On the Molecular Basis of Cystic Fibrosis: The Criticality of the Position of Phenylalanine-508 in the Cystic Fibrosis Transmembrane Conductance Regulator

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Cystic fibrosis (CF) is a life-threatening genetic disease that causes breathing and digestion problems in those who inherit it. The most common type of CF is caused by the deletion of a phenylalanine (also known as ΔF508) in CFTR proteins, which transport chloride ions across the cell membrane. However, the mechanism by which ΔF508 CFTR proteins cause cystic fibrosis is still unknown, so there is no cure for this disease. This investigation tested the importance of phenylalanine's position in CFTR to the molecule's function. By measuring the chloride current running through CFTR with different types of mutations, we were able to determine that the misplacement of phenylalanine in CFTR is not the direct cause of CF; rather, any amino acid deletion in that area will cause similar trafficking and gating defects. Thus, when developing drugs to treat CFTR, one could target the specific amino acid deletions; however, our results show that it could be more efficient to focus on correcting the overall structure of the protein, and thus be able to treat multiple mutations.