The Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene was identified in 1989 by geneticist Lap-Chee Tsui and his research team as the gene associated with cystic fibrosis (CF). Tsui’s research pinpointed the gene, some mutations to which cause CF, and it revealed the underlying disease mechanism. The CFTR gene encodes a protein in cell membranes in epithelial tissues and affects multiple organ systems in the human body. Mutations in the CFTR gene cause dysfunctional regulation of cell electrolytes and water content. Research on the CFTR mutation has shed light on the ways in which this gene is vital to normal human development.

Cystic fibrosis is an autosomal recessive disease, meaning it is inherited when a child receives one mutated copy of the CFTR gene from each parent. If individuals have only one defective copy of the gene, they still express enough normal copies of the gene to be healthy. Individuals who have two mutated CFTR genes cannot regulate their electrolytes properly and will develop CF. As carriers of the mutated CFTR gene appear to be healthy, the mutated CFTR gene may remain undetected without prenatal or genetic screening.

The CFTR gene belongs to a family of genes that regulate the energy transfer that allows a cell to open and close its ion channels. It is located on human chromosome 7 and consists of twenty-seven sequences of DNA that encode 1,480 amino acids. The CFTR gene produces the CFTR protein, which regulates the chloride ion content of epithelial cells that line the nasal cavity, lungs, and stomach. These cells secrete fluids such as sweat, mucus, and tears, which normally are thin and watery. When chloride ions cannot leave the cell properly through the CFTR protein, water is retained in the cell due to osmosis and these fluids are thicker than they should be. Thus, the proper regulation of the chloride channel enables a cell to maintain the correct balance of electrolytes on both sides of the cell membrane.

Although there are more than 1,200 known mutations of the CFTR gene, the most common mutation results from the deletion of a single amino acid in the CFTR protein. Approximately seventy percent of cystic fibrosis cases are caused by this mutation, the deletion of the amino acid at position 508 in the CFTR gene. This mutation, termed ΔF508, causes the CFTR protein to fold improperly during protein synthesis; the protein breaks down shortly after it is made, and it never reaches the cell membrane. Other mutations to the CFTR gene involve changes to the protein’s structure, stability, or production, preventing chloride ion regulation in epithelial cells. Some of the identified mutations are rare, while others account for a few percent of cystic fibrosis cases.

The inability to regulate chloride and some positive ion channels upsets the balance of electrolytes in the body. Therefore a functioning CFTR gene is critical to normal human development. Mutations to this gene are life threatening in most cases because they compromise the function of the pancreas, gastrointestinal tract, and respiratory systems. Lacking a functional CFTR protein, cells produce sweat with a high salt content and thick, sticky mucus. Mucus builds up in the intestinal tract and blocks the movement of pancreatic enzymes through the digestive tract. This destroys pancreatic exocrine function. The mucus also causes intestinal obstructions, so that an affected individual cannot absorb nutrients properly. A developing fetus with a mutated CFTR gene is typically below average intrauterine weight and suffers from intrauterine growth restriction and poor development. These problems are secondary to the obstruction of the pancreas. Infants are diagnosed with failure to thrive at birth and males with a mutated CFTR gene typically have congenital bilateral absence of the vas deferens and are infertile, though not sterile.

Individuals who carry one normal and one mutated copy of the CFTR gene may have an increased resistance to typhoid fever and to cholera toxin. Typhoid fever is caused by Salmonella typhi, which relies on the CFTR protein to enter human cells, and suggests that CFTR gene carriers may be resistant to typhoid fever. Researchers propose that these findings may explain the high rate of individuals within the population who are heterozygotes.
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