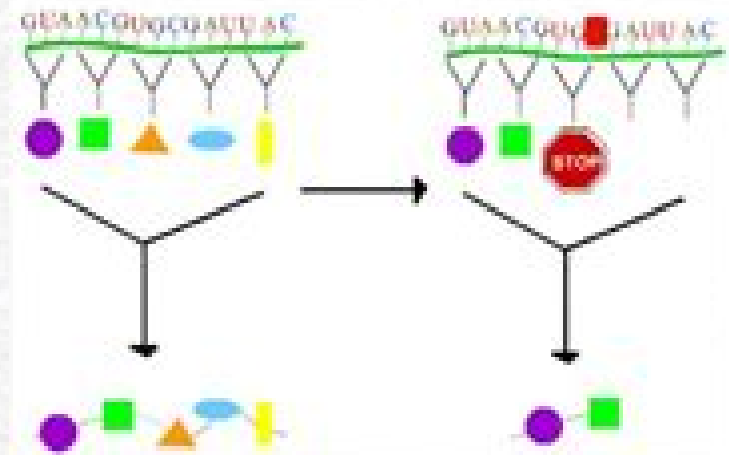


Nonsense vs. Missense Mutations

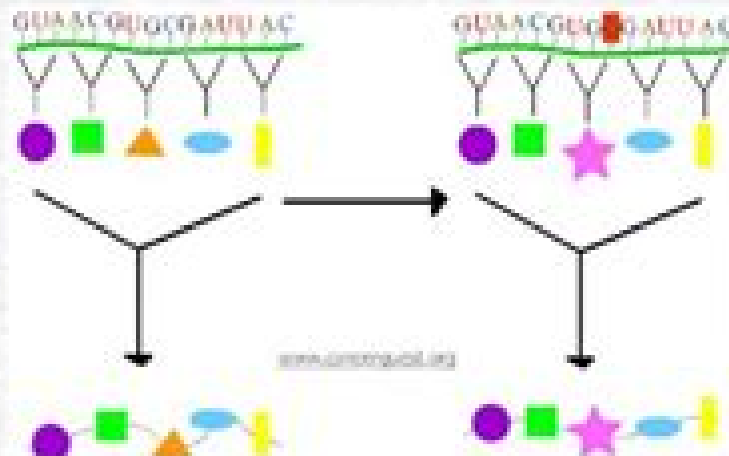
NONSENSE

- The new codon causes the protein to prematurely terminate, producing a product that is shortened and often does not function.



MISSENSE

- The new codon causes an incorrect amino acid to be inserted into the protein. The effects on the function of the protein depend on what is inserted in place of the normal amino acid.



Nonsense And Missense Mutation Pogil

A Gutmann



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Nonsense Mutation Correction in Human Diseases Fabrice Lejeune, Hana Benhabiles, Jieshuang Jia, 2016-02-26 Nonsense Mutation Correction in Human Diseases An Approach for Targeted Medicine provides an introduction on genetic diseases discusses the prevalence of nonsense mutations the consequences of a nonsense mutation for the expression of the mutant gene and the presentation of the nonsense mediated mRNA decay NMD It presents the mechanism of action and rationale associated with each strategy to correct nonsense mutations with the results of clinical trials to further support this basis In addition the book shows how it may be possible to combine several of these strategies to ultimately improve the efficiency of correction also suggesting the future goals and objectives to improve treatment modalities in this evolving sphere of personalized medicine Features basic biological and clinical constructs that inform the application of genomic data to clinical decision making Includes theories and methods that can be used to link bio molecular and clinical phenotypes so as to enable integrative hypothesis discovery testing and downstream evidence based practice Provides design patterns and use cases that contextualize the clinical decision making and evidence based practice relative to real world requirements and stakeholders

Study of Molecules with Nonsense Mutation Correction Capacity Jieshuang Jia, 2015 Nonsense mutations represent approximately 10% of mutations found in the inherited genetic diseases mRNAs harboring a nonsense mutation are rapidly degraded by a quality control mechanism called nonsense mediated mRNA decay NMD to prevent the synthesis of toxic or nonfunctional truncated proteins Some strategies have been developed to correct nonsense mutations In our lab we study 2 of them which are i the NMD inhibition and ii the PTC readthrough activation which is a mechanism leading to the incorporation of an amino acid at the PTC position To design new therapeutic tools for the inherited genetic diseases our lab tested molecules by screening to find ones with the capacity of NMD inhibition For each molecule selected in the screen we measure the efficiency of NMD inhibition and PTC readthrough activation of these molecules in cell lines harboring a nonsense mutation We have shown that amlexanox not only inhibits NMD but also activates PTC readthrough But the efficacy of amlexanox is still low We wanted to find other families of molecules capable of rescuing the expression of nonsense mutation containing mRNA with a higher efficacy or with some specificity In my study I found two special families one is the family of apoptosis inducers and the other is the family of cytoskeleton inhibitors I found that apoptosis inducers can inhibit NMD by activating caspase pathway and cleave NMD factors UPF1 and UPF2 I also found that cytoskeleton inhibitors can inhibit NMD and some of them can activate PTC readthrough by inducing NMD factors UPF1 or and UPF3X to concentrate in P bodies or in other cytoplasmic foci The efficiencies of these molecules on NMD inhibition are similar or higher than amlexanox Apoptosis inducers and cytoskeleton inhibitors demonstrated that molecules which can inhibit NMD or and activate PTC readthrough can be found and can demonstrate a higher correction of nonsense mutation efficiency than the existing molecules ataluren or amlexanox for example

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