

# Autosomal dominant single gene disorder biology essay

[Science](#), [Biology](#)



This essay is designed to determine how mutations in genes can cause genetic disorders such as Familial Hypercholesterolemia and explore how a single mutation for one particular gene can cause such a huge effect.

Familial Hypercholesterolemia (1) is an autosomal dominant single gene disorder where patients often have high levels of cholesterol within their bloodstream often from an early age. The high levels of cholesterol within the blood is caused by a lack of a Low density Lipoprotein receptor which ultimately remove lipoproteins from the blood and the lack of the Low density Lipoprotein receptor means cholesterol is not sufficiently removed from the blood. This means patients with Familial Hypercholesterolemia have high levels of cholesterol which can cause 'Atheroma' which means blood flow to vital organs such as the heart can be significantly reduced and this can cause several cardiovascular diseases for example Myocardial Infarction.

Symptoms (2) included High levels of cholesterol, cholesterol deposition in joints, Myocardial Infarctions, Xanthomas and Cardiovascular disease (Kolovou et al., 2011). Because Familial Hypercholesterolemia is an autosomal dominant single gene disorder and this means that it can be passed down to males and females and if a parent has familial Hypercholesterolemia, then there is a 50% chance that the offspring can have Familial Hypercholesterolemia. In Familial Hypercholesterolemia, there is a mutation on chromosome 19 specifically 19p13.2 which specifically codes for the low density Lipoprotein receptor gene and the mutation causes a reduction of low density Lipoprotein receptor (LDL). so there is an increased chance of Myocardial infarctions so patients suffering from Familial Hypercholesterolemia suffer from an increased probability of cardiovascular

disease. Because it is an autosomal dominant disorder, this means that the individual only has to receive one allele from the parent, which contains the defective LDLR gene to have Familial Hypercholesterolemia so when the individual receives one allele from the parent which has the defective LDLR gene, he has heterozygous Familial Hypercholesterolemia and when he receives two alleles with the defective LDLR gene, he has Homozygous Familial Hypercholesterolemia. Familial Hypercholesterolemia (3) has an incidence of 1 in 1 million live births in its most severe form where people who are Homozygous dominant for lacking the low density Lipoprotein receptor gene and people who are heterozygous only have an incidence of 1 in 500 live births. However Homozygotes for Familial Hypercholesterolemia have a much higher probability of having Myocardial infarctions and they can begin from the early age of two whereas Heterozygotes for Familial Hypercholesterolemia have a lower probability of having Myocardial infarctions and they can begin from the age of 35. This is because Familial Hypercholesterolemia is also an example of incomplete dominance where one allele does not completely mask activity of the recessive allele, therefore in Familial Hypercholesterolemia, people who Heterozygous have much less severe symptoms (Goldstein et al., 2001) In familial Hypercholesterolemia (4), mutations can occur on the LDL Receptor gene, apolipoprotein B-100 gene and the PCSK9 gene however most mutations occur in the LDL Receptor gene and there are over several hundred mutations on the LDLR gene (Austin et al., 2004). The low density Lipoprotein receptor is a protein, found on the chromosome 19p13, which specifically recognises the apolipoprotein B-100 which is the component Low density lipoprotein. It can

then remove cholesterol from the blood and it controls the endocytosis of cholesterol- rich Low density lipoprotein. LDL receptors are mainly found in the liver on the outer surface of the hepatocytes and the higher the number of LDL receptors, the more cholesterol is eliminated from the bloodstream. The molecular genetics of familial hypercholesterolemia (5) shows that the low density Lipoprotein receptor originally exists as a 120 kD precursor molecule and this is converted to a 160-kD glycoprotein by glycosylation in the Endoplasmic Reticulum. The Low density Lipoprotein receptor precursor loses its signal peptide and when it is transported to the Golgi apparatus, it is modified by the addition of sugars and becomes a larger protein (Tolleshaug et al., 1982) . It is a 839 amino acid protein (6) which has lots of cysteine residues and several DNA repeats and the LDL receptor consists of a promoter region alongside 18 exons including five specific domains where the first domain allows for the ligand to bind and this is encoded for in exons 2-6. The second domain has a sequence similar to Human epidermal growth factor receptor and this lies within exons 7-14. The third domain consists of lots of sugars in exon 15, the fourth domain is the transmembrane region coded by exons 16 and 17 and the fifth domain is the cytoplasmic region which is coded by exons 17 and 18 (Südhof et al., 1985). There are five major types of mutations which cause changes to the low density Lipoprotein receptor so as a result, the LDL receptor cannot remove cholesterol from the blood efficiently or sometimes they are not synthesised at all. The mutations are classified as Class 1, Class 2, Class 3, Class 4 and Class 5. In Class 1 mutations, the LDL receptor is not synthesised at all. In Class 2 mutations, the LDL receptor is unable to be exported from the endoplasmic reticulum to

the Golgi apparatus so it is unable to become present on the surface of the cell. In class 3 mutations the receptor has difficulty in binding to the LDL on the cell surface. In class 4 mutations the LDL receptor can bind to the LDL however it does not allow the cholesterol to be endocytosed in vesicles and class 5 mutations is where the LDL receptor cannot circulate back to the surface of the cell (Hobbs et al., 1990). Many of the mutations shown above are caused by point mutations where changes in the amino acid sequence of the LDLR gene causing a conformational change to the LDL receptor protein hence the protein can be dysfunctional. According to the LDL receptor database (8) approximately 70% of the mutations are substitutions and 19% are deletions and most of these mutations affect the ligand-binding domain encoded by exons 2-6 (Leigh et al., 2008) Another mutation was determined by clinical trials (9) on patients with familial hypercholesterolemia in Pakistan where PCR-RFLP analysis showed that most patients has a mis-sense mutation in exon 13 where C. 1916t had been changed to the G mutation. In this mis-sense mutation, there was a substitution of an amino acid from Valine to Glycine and this mutation causes a loss of hydrogen bonding which causes a conformational change to the Low Density Lipoprotein receptor and as a result, it cannot remove cholesterol efficiently from the blood and patients have Familial Hypercholesterolemia (Ahmed et al., 2012). A mutation (10) in exon 10 in the Low density Lipoprotein receptor showed a change of the codon TGG at amino acid position 1448 to TGA and this causes a substitution of a tryptophan to a stop codon which had lead to a truncated protein and a defective Low Density Lipoprotein receptor (Wang et al., 2009). In people with heterozygous Familial Hypercholesterolemia, they have a

reduced number of LDL receptors so they have much milder forms of cardiovascular disease and as a result they have heart attacks at a later age i. e. 35 years of age however individuals with the rarer homozygous Familial Hypercholesterolemia have virtually no LDL receptors so they are unable to remove cholesterol from the blood so they have large amounts of cholesterol within their bloodstream which leads to the development of atherosclerosis which can ultimately lead to atherosclerotic plaques which cause cardiovascular disease so this explains why individuals with homozygous Familial Hypercholesterolemia have heart attacks at the age of two.

Diagnosis of Familial Hypercholesterolemia involves monitoring the levels of Low Density Lipoprotein-Cholesterol (LDL-C) within the blood stream and if the LDL-C levels are above 190 mg/dl for an adult, this means they have Familial Hypercholesterolemia and DNA analysis is also used to detect any mutations to the LDLR gene and these are effective methods of diagnosis. Treatment methods include statins such as HMG-CoA reductase inhibitors, LDL apheresis which removes cholesterol from the plasma and Liver transplants. Potential new treatments involve gene therapy using viruses as vectors which replace the LDL receptor gene however currently they have shown to be eliminated by the hosts immune system, so gene therapy as a treatment for Familial Hypercholesterolemia is currently in development (Hopkins, 2003). Overall this essay demonstrates that Familial Hypercholesterolemia is a very common autosomal dominant disorder where most of the time point mutations, in the ligand binding domain of the LDL receptor, create a truncated protein which causes an increase in the cholesterol concentration within the bloodstream as the LDL receptor cannot efficiently remove the

cholesterol from the blood stream and this can lead to cardiovascular disease and patients often suffer from heart attacks. There is a heterozygous advantage in familial Hypercholesterolemia as patients who are heterozygous have less severe symptoms but it is still a very serious disease. Although there is no cure, there is long term treatment involving Liver transplants and statins and gene therapy can also be a potential treatment and overall this essay demonstrates, that even a simple point mutation in one gene can cause serious and debilitating disease such as Familial Hypercholesterolemia.