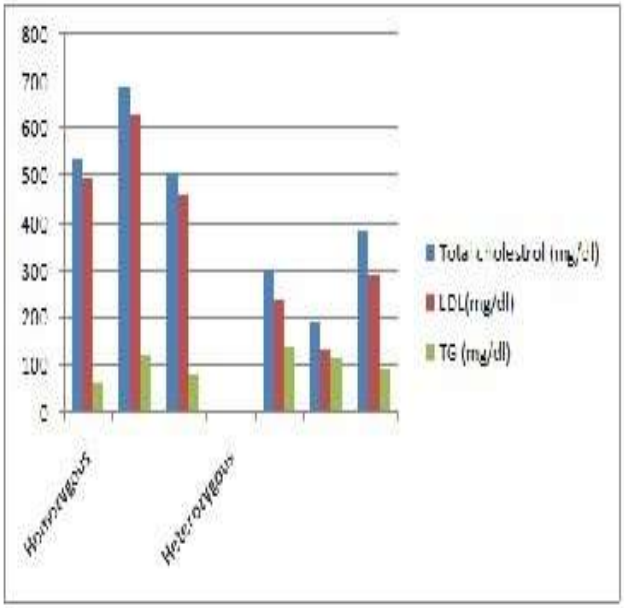
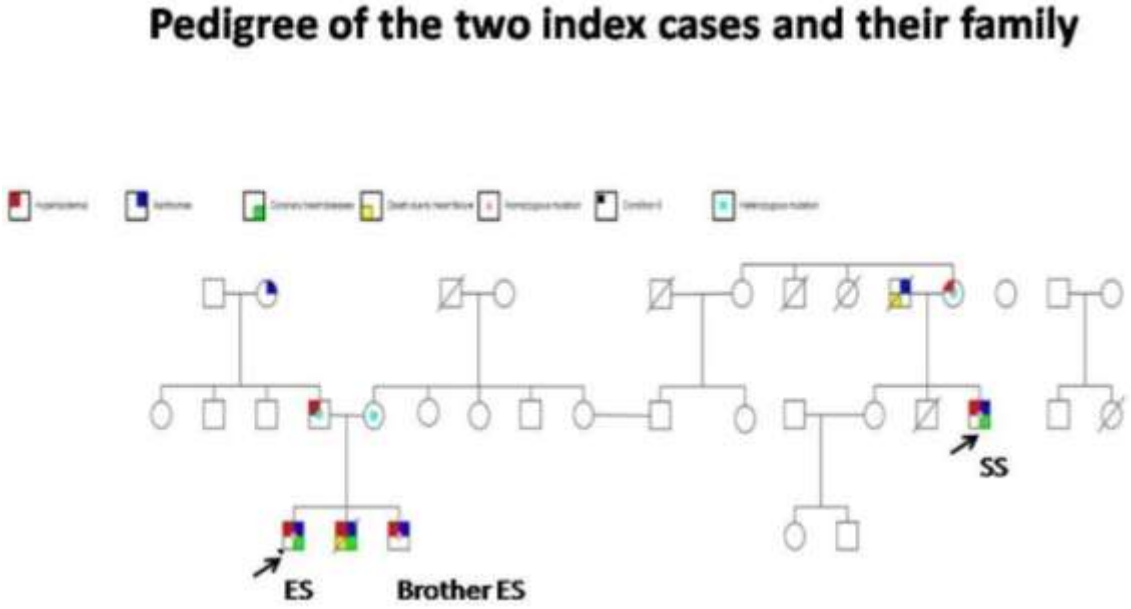


Fig2A Fig2B

(a) Comparison of total cholesterol, LDL cholesterol and triglycerides levels in proband 1 and 2 along with their family members.

(b) Comparison of total cholesterol and LDL cholesterol levels in subjects with homozygous and heterozygous mutations

Fig. 3:- Represents pedigree analysis and relation of Proband 1(ES) and Proband 2 (SS).



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