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LMBBS genes and how BBS can be inherited.

17 LMBBS (called BBS) genes (*BBS1-12, MKS1, CEP290, WDPCP, SDCCAG8 and LZTFL1*) have, so far, been identified and scientists know that there are still more genes to find. Not all patients have an identified mutation in any of those BBS genes, implying that these patients must have mutations in other genes. Some genes are more common than others; a quarter of patients have mutations in BBS1 and another quarter have mutations in BBS10. Patients who carry mutations in the same BBS gene can display quite different versions of the syndrome; one might have extra digits at birth whereas another person with an identical mutation may not have polydactyly at all. It is hoped that comprehensive genetic testing will better inform predictions about disease progression in the future.

Once two mutations in a BBS gene are discovered in a person with LMBBS then this information can benefit parents and relatives. For example, a simple carrier test is possible in at-risk relatives (e.g. siblings) to help determine their own risk of having affected children if their partner is also a carrier. Knowledge of the BBS mutations can also provide the basis for prenatal screening tests, should parents need to know if an early pregnancy might be affected.

Parents who already have an affected child run a risk of further affected children and should be counseled as such (the child from each pregnancy has a I in 4 chance of being affected). There is a 2 in 3 chance that the child from any subsequent pregnancy, if not affected, will be a carrier of the BBS gene in that family. As the syndrome is rare (1 in 125,000 - see earlier), a gene carrier is unlikely to have affected children unless their partner is also a carrier. This risk of encountering another carrier increases if they marry within their own family. As

some BBS genes are more common than others the frequency with which they are being carried silently in the population varies. For the most common BBS genes, BBS1 and BBS10, the frequency is estimated to be 1 in 250, whereas for a rarer gene such as BBS9, the frequency is closer to 1 in 820.

Gene	Gene OMIM	Protein
BBS1	209901	Bardet-Biedl syndrome 1 protein
BBS2	606151	Bardet-Biedl syndrome 2 protein
ARL6	608845	ADP-ribosylation factor-like protein 6
BBS4	600374	Bardet-Biedl syndrome 4 protein
BBS5	603650	Bardet-Biedl syndrome 5 protein
MKKS	604896	McKusick-Kaufman/Bardet-Biedl syndromes putative chaperonin
BBS7	607590	Bardet-Biedl syndrome 7 protein
TTC8	608132	Tetratricopeptide repeat protein 8
BBS9	607968	Parathyroid hormone-responsive B1 (PTHB1) protein
BBS10	610148	Bardet-Biedl syndrome 10 protein
TRIM32	602290	Tripartite motif-containing protein 32
BBS12	610683	Bardet-Biedl syndrome 12 protein
MKS1	609883	Meckel syndrome type 1 protein (MKS1)
CEP290	610142	Centrosomal protein of 290 kDa
WDPCP	613580	WD repeat-containing and planar cell polarity effector protein fritz homolog
SDCCAG8	613524	Serologically defined colon cancer antigen 8
LZTFL1	606568	Leucine zipper transcription factor-like protein 1

LMBBS gene and protein names with OMIM (Online Mendelian Inheritance in Man, www.omim.org) numbers

What is a gene?

A gene is a specific section of DNA that gives the cell instructions to make a particular protein.

Every single cell in our body has a nucleus. The nucleus is the control center for each cell, dictating how the cell grows, its identity and replication. All of a cell's chromosomes are housed within the nucleus. Chromosomes are thread-like structures made up of a molecule called deoxyribonucleic acid or 'DNA' for short.

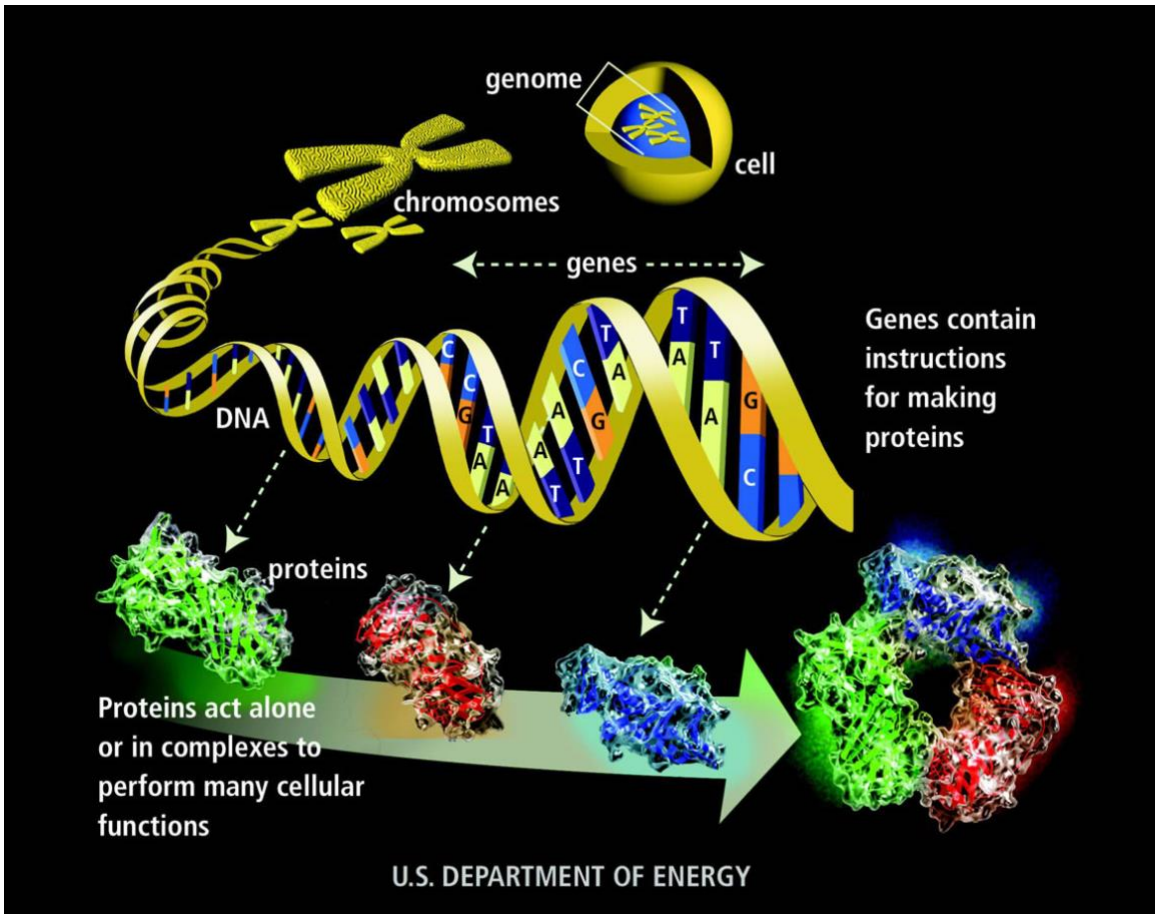
DNA is passed on from one generation to the next and contains the specific information that makes us unique. A **gene** is a specific section of DNA that gives the cell instructions to make a particular **protein**. Humans have just over 20,000 genes which can be 'read' by the cell in different ways to make hundreds and thousands of different proteins.

What is a protein?

A protein is a long strand of amino acids that fold together to make 'building blocks'.

Proteins are made by the cells by 'reading' the information from the genes. Different genes make different proteins. Every protein has a specific function and they are required for virtually all cellular processes. A protein is comprised of a stretch of molecules called 'amino acids' that fold together like building blocks.

There are 20 different types of amino acids, which can be combined to make an infinite number of different types of proteins. The unique sequence of amino acids that makes a particular protein determines the final structure and function of a protein. Having the correct order of amino acids in a sequence is important otherwise the protein might not be made properly.

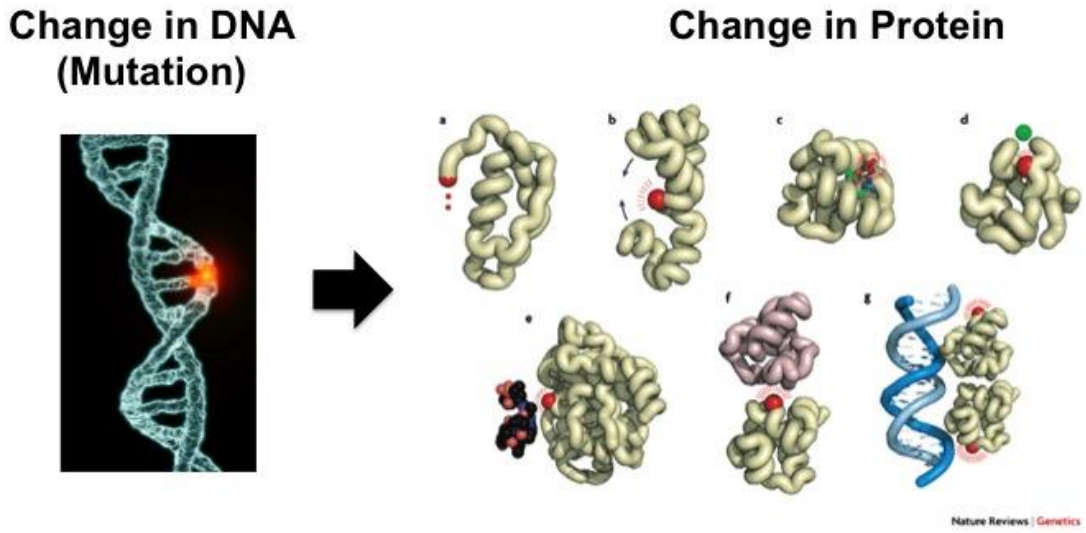


What is a genetic mutation /disease?

A gene mutation is a permanent change in the DNA sequence that makes up a gene. Sometimes these changes can cause different diseases or genetic syndromes.

A change (a mutation) in the DNA sequence can cause a change in the amino acid sequence of a protein. Such an amino acid change can disrupt a protein's structure or function. Just how deleterious a mutation can be depends

on which gene carries the mutation, what type of mutation is present and where in the gene/protein the mutation is.



A change in the DNA sequence might cause a disruption to the protein, which may affect how the protein functions in the cell.

What is LMBBS?

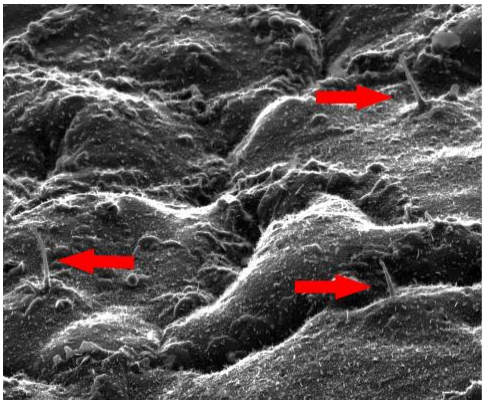
LMBBS is a genetic syndrome, which is caused by mutations in BBS genes.

Mutations in these genes cause changes in the proteins that are needed for the correct functioning of a particular part of the cell called a primary cilium. For this reason, LMBBS has been categorized medically as a **ciliopathy**. Ciliopathies are a range of human disease syndromes all caused by defects in primary cilia function. So far 17 genes have been found to be associated with LMBBS (see previous section). Examples of other ciliopathies include Alström Syndrome, Joubert Syndrome and Meckel Syndrome, which have overlapping symptoms and are all caused by defects in cilia proteins.

What are cilia and what do they do?

Cilia are long thin, hair like projections that stick out of the surface of a cell. There are two types of cilia, motile and non-motile or primary cilia (also called sensory cilia). Motile cilia wave about and are important for moving fluid (e.g. mucus) in various parts of the body. Motile cilia have been studied for many years and defects in their beating cause diseases such as Kartagner syndrome. Primary cilia however had long been ignored by biologists and were considered to be a vestigial remnant of evolution, similar to the human appendix. It was the initial identification of mutations in primary cilia genes in LMBBS patients, which alerted us to the importance of primary cilia in disease.

Tufts of motile cilia



Single primary cilia

Many cell types in the body rely on having a fully functional primary cilium. Important examples include the retinal photoreceptor in the eye, and cells in the kidney, which explains many of the symptoms experienced in patients with LMBBS. The scientific community is trying to understand exactly what roles the BBS proteins play in cilia formation and function. One role we know about is that they are important in trafficking other cilia proteins along the cilium. More specifically they are thought to be adaptors for cargo undergoing ciliary transport. Other functions for BBS proteins are also being examined.

There are still many unanswered questions that the research community is trying to figure out. We still don't know exactly how cilia work and all the different functions that they are involved in, but further research could lead to therapies to alleviate some of the symptoms caused by ciliary dysfunction.

Suggested further reading:

Bardet-Biedl syndrome. Forsythe E, Beales PL.
European Journal Human Genetics. 2013 Jan;21(1):8-13

Cilia is an open access peer-reviewed journal that publishes high quality basic and translational research on the biology of cilia and diseases associated with ciliary dysfunction. Research approaches include cell and developmental biology, use of model organisms, and human and molecular genetics.
http://www.ciliajournal.com/