

Beneficial Gene Mutations!

M.S.S. Murthy

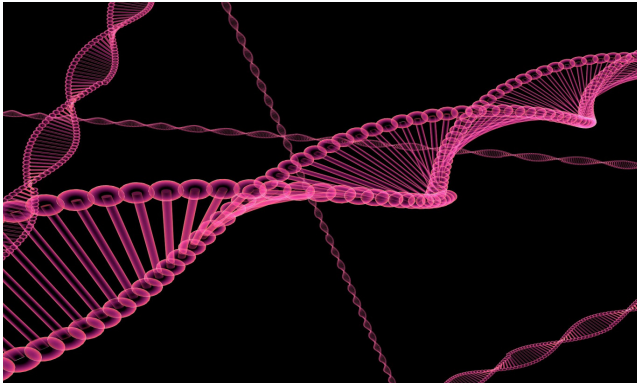


Image credit: Pixabay

THE words ‘gene mutation’ often ring alarm bells. This is because gene mutations are popularly associated with many debilitating and life-threatening diseases. So, as a concept, ‘beneficial mutations’ are hard to believe. But beneficial mutations do occur in all living beings, including humans. Many people carry such mutations, though they may be unaware. And scientists are studying them to develop super drugs for diseases that plague humans.

Gene Mutations

Mutations are defined as alterations in the DNA sequence or the genetic code. Mutations can occur in many ways: change of a single base from one form to another (point mutations), deletions or insertions of one or more bases (frameshift mutations), and structural and numerical changes in the chromosomes which contain the genes (chromosomal mutations).

If mutations occur in germ cells, they may be passed on to the offspring. This means every cell in the offspring carries this mutation. If only one of the parents had a mutation in a gene, then the offspring will have one mutated copy of the gene, the other copy being normal. If both the parents carried a mutation in the same gene, then the offspring will have both copies mutated.

Mutations are caused by some type of errors that occur during natural biochemical processes such as DNA duplication during cell division. External agents like chemical pollutants, UV and X-radiations can also cause mutations. Though cells have an extensive network of DNA repair systems to address such situations, some mutations do escape. Geneticists say that we are all born with some mutations inherited from our parents. In addition, we may also acquire mutations during our lifetime.

Majority of the mutations are known to be neutral in the sense that they do not produce any discernible effects; they

remain undetected unless genetically analysed. Some mutations are detrimental and cause diseases such as cystic fibrosis, sickle cell anaemia, Tay-Sachs disease, phenylketonuria, colour-blindness, and a few others. Some forms of cancers are also due to inherited mutations.

Beneficial Mutations

However, mutations can also improve an existing useful function (gain-of-function mutations), or turn off functions that become pathological (loss-of-function mutations) and thus can be beneficial to the individual inheriting them. These mutations produce characteristics that enable the individual to better adapt to a changing environment. Hence they are passed on to the offspring at an increased rate by natural selection, which at the same time weeds out the deleterious ones.

Now, how are beneficial mutations detected? Geneticists examine sick people genetically to determine the cause for their sickness. For example, sickle cell anaemia is found to be the result of a point mutation in which just one base in the DNA sequence for the gene that codes for a sub-unit of haemoglobin has been changed. Because of this small change, the structure of the haemoglobin molecule, which is responsible for carrying oxygen in the blood, changes shape – instead of being round, it takes a curved shape like a sickle. A sickle-shaped haemoglobin molecule is less efficient in carrying oxygen and also blocks the flow of blood in the arteries, leading to the disease. Likewise, genetic causes of several other diseases like coronary artery diseases including heart attacks, Type 2 diabetes, Parkinson’s disease, Alzheimer’s dementia, etc. are now well established. Many of these diseases are caused by mutations in not just one gene but in many coordinating genes and also carry several risk factors like obesity, age, lifestyle, etc.

Geneticists are now looking at the elderly population, who in spite of having some risk factors are free from some of these chronic diseases. What makes them so? It is generally presumed that such people are not obese, have perfect genome, no disease-causing mutations, follow healthy lifestyle practices like regular exercise, non-smoking and vegetarianism.

However, in 2014 when geneticists Nir Barzilai and colleagues of the Albert Einstein College of Medicine, USA analysed the genome sequences of 44 centenarians for mutations associated with some specific diseases, they were surprised. In total, the group had 250 mutations linked to Parkinson’s disease, Alzheimer’s dementia, cardiovascular diseases and other chronic diseases! In addition, some of them were obese, others had been life-long smokers, and many never regularly exercised. However, the astonishing

fact was they all lived a century and never developed chronic diseases. “That leaves us with the fact that they must have some genomic reasons,” says Nir Barzilai.

Following such line of thinking, several researchers are now analyzing elderly people who are also healthy (the ‘welllderly group’) to look for protective mutations that could offset the effects of disease-linked genes. For example, researchers at the Board Institute, Boston recruited elderly, obese individuals for a study. Obesity is a critical risk factor for several diseases such as Type 2 diabetes and cardiovascular diseases since many genes that have been implicated with obesity have also been associated with these diseases. So, by all means, they ought to have had Type 2 diabetes, but did not. The study revealed that people who have inherited a particular mutation in a gene called *SLC30A8* are 65% less likely to get diabetes, even when they have risk factors like obesity. Gene *SLC30A8* has some subtle effects on the secretion and transport of insulin. One of its mutated forms is known to be associated with susceptibility to Type 2 diabetes. However, a knock out mutation, which leads to loss-of-function of the gene, has a protective action against Type 2 diabetes.

Similarly, certain mutations in a gene called *SGK1* are known to offer protection against Parkinson’s disease by turning off pathways involved in neurodegeneration.

One of the long-known beneficial mutations is the one that confers lactose tolerance. Human babies (also mammalian babies) survive their infancy on mother’s milk. Mother’s milk, in addition to providing the necessary nutrients also provides instant energy to the baby, because it contains a sugar known as lactose. The infant’s body produces an enzyme known as lactase, which breaks down the lactose in milk to produce energy. However, as we grow up, the body stops producing lactase. Hence, if grown-ups consume, say cow’s milk or any of its products like ice cream, cheese, etc., the lactose remains undigested resulting in various problems like diarrhoea, bloating of stomach, cramps, gas, vomiting and so on – all together known as lactose intolerance. However, in the course of evolution, after the domestication of cows as a source of milk, a good percentage of the population have become lactose tolerant – that is, they can tolerate milk.

We all have a gene called *MCM6*. One of its functions is to regulate another gene *LCT*, which in turn directs the production of the enzyme lactase. In adulthood, *MCM6* turns off the *LCT* gene. So the body stops producing lactase and the person becomes lactose intolerant. However, nearly 35% of the population inherit a mutation in the *MCM6* gene, which stops it from turning off the *LCT* gene, so that the body goes on producing lactase and conferring lactose tolerance even in adulthood.

Another interesting case of protective mutation is revealed by the gene *PCSK 9*. The protein coded by the gene regulates the level of low-density lipoprotein (LDL), the so-called bad cholesterol in blood. LDL cholesterol is contained in some diets and is also produced in the body during normal metabolism. While it has some useful biochemical functions, if present in excess, it clogs the arteries, leading to a condition called hypercholesterolemia – a risk factor for coronary artery

diseases including heart attack and stroke. Normally, a high concentration of LDL in blood is prevented by what is called LDL receptors (LDL-R) situated on the surface of cells of tissues like liver. These receptors bind to LDL and transport them to inside the cell where they are metabolised. The normal function of the PCSK 9 protein is to bind to LDL-R and degrade them in order to maintain an LDL homeostasis in the body.

Recently, a French study revealed a mutation in the *PCSK 9* gene, which is classified as a gain of function mutation. The altered PCSK 9 protein was found to cause more of the LDL-R to be broken down than normal. With fewer receptors to remove LDL from blood, persons carrying the mutation will have very high levels of LDL in blood, with an increased risk of hypercholesterolemia.

Meanwhile, Dr Helen Hobbs and colleagues at the University of Texas, who had been studying people with very high and very low levels of LDL in blood, wondered if a mutation in the *PCSK 9* gene can lead to enhanced level of LDL, can another mutation have the opposite effect – reduce the LDL levels in blood? Sequencing the *PCSK 9* gene in persons with very low levels of LDL in blood, they indeed discovered a mutation in the *PCSK 9* gene that knocked out the production of the protein that destroyed the LDL receptors. People who inherited that mutation had very low levels of LDL in blood and thus were protected from hypercholesterolemia.

So far this mutation has been seen only in a handful of African Americans and those with two copies of this are known to have 90% reduced risk of heart diseases without any side effects. Lactose tolerance, high altitude living, etc. are examples of evolutionary adaptation in the human lineage. Geneticists believe that these other beneficial mutations too may be taken up by natural selection and spread through the population in due course.

Drug Development

A number of protective mutations have been discovered covering a wide range of human traits from susceptibility to Type 2 diabetes to the ability to live at high altitudes. However, many of these are found only in a small percentage of the population. The question geneticists are asking is how can the benefits of these mutations be extended to members of the larger public, who have inherited some of the risk factors?

Dr Sekar Kathiresan, a cardiologist and geneticist at the Board Institute, Boston says, “....these immediately tell us if you can develop a drug that mimics the mutation, it would work in other high-risk persons.” Pharmaceutical companies are now trying to do exactly that – develop drugs that mimic the products of beneficial mutations.

The approach may be different depending upon the type of mutation. If a mutation produces a gene product that offers protection in the cell, the drug manufacturer will try to develop a drug that mimics the gene product. Alternatively, if the protection is offered by a knock-out mutation in which people are naturally missing a working copy of the gene,

Table 1: Some examples of beneficial mutations

Gene	Mutation	Protection against
<i>SLC30A8</i> : Has subtle effects on insulin secretion and transport	Loss of function	Type 2 diabetes
<i>PCSK9</i> : Regulates the level of LDL cholesterol in blood	Loss of function	Coronary heart diseases
<i>CCR5</i> : Codes for receptors on red blood cells	Loss of function	HIV infection
<i>ADIPOQ</i>	Deletion mutation	Inflammation of arteries
<i>CETP</i>	Single nucleotide polymorphism	High cholesterol levels and cognitive disorders
<i>SGK1</i> : Mediates the way cells respond to stress	Gain of function mutation	Parkinson's disease
<i>FY</i> : Codes for Duffy antigen on haemoglobin	Single point mutation	Malaria caused by <i>Plasmodium vivax</i> virus
<i>NPC1L1</i> : The gene product is involved in the intracellular transport of LDL cholesterol	Loss of function	Heart attacks
<i>APOA1</i> : Codes for a protein which is a component of HDL cholesterol	Gain of function	Protects against heart attacks
<i>LPR 5</i> : Codes for Low-density lipoprotein receptor-related protein 5	Gain of function	Increases bone mass and density and protects against osteoporosis
<i>MCM6</i> : Regulates another gene LCT, which produces lactase	Loss of function	Lactose intolerance
<i>EPAS1</i> : Codes for protein which regulates production of RBCs	Gain of function	Protects people living in high altitudes (Tibet) from altitude sickness
<i>CD33</i> : Codes for the receptor protein CD33	Loss of function	Alzheimer's disease and age-related cognitive decline
<i>APOC3</i> : The protein inhibits hepatic uptake of triglycerides	Loss of function	Ischemic vascular diseases
<i>CASP12</i> : Codes for an enzyme involved in programmed cell death and inflammation	Loss of function	Sepsis

without any side effects, the drug manufacturer will aim at a drug that will block the concerned gene.

For instance, Regeneron Pharmaceuticals in New York have developed, based on Hr. Hobbs' findings, two drugs Evolocumab and Alirocumab which are *PCSK 9* gene inhibitors. These drugs knock out the *PCSK 9* protein, which otherwise would have destroyed LDL receptors. Saving the LDL receptors pushes down the LDL levels in blood thus helping persons suffering from familial hypercholesterolemia. Early trials have shown that patients who take these drugs experience 75% reduction in their blood LDL cholesterol level. More drugs to prevent neurodegenerative diseases like Alzheimer's, Parkinson's, cardiac diseases, bone diseases like osteoporosis, etc. are on the anvil to spread the benefits of protective mutations to those who are not born with them.

In the final analysis, mutations occur, irrespective of their effect on the organism. So, whether a mutation is

good or bad depends upon a number of factors including the context and the environment in which the organism lives in. For example, a mutation causing sickle cell anaemia, if present in a single copy, produces no symptoms of the disease, but protects against malaria. As result, it is very much prevalent in several parts of Africa where malaria is endemic. However, if present in both copies of the gene, it is deadly.

However, one of the serious public health problems today is the emergence of drug-resistant bacteria. Bacteria have developed mutations that protect them from even the most potent antibiotics available today. Certainly, it must be good for them and they must be 'happy' about it!

//////////
M.S.S. Murthy, I Block, No. 304, Mantri Alpyne Apartments,
Dr Vishnuvardhan Road, Subramanyapura post,
Bengaluru- 560061