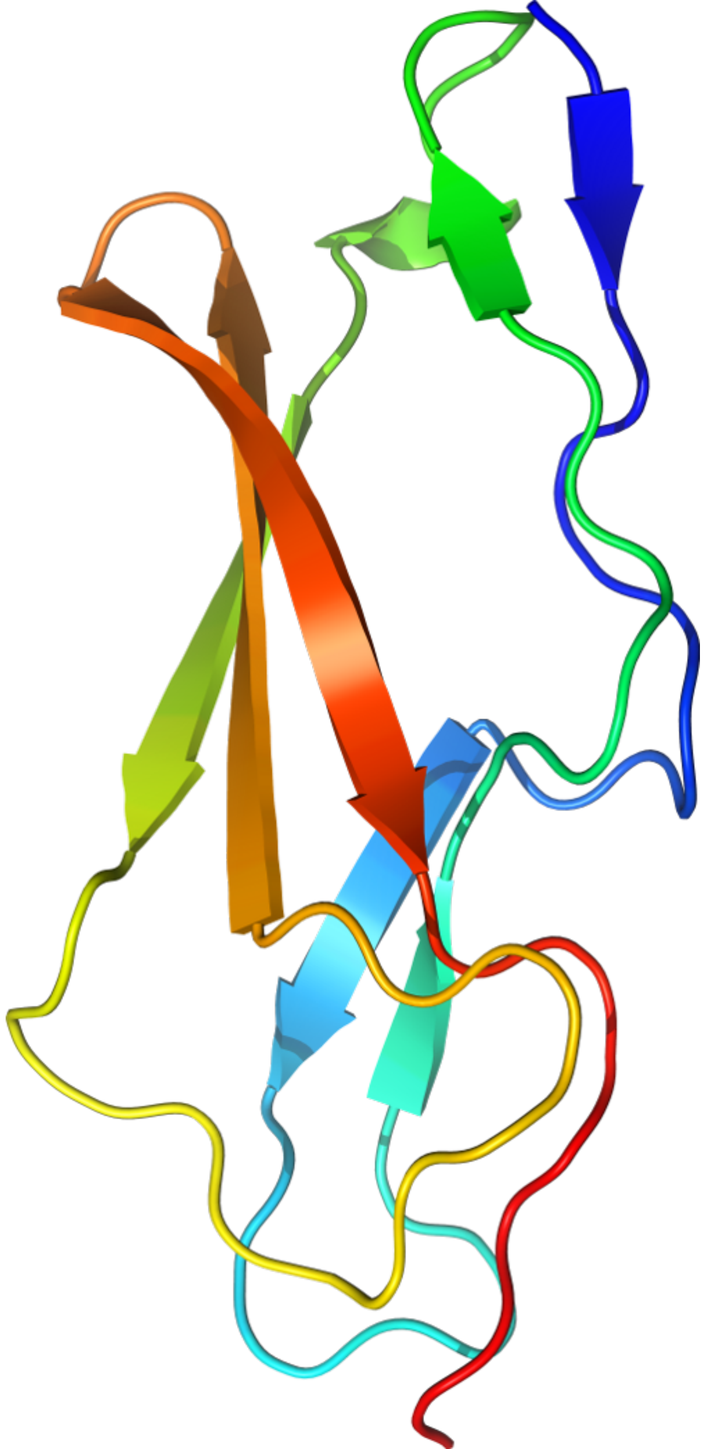
Genetik Mutasyon - Hastalık İlişkisinin Biyoinformatik Analizi

Bioinformatic Analysis of Genetic mutation - Disease Association

Biyomedikal Anabilim Dalı

Yüksek Lisans - Seminer

Danışman: Doç. Dr. Esma ERYILMAZ DOĞAN



Doğukan Sahil - 2025

Genetik Mutasyon - Hastalık İlişkisinin Biyoinformatik Analizi

1. PROTEİN SENTEZ SÜRECİ VE GENEL ÖZELLİKLERİ

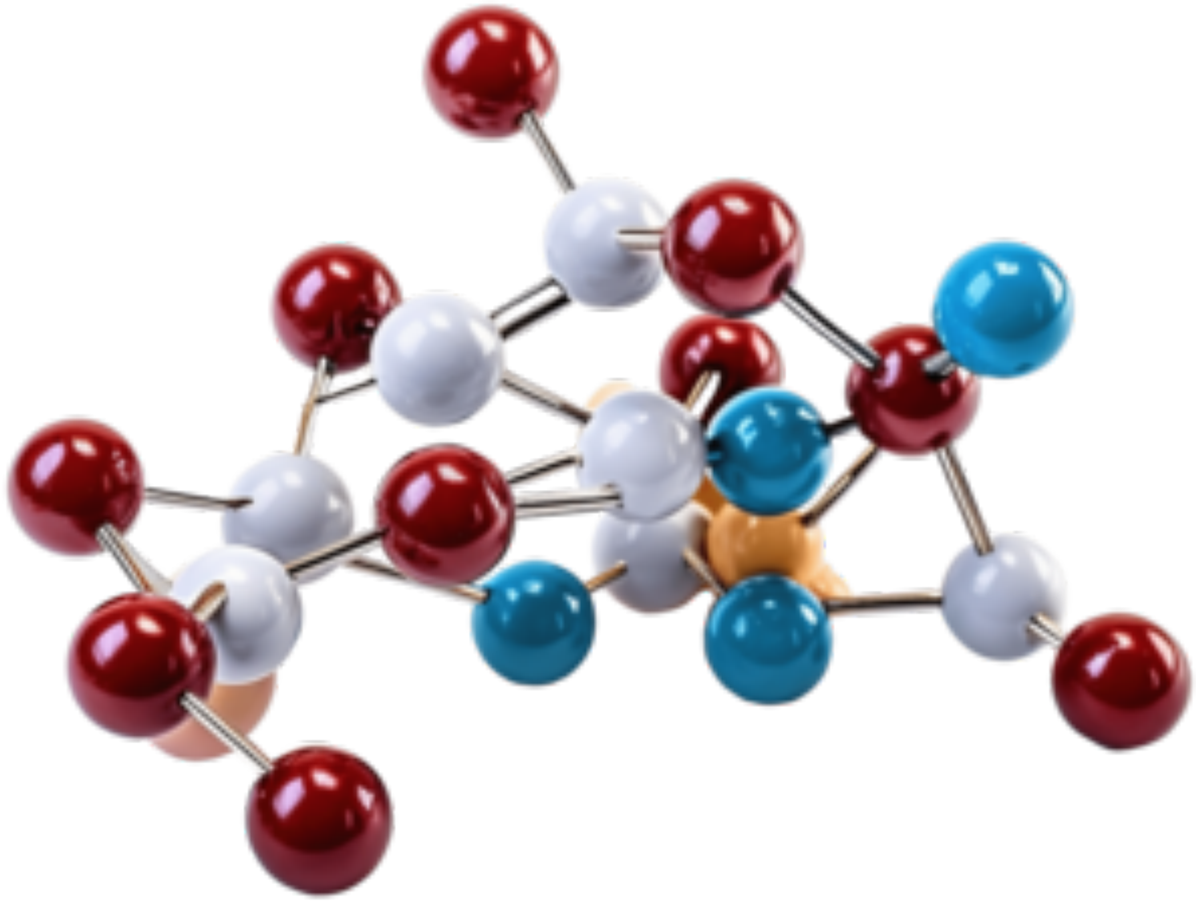
2.MUTASYON TÜRLERİ

3.BİYOINFORMATİK ANALİZ VE LİTERATÜR TARAMASI

4.HASTALIKLARLA İLİŞKİSİ & GELECEK ÖNERİLERİ

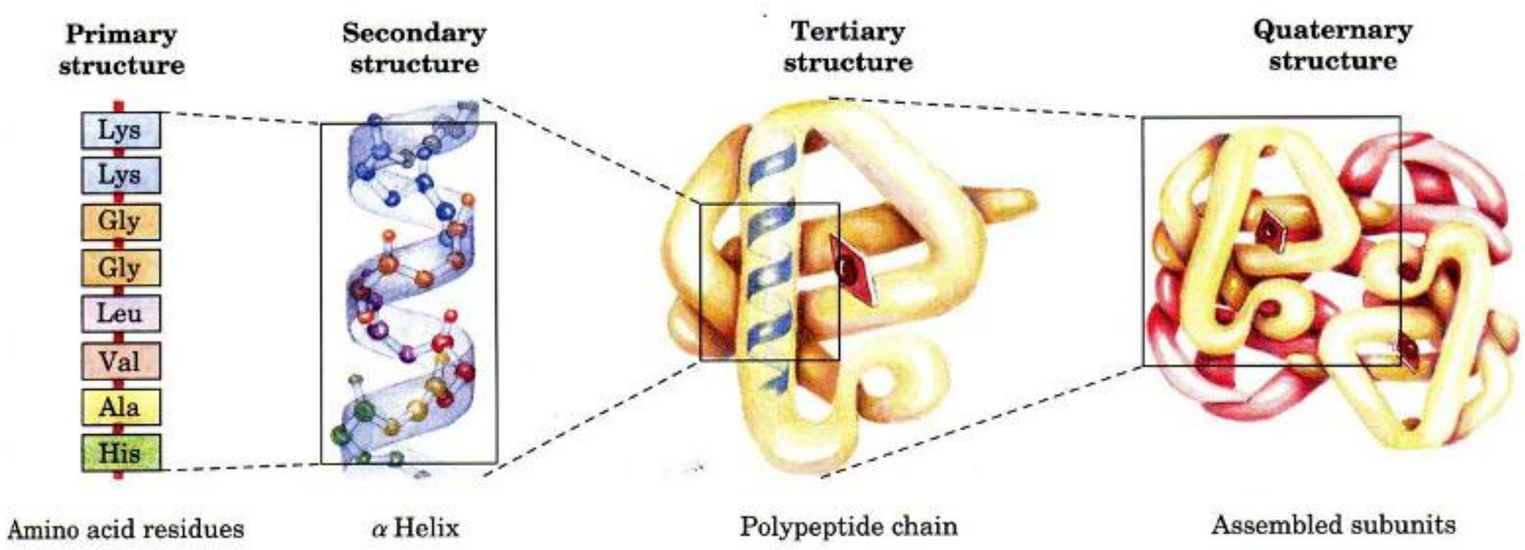
1. PROTEİN YAPILARININ GENEL ÖZELLİKLERİ

- Spesifik **Yapı-Fonksiyon** İlişkisi
- **Amino Asit** Dizisine Göre Belirlenir
- **Genetik Kod** ile Doğrudan İlişkilidir

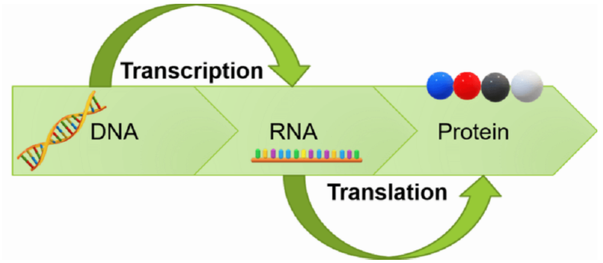


Protein Organizasyonunun Seviyeleri

- **Birincil** Yapı (Aminoasit dizisi)
- **İkincil** Yapı (Yerel katlanma)
- **Üçüncül** Yapı (3 boyutlu şekil başlangıcı)
- **Dördüncül** Yapı (Birden fazla protein dizisinin bir araya geldiği)

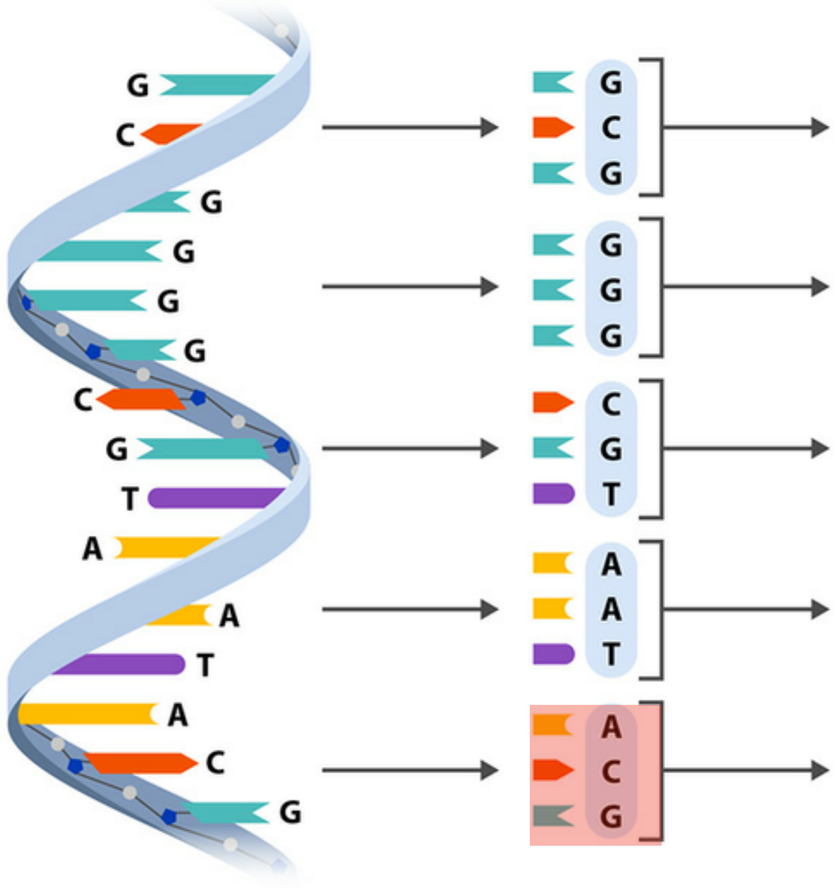


PROTEİN SENTEZİ

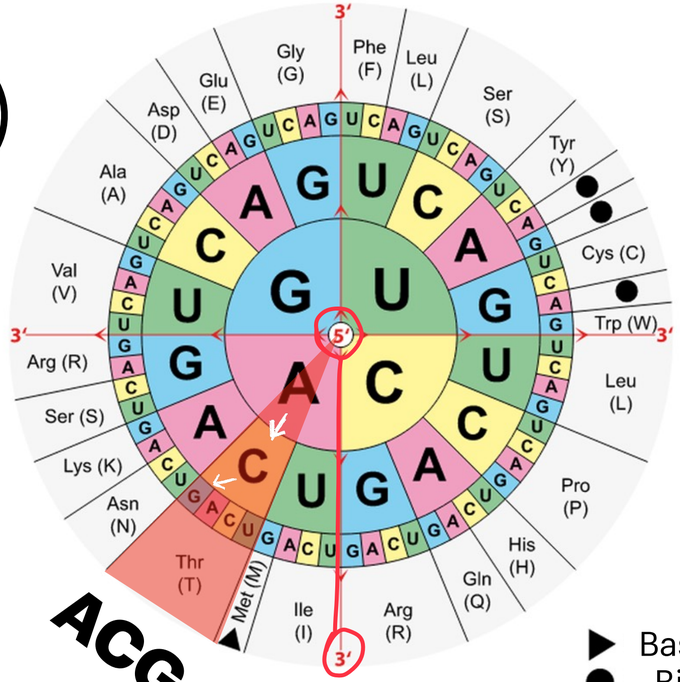


1

DNA



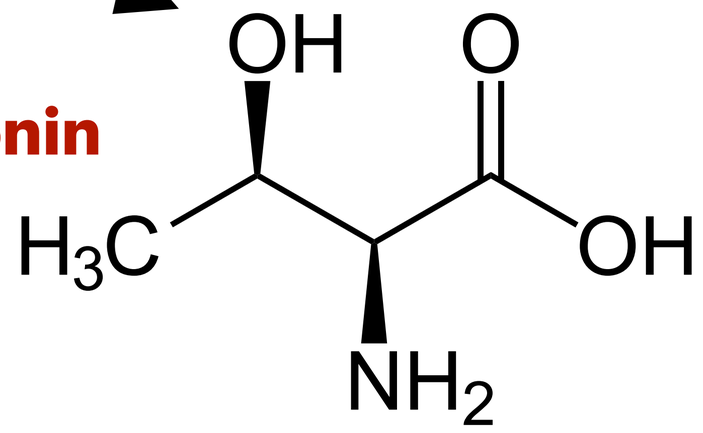
2

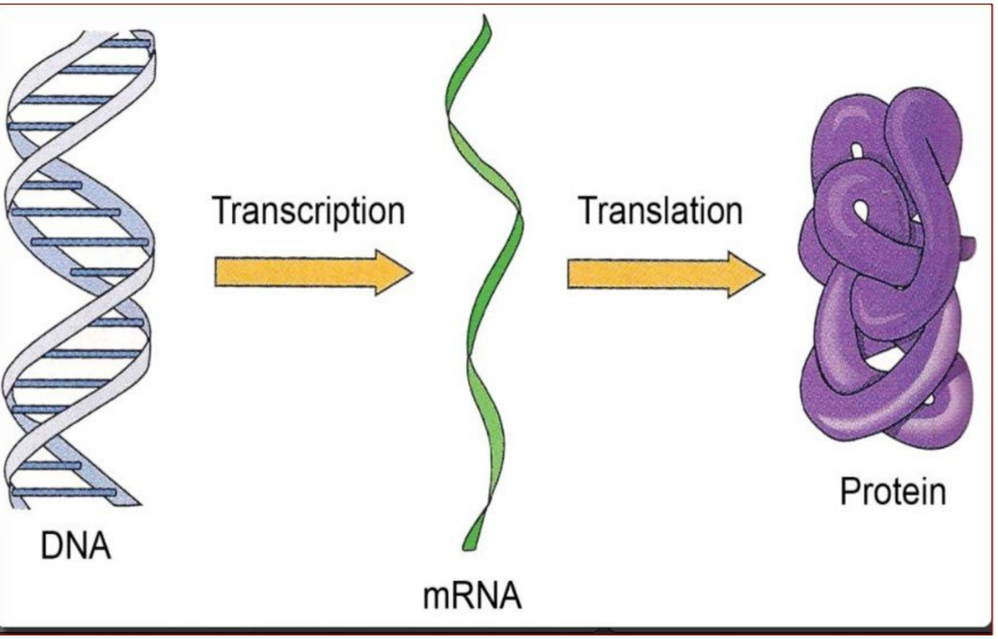


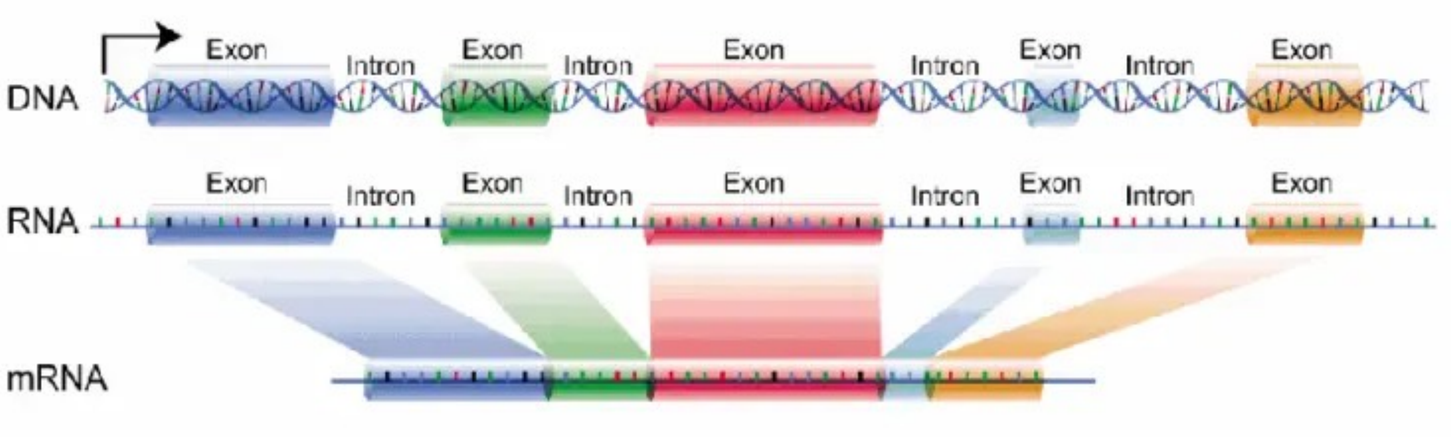
ACG

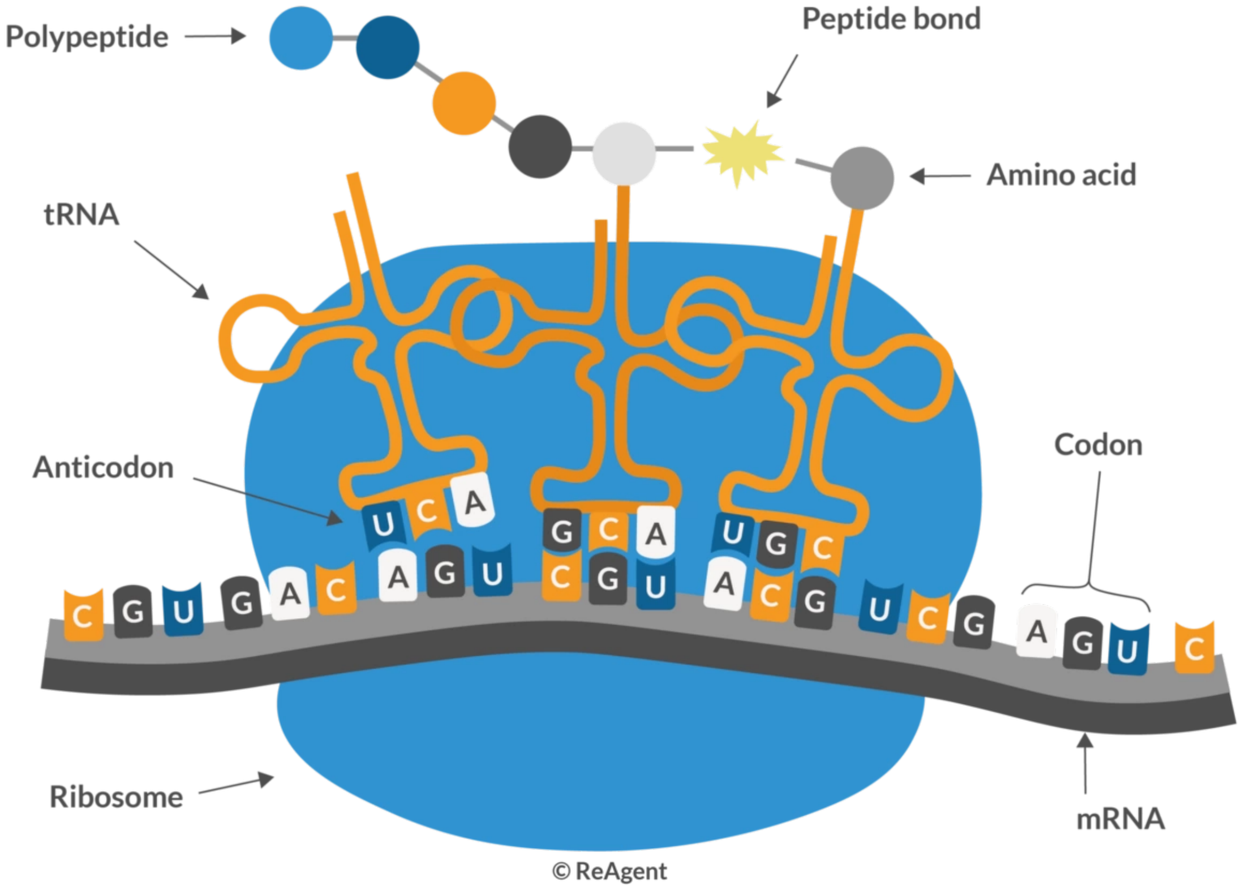
3

Treonin




Transcription
Translation
DNA
mRNA
Protein


DNA
RNA
mRNA
Exon
Intron
Exon
Intron
Exon
Intron
Exon
Intron
Exon

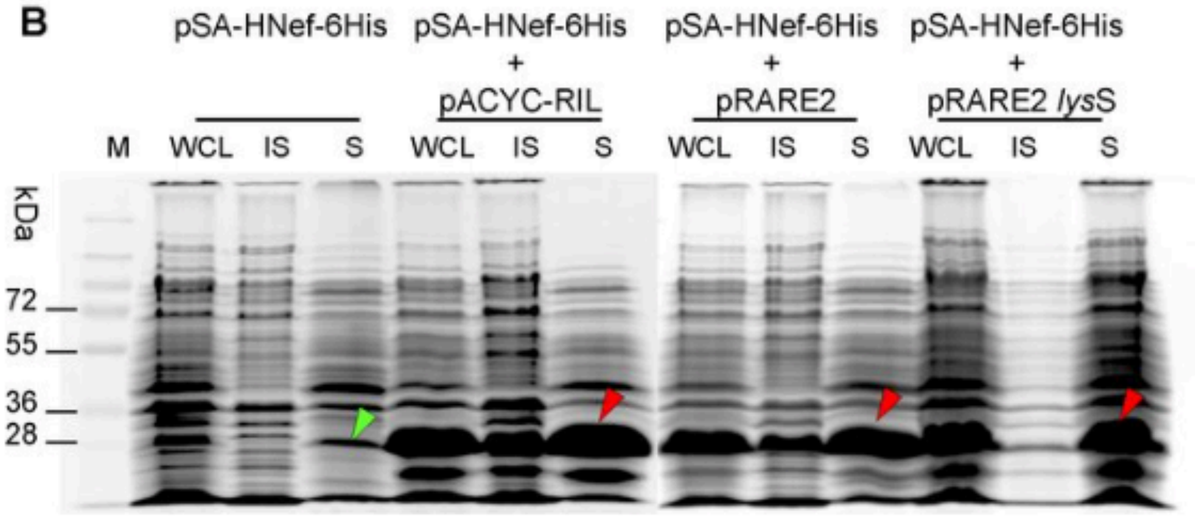


A

Amino acid	Rare codon(s)	Amino acid position in Nef ORF
Arginine (Arg)	AGG	17,184
	AGA	19, 21,77,105,106,134,178
	CGA	22, 35,196
Leucine (Leu)	CTA	37,58,100,145,189
Isoleucine (Ile)	ATA	-
Proline (Pro)	CCC	-

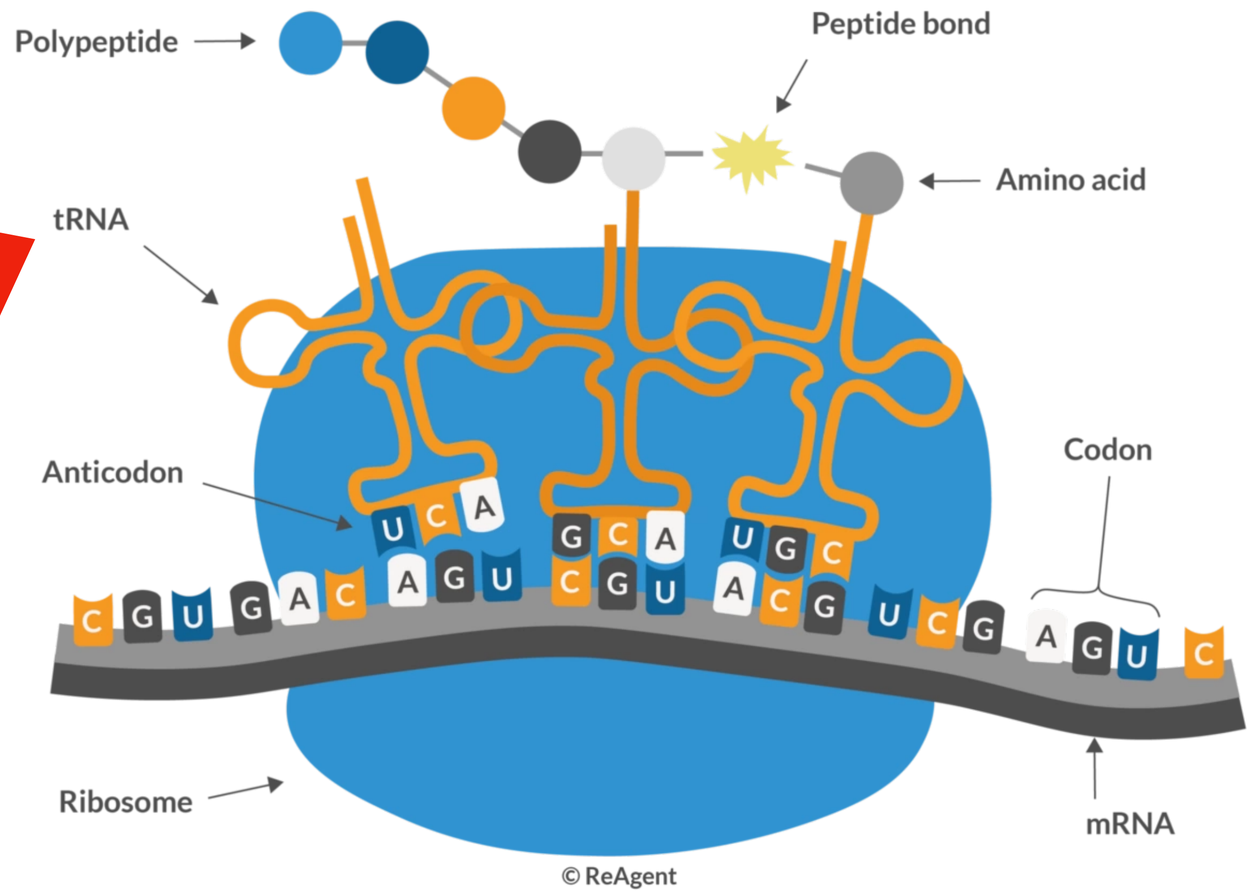
*Tandem rare Arg codon double repeats = **2** (22, 106)

B



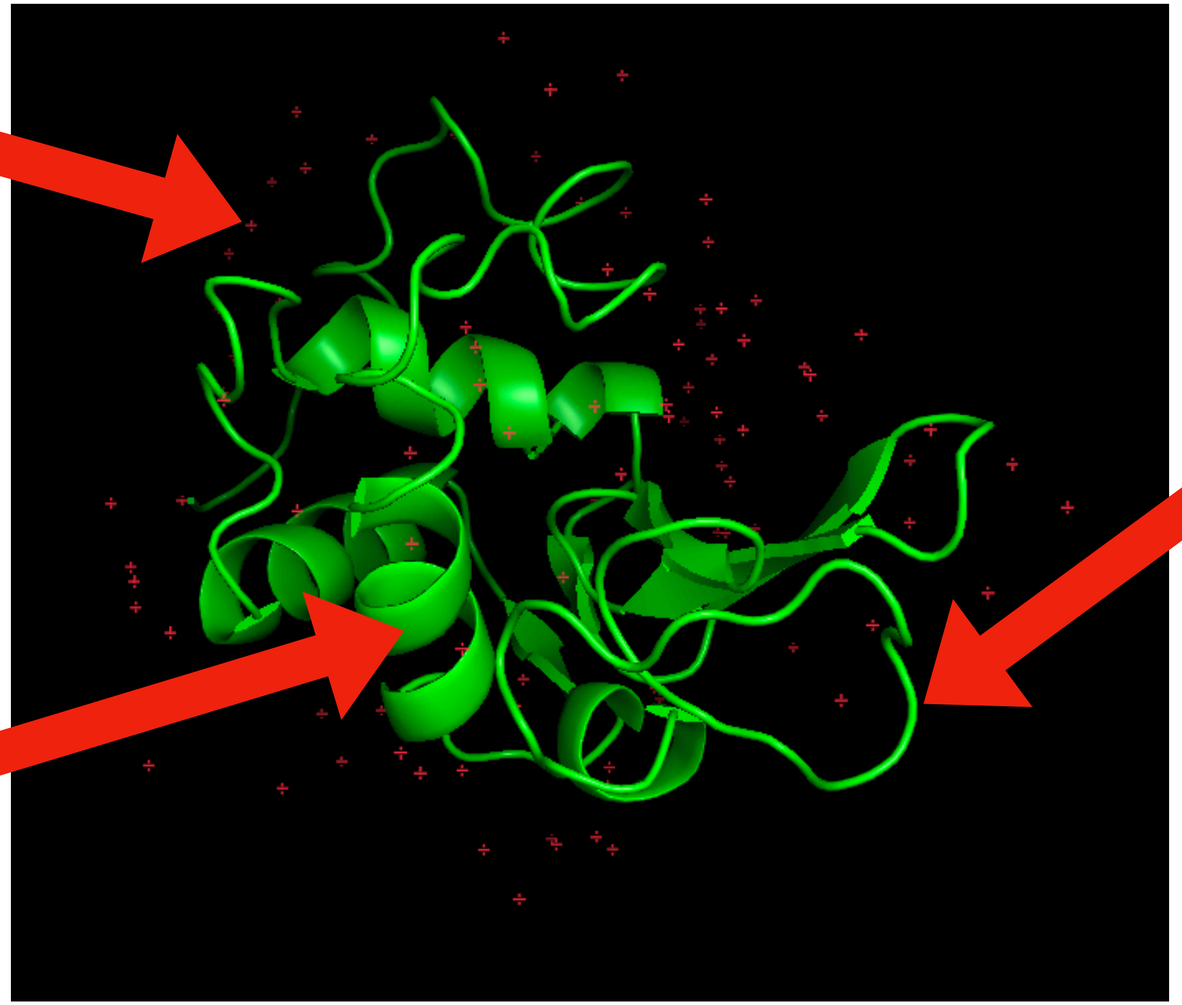
Protein Katlanması

- **73-93 tRNA**
- Polipeptit -> Protein
  - Stabilizasyon;
  - Sıcaklık (-H bağları)
  - Hidrofobik etkileşimler
  - pH değişikliği



Protein Yapısı

Hidrojen Bağı Alıcıları



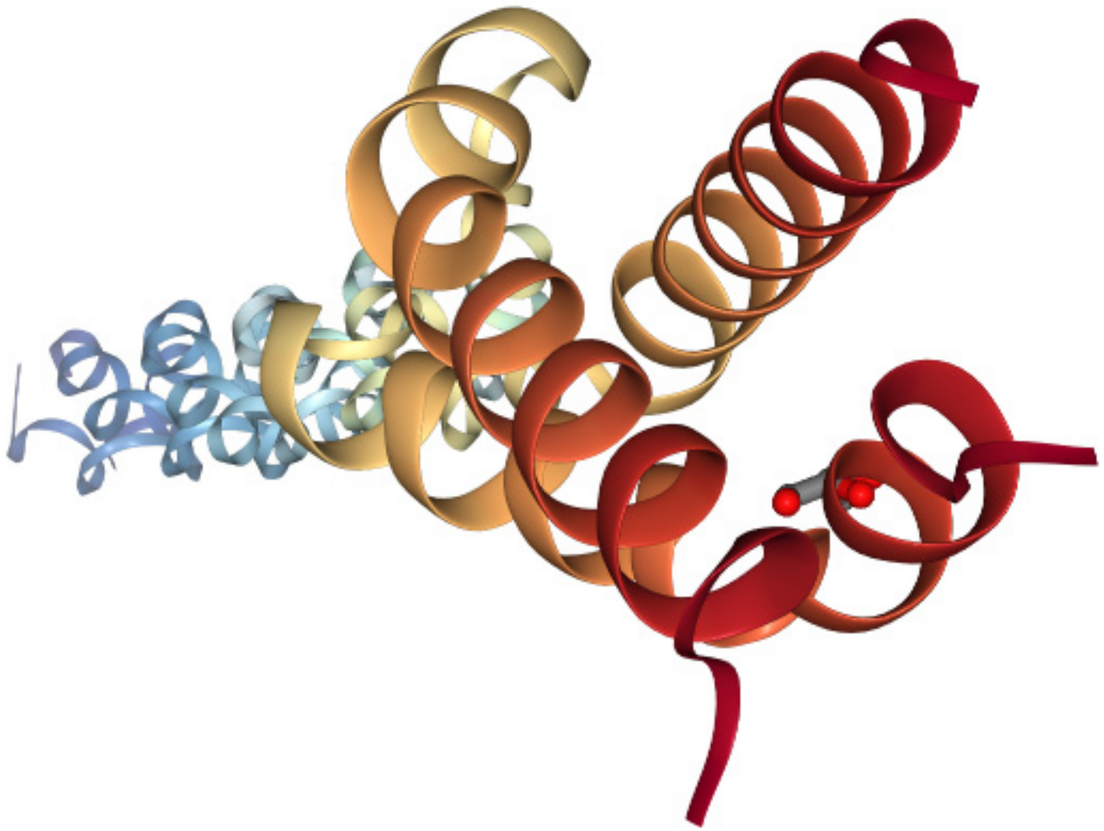
Loops (Bağlantı Çizgileri)

Alfa Heliks

1LYZ proteini https://www.rcsb.org/3d-view/jsmol/1lyz/0

https://www.sciencedirect.com/science/article/abs/pii/S0022283613004464

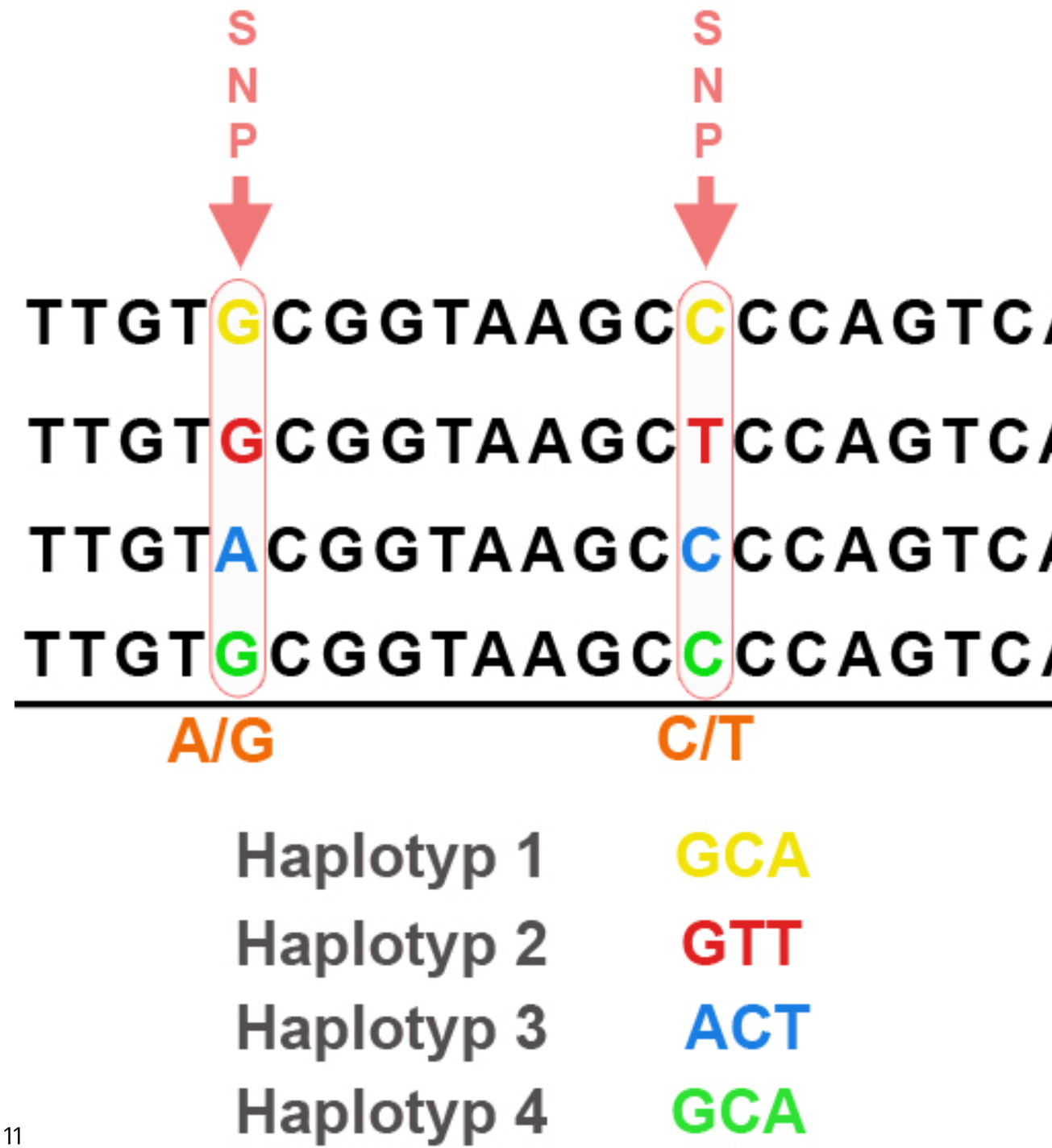
2. MUTASYON TÜRLERİ



SNP

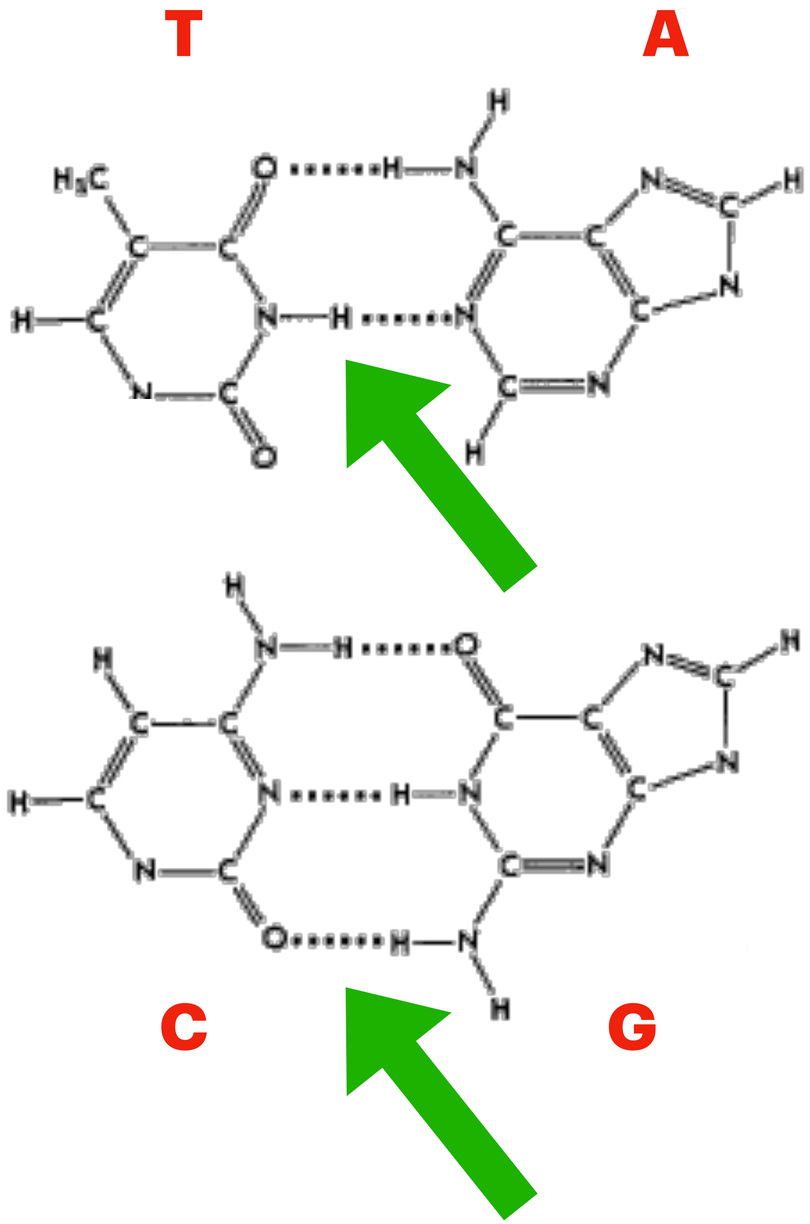
Tek Nükleotid Polimorfizmi

- %1>
- İki insan arasında benzerlik %99,9 olmasına rağmen SNP 30 - 300 milyon vardır.
- Her **SNP** ayrıca **SNV**'dir.



Esnek**, az stabil**

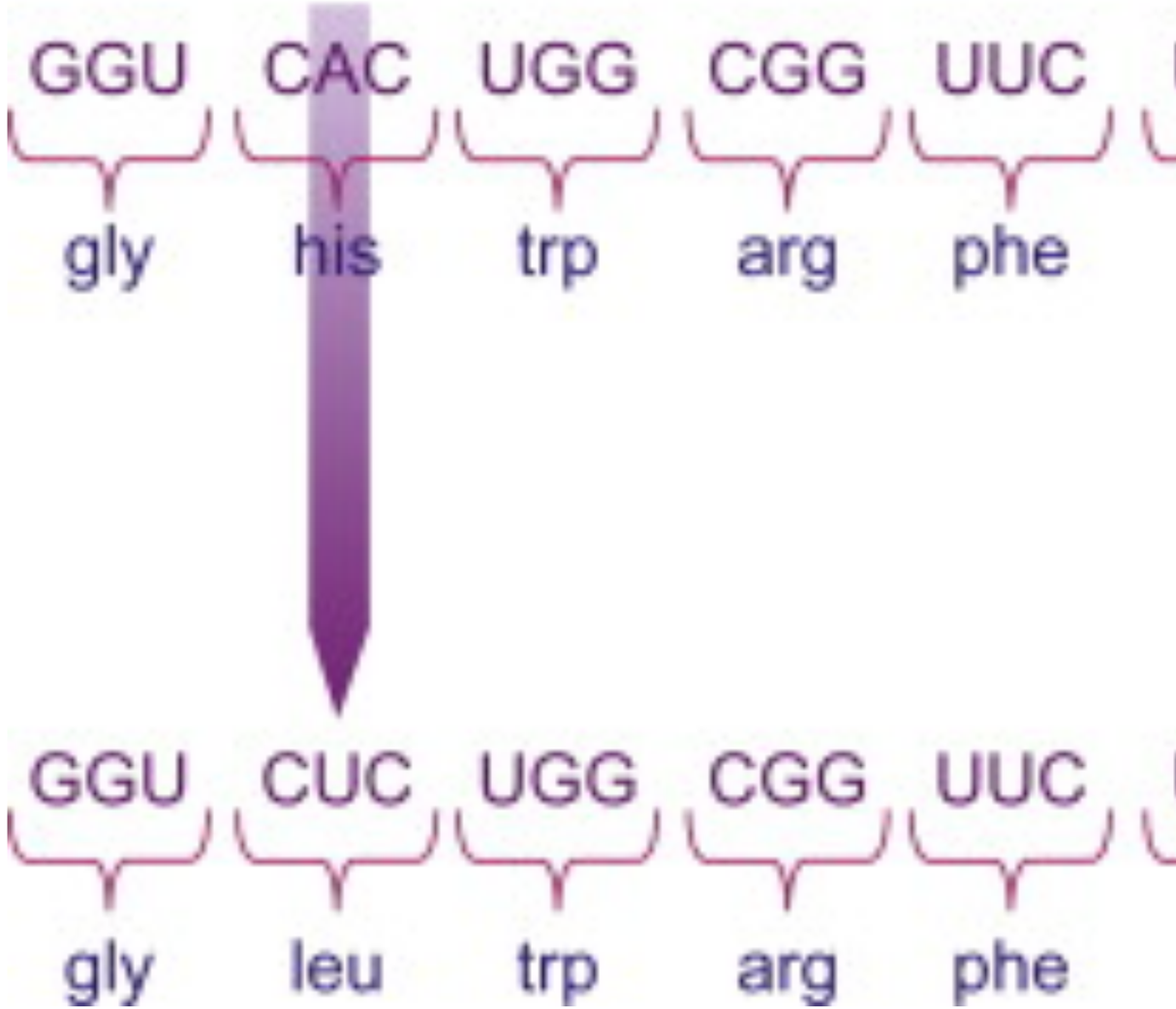
Sert, stabil



Missense Mutation

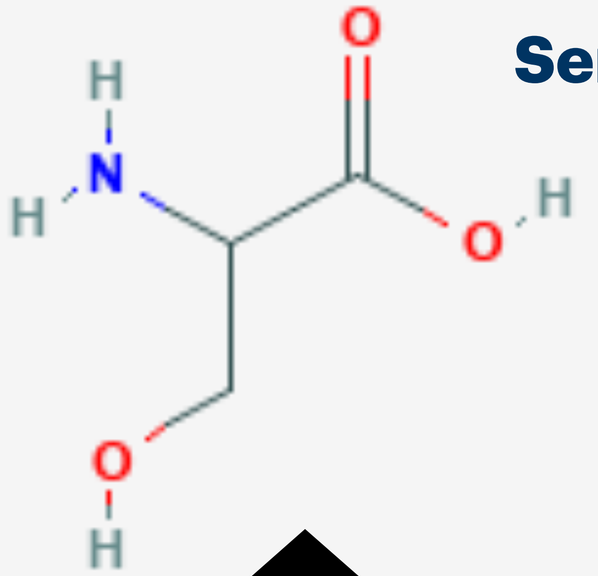
Yanlış Anlamlı Mutasyon

- Aminoasit değişmesine sebep olur.
- Proteinin yapısı, stabilitesi veya fonksiyonunu da değiştirebilir.
- Hastalıklarla doğrudan ilişkili.

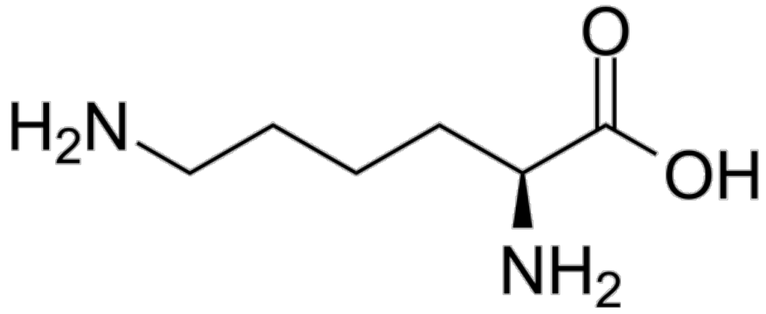


https://pmc.ncbi.nlm.nih.gov/articles/PMC3346971/

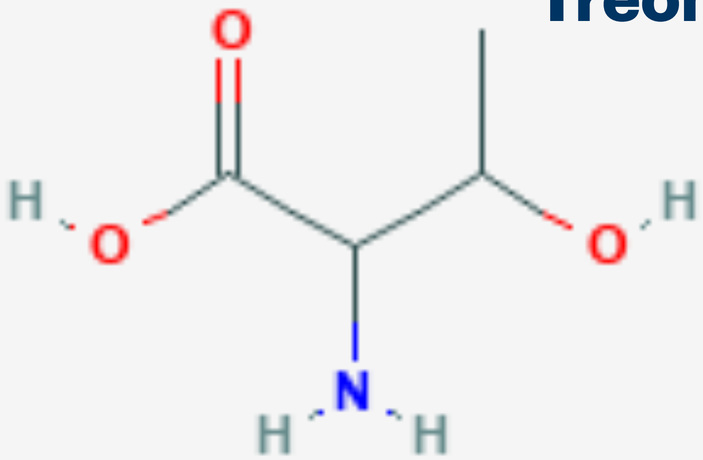
Serin



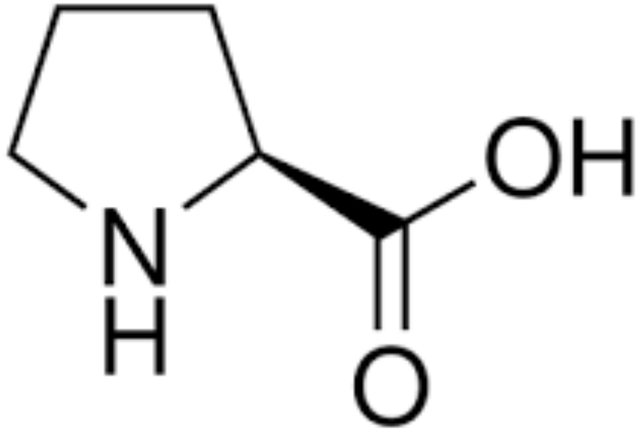
Lizin



Treonin

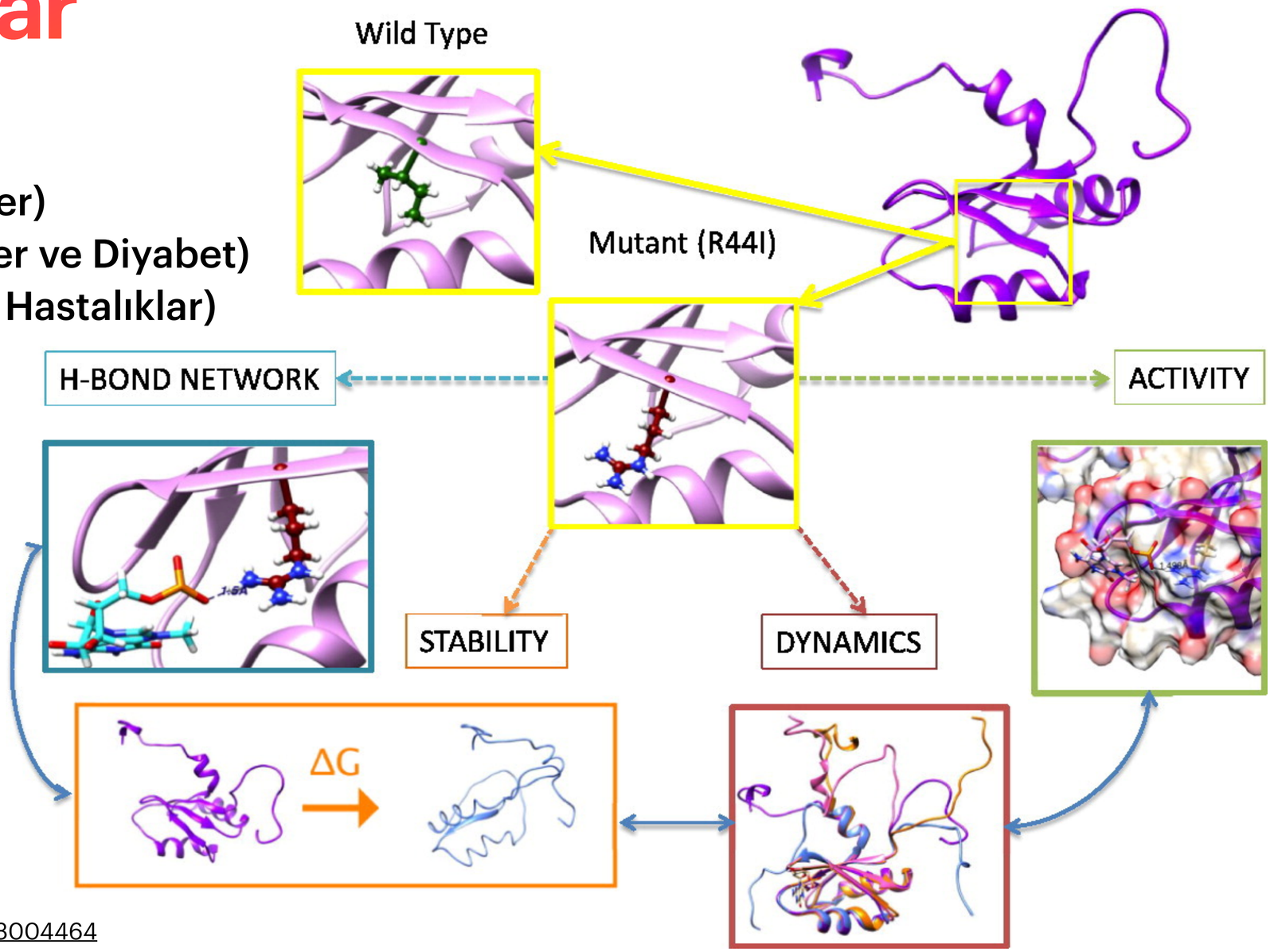


Prolin



Missense İlişkili Hastalıklar

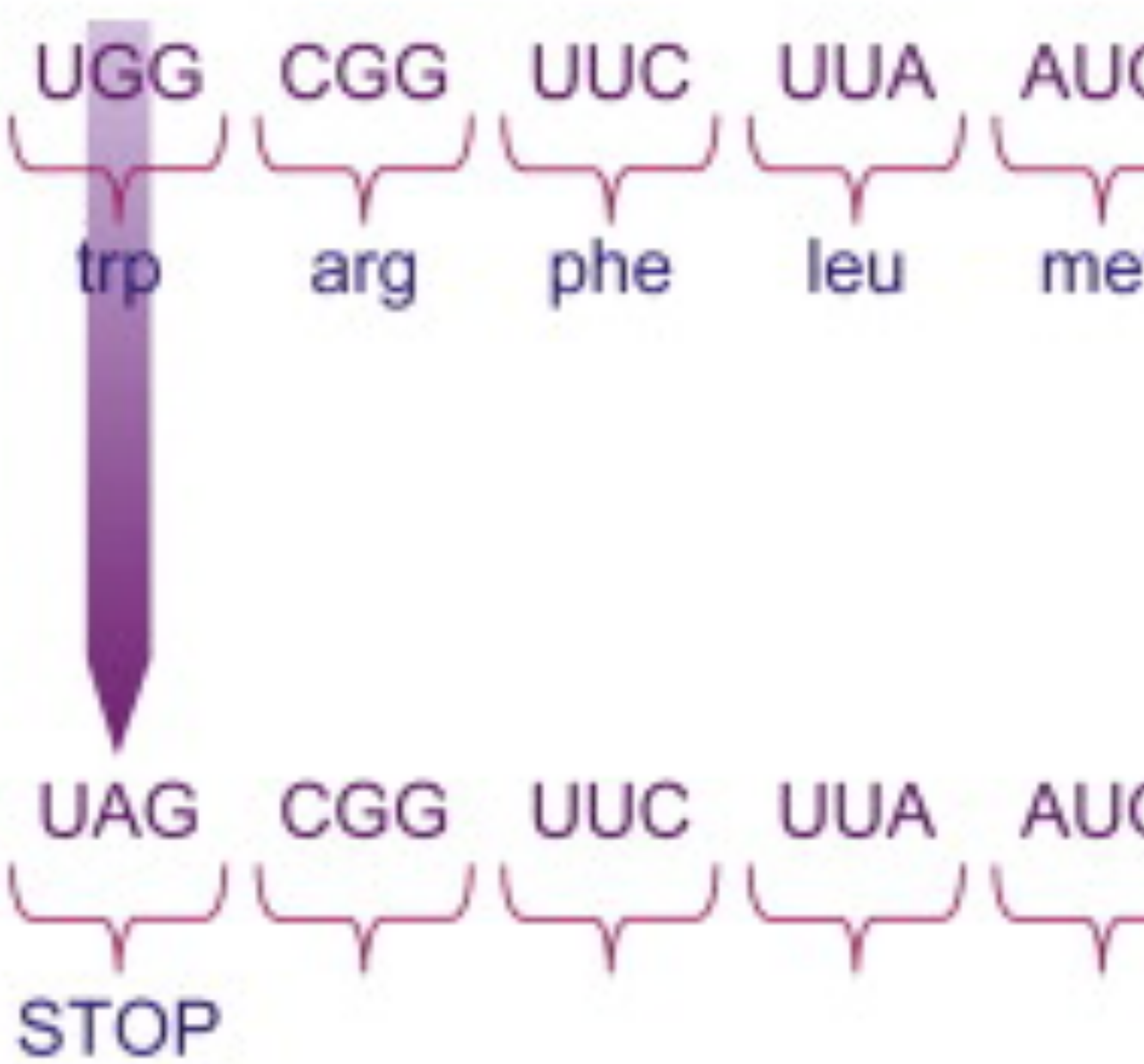
A. Protein **stabilitesi** (KAS)
B. **Hidrojen bağı** değişikliği (Alzheimer)
C. Protein **esnekliği** değişikliği (Kanser ve Diyabet)
D. Protein aktivitesi değişikliği (Nadir Hastalıklar)



https://pmc.ncbi.nlm.nih.gov/articles/PMC3796015/
https://www.sciencedirect.com/science/article/abs/pii/S0022283613004464

Nonsense Mutation

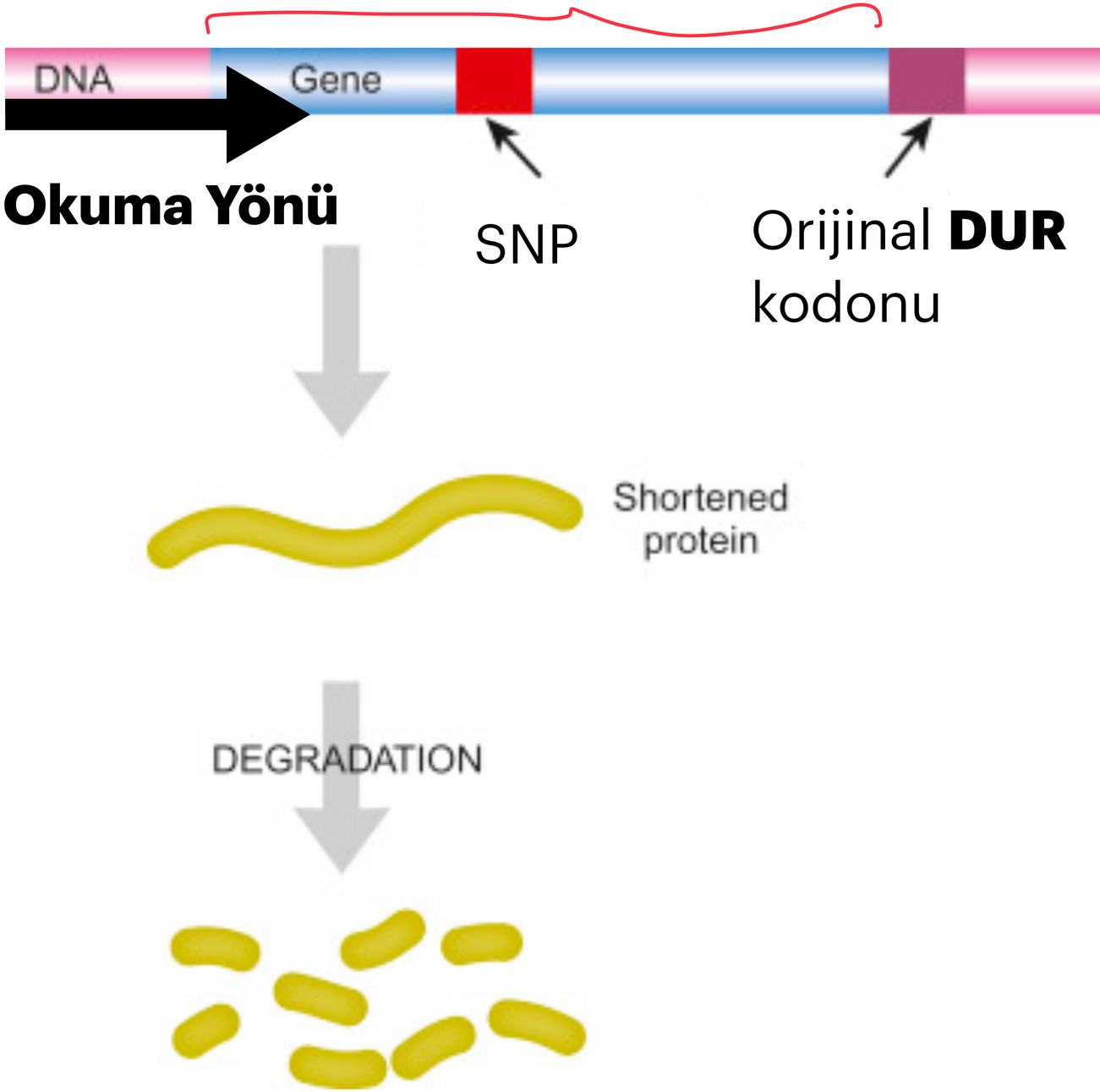
- Durdurma
- İşlevsiz veya eksik protein
- **Readthrough**



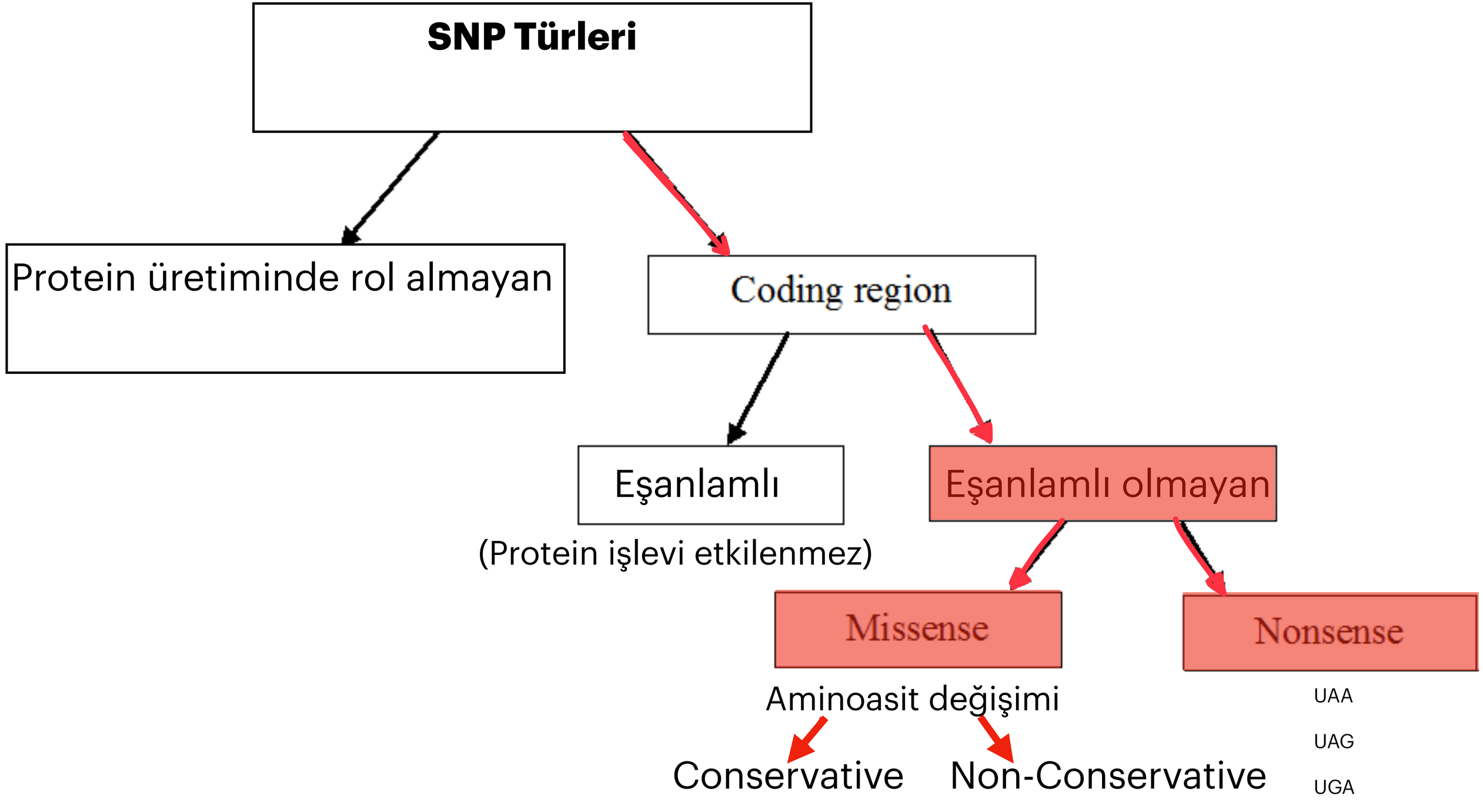
https://pmc.ncbi.nlm.nih.gov/articles/PMC7437896/

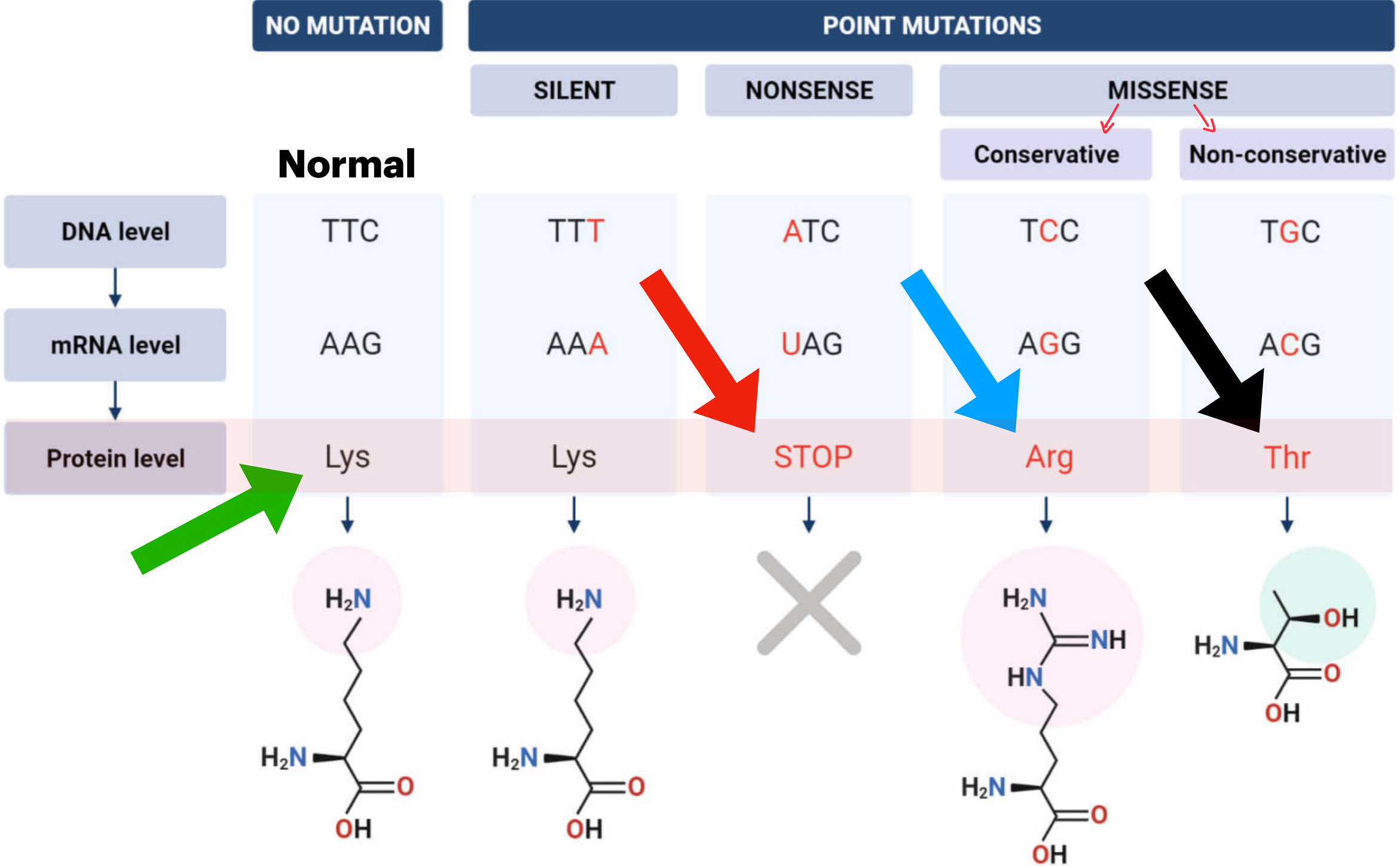
Nonsense İlişkili Hastalıklar

Kas hastalıkları, Görme kayıpları, kistik fibrozis ve kanserler



https://pubmed.ncbi.nlm.nih.gov/18454449/
https://pmc.ncbi.nlm.nih.gov/articles/PMC7352488/

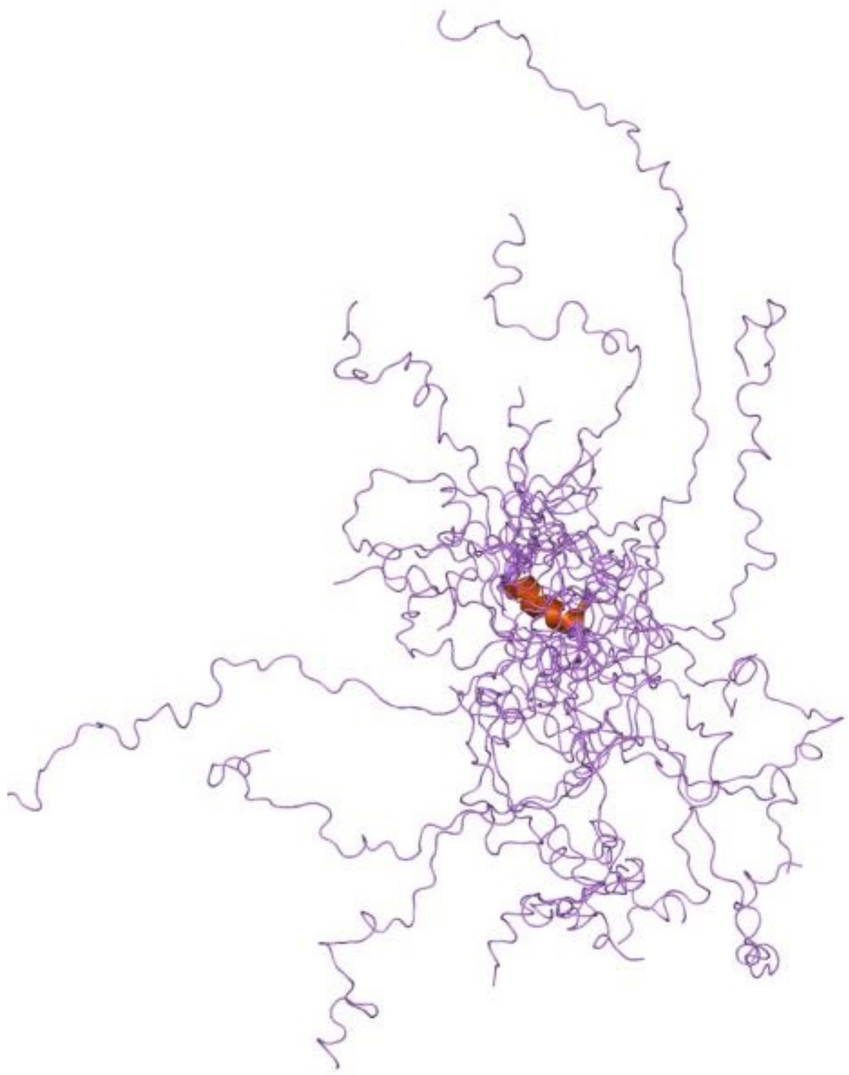

SNP Türleri
Protein üretiminde rol almayan
Coding region
Eşanlamlı
(Protein işlevi etkilenmez)
Eşanlamlı olmayan
Missense
Nonsense
Aminoasit değişimi
Conservative
Non-Conservative
UAA
UAG
UGA


NO MUTATION
POINT MUTATIONS
SILENT
NONSENSE
MISSENSE
Conservative
Non-conservative
Normal
DNA level
mRNA level
Protein level
TTC
AAG
Lys
TTT
AAA
Lys
ATC
UAG
STOP
TCC
AGG
Arg
TGC
ACG
Thr

Tür	Amino Asit Özellikleri	Örnek Değişim	Etkisi	Protein Yapısı ve İşlevine Etkisi	Klinik Örnek
Conservative	- Yeni amino asit, orijinaline benzer özellikler taşır (yük, polarite, hidrofobiklik).	Serin → Treonin	- Protein fonksiyonu büyük oranda korunur.	- Protein yapısı korunur. - Genelde stabil kalır ve katlanma bozulmaz.	**- Genelde klinik sonuçlar yaratmaz.**
Non-Conservative	- Yeni amino asit, orijinaline farklı özellikler taşır (yük, polarite, hidrofobiklik).	Lizin → Prolin	- Protein fonksiyonunu bozabilir.	- Protein yapısı ve katlanması değişir. - Biyolojik aktivite kaybı olabilir.	**- Klinik sonuçlar bekleniyor.**

Intrinsically Disordered Region (IDR) ve Mutasyon Hassasiyeti

- IDR, proteinin katlanmamış, esnek ve yapısız bölgeleridir.
- Bu bölgeler genellikle bağlanma, sinyal iletimi ve modifikasyon noktaları içerir.
- Missense mutasyonlar, IDR’nin işlevini bozarak bağlanma kaybı veya yeni etkileşimler oluşturabilir.



3. BİYOINFORMATİK ANALİZ VE LİTERATÜR TARAMASI

- NCBI
- UniProt

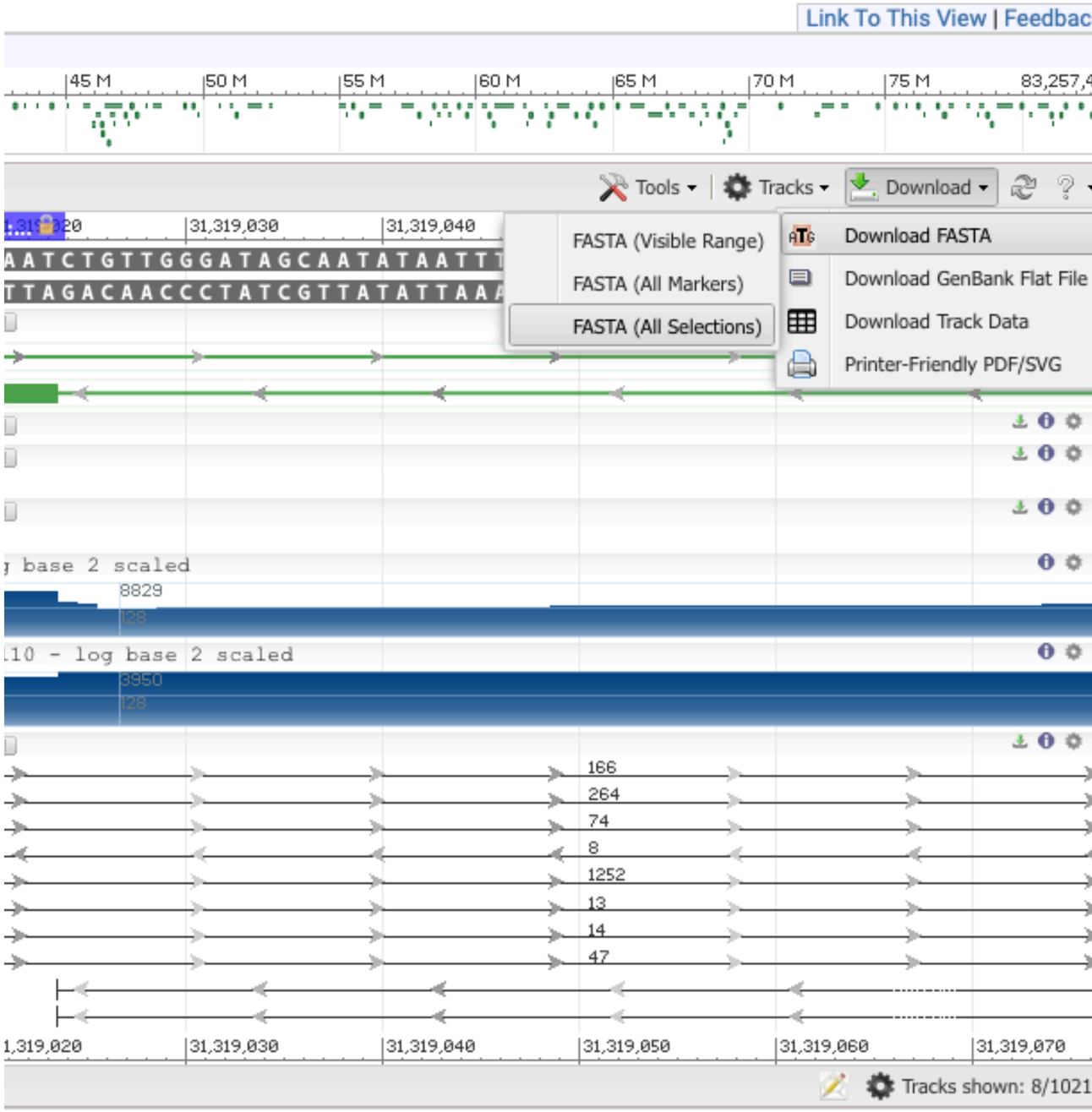
Protein Veritabanları

- UniProt
- RefSeq
- KEGG

- DisProt, yapıdan yoksun (intrinsically disordered) protein bölgelerini tanımlayan bir biyoinformatik veritabanıdır.
- Bu bölgeler klasik yapısal biyolojide göz ardı edilse de, sinyal iletimi, bağlanma ve regülasyon gibi fonksiyonlarda kritik rol oynarlar.
- Mutasyonlar, bu disordered bölgelerin işlevini değiştirebilir; DisProt bu etkilerin analizine katkı sağlar.

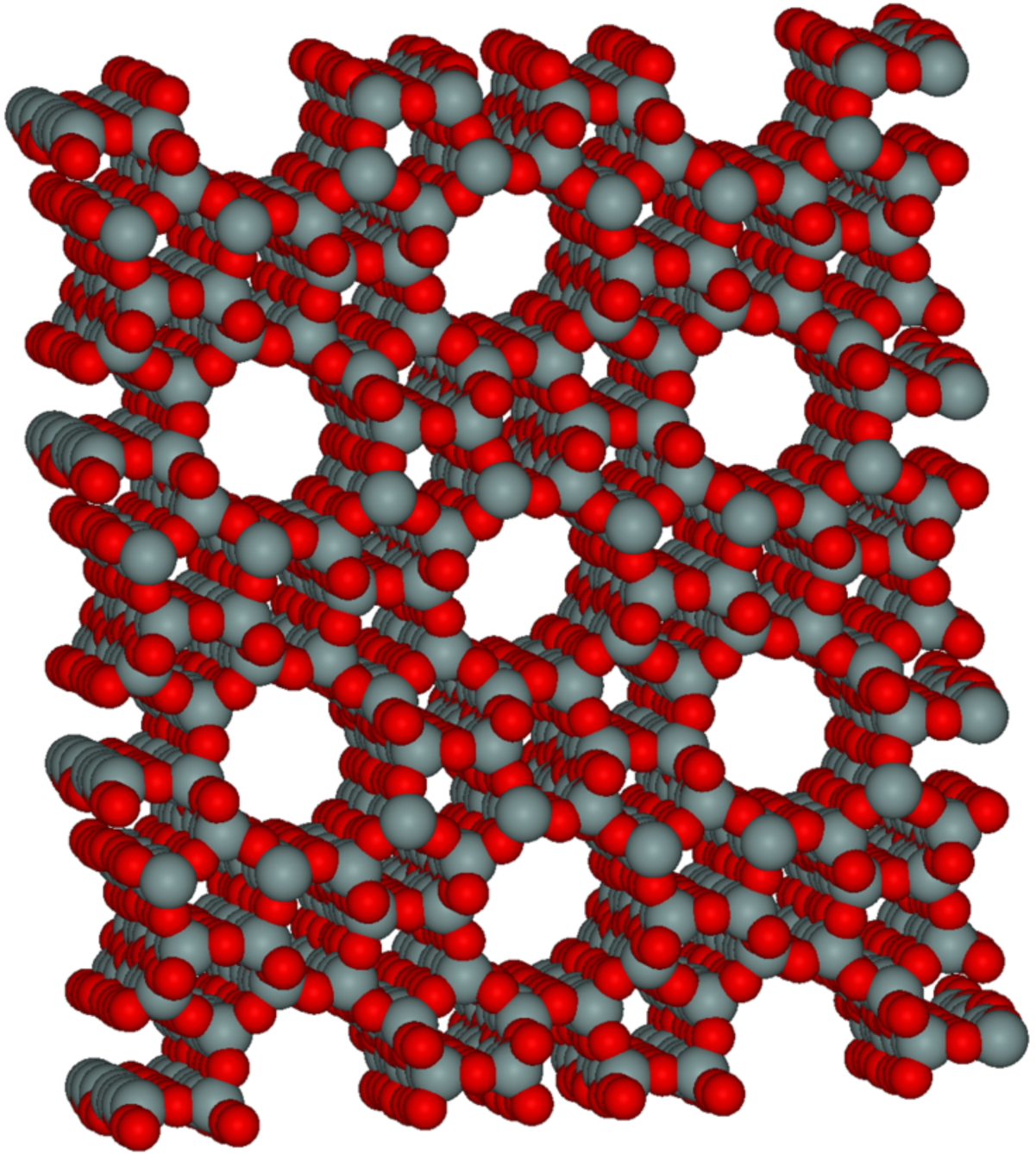
FASTA

- Metin belgesi
- A(U),T,G,C'den oluşur
- DNA/RNA veya Protein



X-Ray Kristalografi ve Yetersizlikleri

- Kristalleşme zorunluluğu
- Statik yapı gösterir
- Fizyolojik koşullardan sapmalar



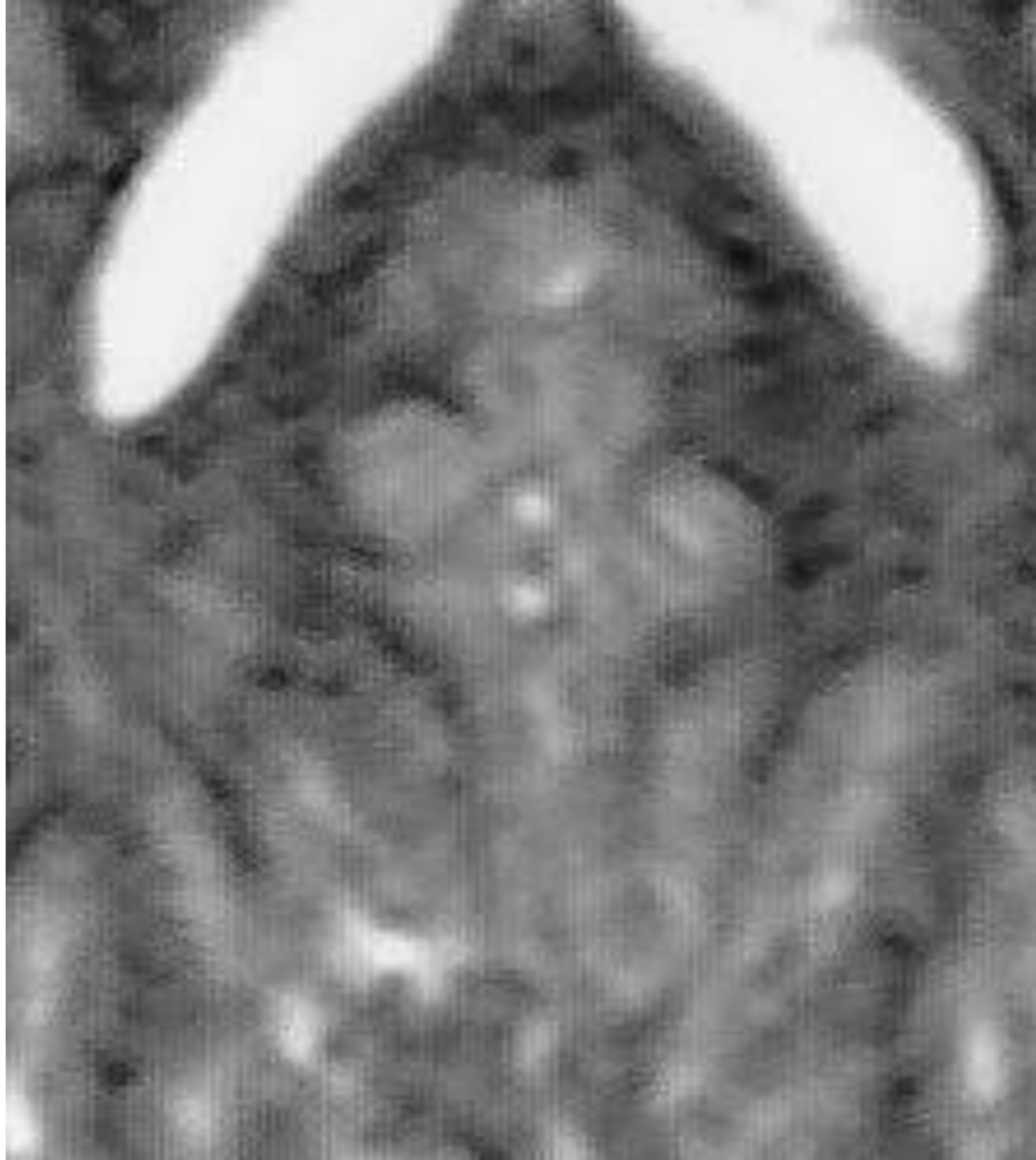
NMR (Nükleer Manyetik Rezonans) Spektroskopisi

- Dinamik yapı analizi yapabilir
- Kristalleşme gerekmez
- Disordered bölgeleri gözlemleyebilir

4. HASTALIKLARLA İLİŞKİSİ & GELECEK ÖNERİLERİ

- **2020 yılında yayınlanan "How many rare diseases are there?" adlı çalışmaya göre;** +10.000 üzerinde nadir hastalık tanısı konmuştur.
- Nadir hastalık; AB'de 2.000 kişide 1'den az, ABD'de ise 200.000'den az kişiyi etkileyen.
- *Riboz 5 Fosfat İzomeraz Eksikliği*

https://pmc.ncbi.nlm.nih.gov/articles/PMC7771654/
https://pmc.ncbi.nlm.nih.gov/articles/PMC6174191/
https://pmc.ncbi.nlm.nih.gov/articles/PMC1181951/



View PDF Download full issue

Outline

Show full outline

jmb Journal of Molecular Biology
Volume 436, Issue 14, 15 July 2024, 168384

Review Article

Translation Rates and Protein Folding

Anton A. Komar [1 2], Ekaterina Samatova [3], Marina V. Rodnina [3]

Show more

Add to Mendeley Share Cite

https://doi.org/10.1016/j.jmb.2023.168384

Get rights and content

Highlights

- Evolutionary adjusted pace of translation is important to maintain correct protein folding

Part of special issue

Proteostasis and Protein Quality Control

Edited by Johannes Buchner

Download full issue

Other articles from this issue

Interplay of Proteostasis Capacity and Protein Aggregation: Implications fo...

15 July 2024

Mark S. Hipp, F. Ulrich Hartl

View PDF

Supersaturation, a Critical Factor Underlying Proteostasis of Amyloid...

15 July 2024

Yuji Goto, ..., Keiichi Yamaguchi

View PDF

https://www.sciencedirect.com/science/article/pii/S0022283623004953

Article | Open access | Published: 03 September 2018

Machine learning identifies interacting genetic variants contributing to breast cancer risk: A case study in Finnish cases and controls

Hamid Behravan ✉, Jaana M. Hartikainen, Maria Tengström, Katri Pylkäs, Robert Winqvist, Veli–Matti Kosma & Arto Mannermaa

Scientific Reports **8**, Article number: 13149 (2018) | Cite this article

Abstract

We propose an effective machine learning approach to identify group of interacting single nucleotide polymorphisms (SNPs), which contribute most to the breast cancer (BC) risk by assuming dependencies among BCAC iCOGS SNPs. We adopt a gradient tree boosting method followed by an adaptive iterative SNP search to capture complex non-linear SNP-SNP interactions and consequently, obtain group of interacting SNPs with high BC risk-predictive potential. We also propose a support vector machine formed by the identified SNPs to classify BC cases and controls. Our approach achieves mean average precision (mAP) of 72.66, 67.24 and 69.25 in discriminating BC cases and controls in KBCP, OBCS and merged

https://www.nature.com/articles/s41598-018-31573-5

OXFORD

JNCI J Natl Cancer Inst (2022) 114(8): djac090

https://doi.org/10.1093/jnci/djac090
First published online April 27, 2022
Review

Synonymous Variants: Necessary Nuance in Our Understanding of Cancer Drivers and Treatment Outcomes

Nayiri M. Kaissarian, PhD,[†] Douglas Meyer, BS,[†] and Chava Kimchi-Sarfaty, PhD[*]

Hemostasis Branch, Division of Plasma Protein Therapeutics, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation & Research, US Food and Drug Administration, Silver Spring, MD 20993-0002, USA

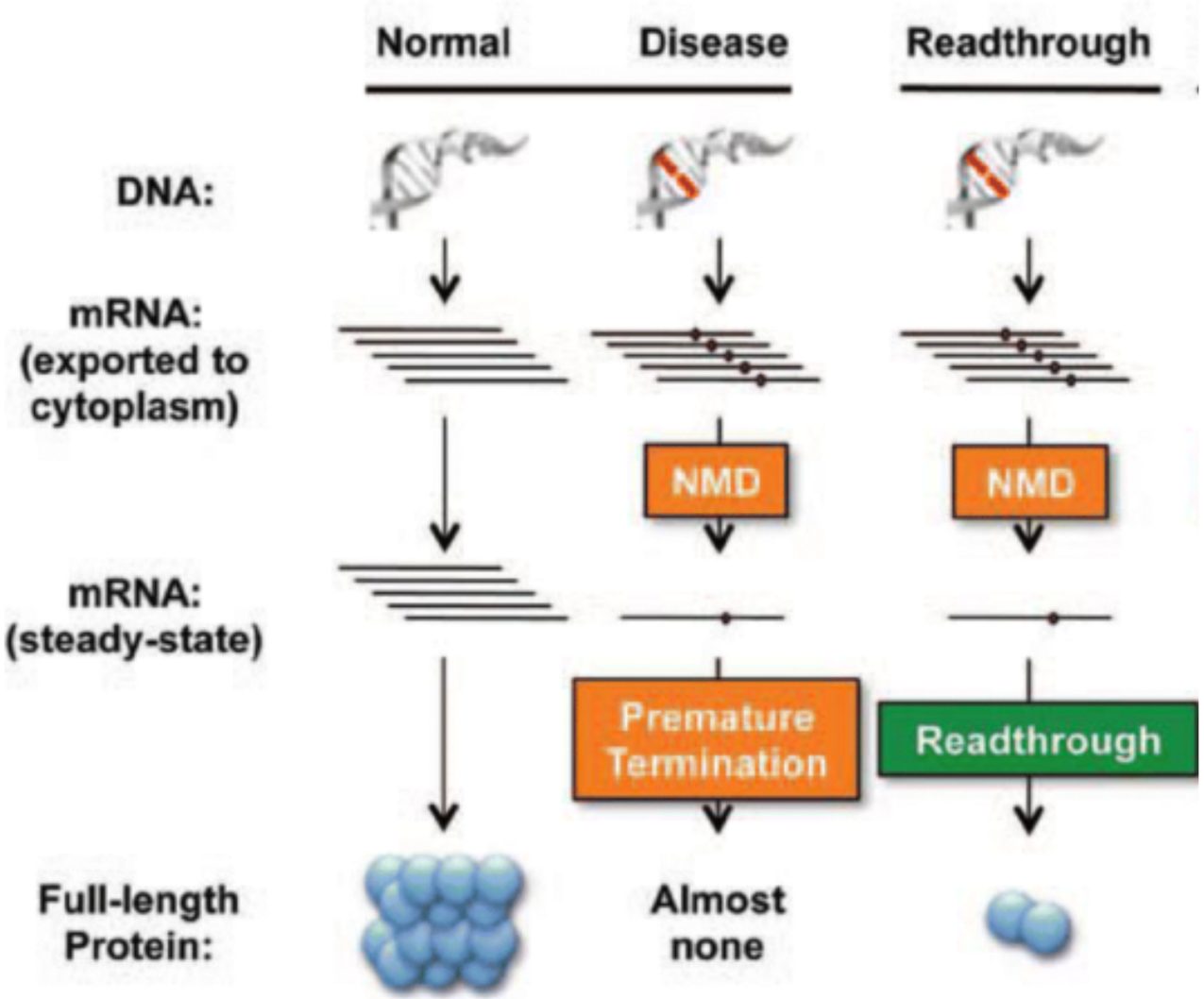
[†]Authors contributed equally to this work.

[*]**Correspondence to:** Chava Kimchi-Sarfaty, PhD, OTAT Deputy Associate Director for Research, Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA), Building 52/72, Room 4118, 10903 New Hampshire Avenue, Silver Spring, MD, 20993-0002, USA (e-mail: Chava.kimchi-sarfaty@fda.hhs.gov).

REVIEW

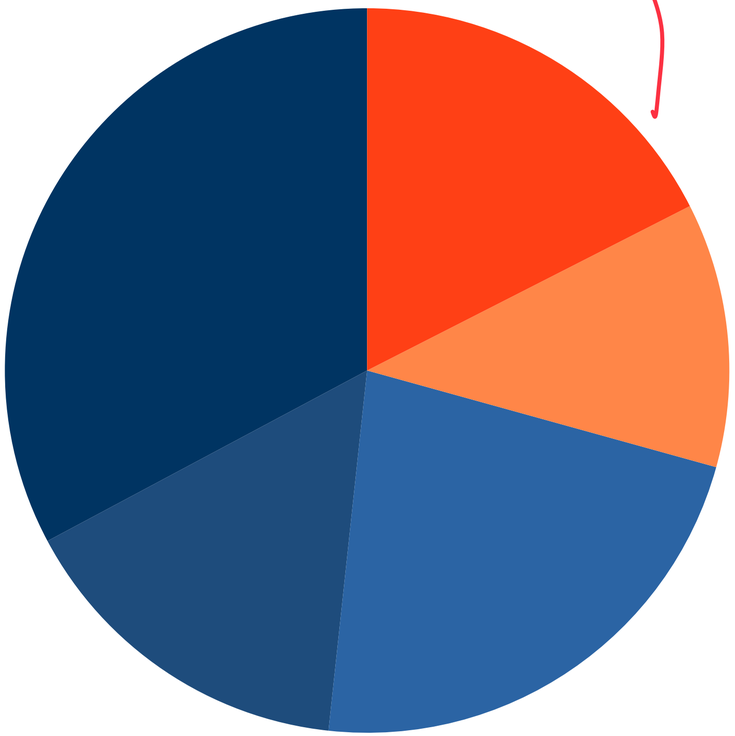
Abstract

Once called "silent mutations" and assumed to have no effect on protein structure and function, synonymous variants are now recognized to be drivers for some cancers. There have been significant advances in our understanding of the numerous mechanisms by which synonymous single nucleotide variants (sSNVs) can affect protein structure and function by affecting pre-mRNA splicing, mRNA expression, stability, folding, micro-RNA binding, translation kinetics, and co-translational folding. This review highlights the need for considering sSNVs in cancer biology to gain a better understanding of the genetic determinants of human cancers and to improve their diagnosis and treatment. We surveyed the literature for reports of sSNVs in cancer and found numerous studies on the consequences of sSNVs on gene function with supporting in vitro evidence. We also found reports of sSNVs that have statistically significant associations with specific cancer types but for which in vitro studies are lacking to support the reported associations. Additionally, we found reports of germline and somatic sSNVs that were observed in numerous clinical studies and for which in silico analysis predicts possible effects on gene function. We provide a review of these investigations and discuss necessary future studies to elucidate the mechanisms by which sSNVs disrupt protein function and play a role in tumorigeneses, cancer progression, and treatment efficacy. As splicing dysregulation is one of the most well-recognized mechanisms by which sSNVs impact protein function, we also include our own in silico analysis for predicting which sSNVs may disrupt pre-mRNA splicing.



+200.000 £

https://www.bbc.com/news/health-36056759



Acta Oncologica Turcica 2009; 42: 13-16

Türk Toplumundaki Nörofibromatozis Tip 1'li Hastalarda Gen Mutasyonlarının Araştırılması*

Research of Gene Mutations in Patient Suffering from Neurofibromatozis Type 1 in Turkey

Sacide PEHLİVAN[1,2], Hüseyin ONAY[2], Gülçin ITIRLI[2], Ayşe ERBAY[3], Ahmet KOMAN[4], Duri Şehvar ÖZEL ÜNAL[4], Ferda ÖZKINAY[2]

[1] Gaziantep Üniversitesi Tıp Fakültesi, Tıbbi Biyoloji Anabilim Dalı, GAZİANTEP
2 Ege Üniversitesi Tıp Fakültesi, Tıbbi Genetik Anabilim Dalı,
3 Dr. Behçet Uz Çocuk Hastanesi, Onkoloji Birimi, İZMİR
4 Boğaziçi Üniversitesi Fen Fakültesi, Moleküler Biyoloji ve Genetik Anabilim Dalı, İSTANBUL

* Bu çalışma; XII. International Biomedical Science and Technology Symposium, 20-23 September 2005, Izmir-Turkey toplantısında sözlü olarak sunulmuştur.

Alpafold

- Aminoasit dizisinden yüksek doğrulukla 3D protein yapısı tahmini yapar.
- Mutasyonların protein kıvrımı üzerindeki yapısal etkilerini modellemeye olanak tanır.
- Hastalıkla ilişkili varyantların fonksiyonel etkilerini öngörmede biyoinformatik analizleri güçlendirir.

Kaynaklar

Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts ve P. Walter, 2002a. From dna to rna. İçinde: Molecular Biology of the Cell. 4th edition, Garland Science

Alberts, B., A. Johnson, J. Lewis, M. Raff, K. Roberts ve P. Walter, 2002b. The structure and function of dna. İçinde: Molecular Biology of the Cell. 4th edition, Garland Science

LaPelusa, A. ve R. Kaushik, 2025. Physiology, proteins. İçinde: StatPearls, StatPearls Publishing, Treasure Island (FL)

Mercadante, A.A., M. Dimri ve S.S. Mohiuddin, 2025. Biochemistry, replication and transcription. İçinde: StatPearls, StatPearls Publishing, Treasure Island (FL)

Morais, P., H. Adachi ve Y.-T. Yu, 2020. Suppression of nonsense mutations by new emerging technologies. International Journal of Molecular Sciences, 21, (12), 4394

NCBI Resource Coordinators, 2013. Database resources of the national center for biotechnology ınformation. Nucleic Acids Research, 41, (D1), D8

Puglisi, R., 2022. Protein mutations and stability, a link with disease: the case study of frataxin. Biomedicines, 10, (2), 425

Sanvictores, T. ve F. Farci, 2025. Biochemistry, primary protein structure. İçinde: StatPearls, StatPearls Publishing, Treasure Island (FL)

Stefl, S., H. Nishi, M. Petukh, A.R. Panchenko ve E. Alexov, 2013. Molecular mechanisms of disease-causing missense mutations. Journal of molecular biology, 425, (21), 3919

Tian, J., C.D. McFarland ve J. Woodard, 2023. Editorial: structural understanding of the functional consequences of missense mutation. Frontiers in Genetics, 14, 1325326