GENETIC TESTING:

THE USH2A GENE

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The USH2A gene

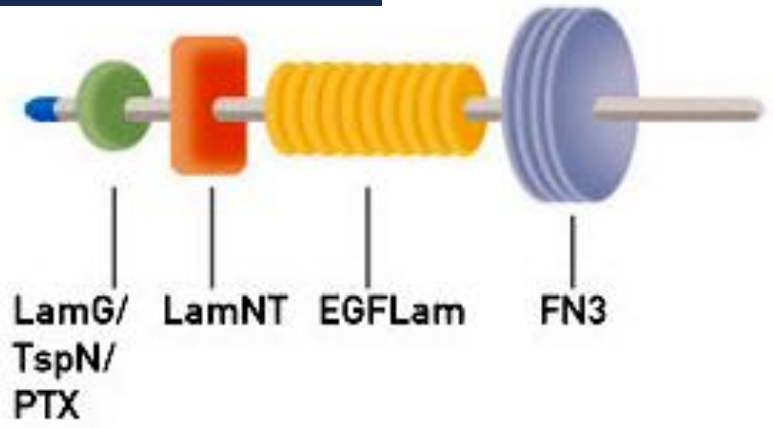
- The *USH2A* gene is very large (73 exons)

- Defects (Mutations) in the USH2A gene are responsible for
  - 60-90% of the cases with Usher syndrome type II
  - 5-10% of the cases with non-syndromic retinitis pigmentosa

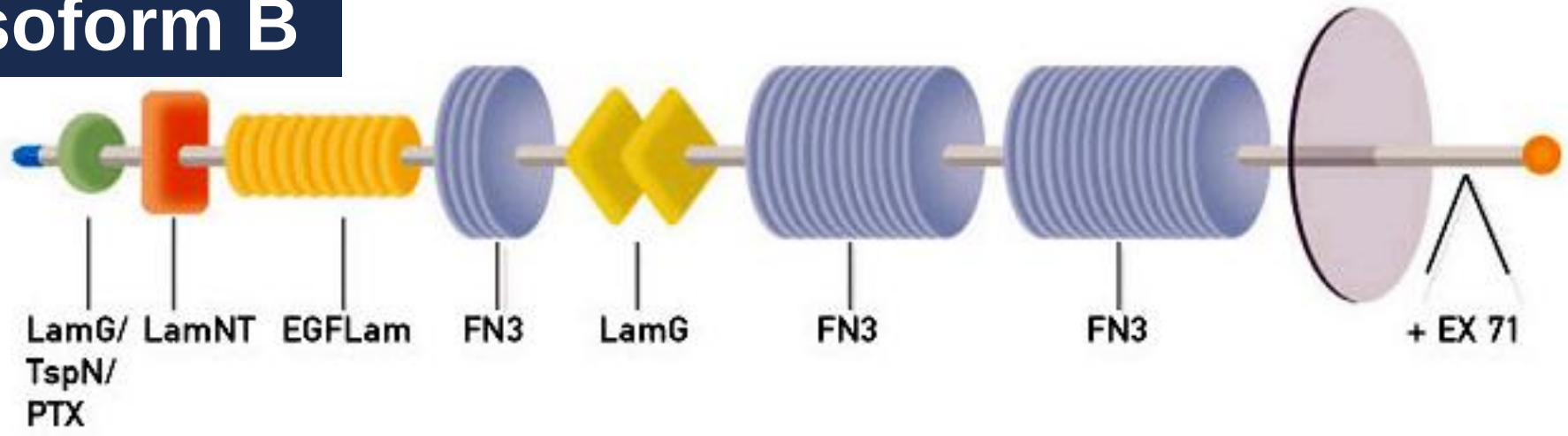
- The *USH2A* gene encodes at least 2 different USH2A proteins, also called Usherin

USH2A protein isoforms

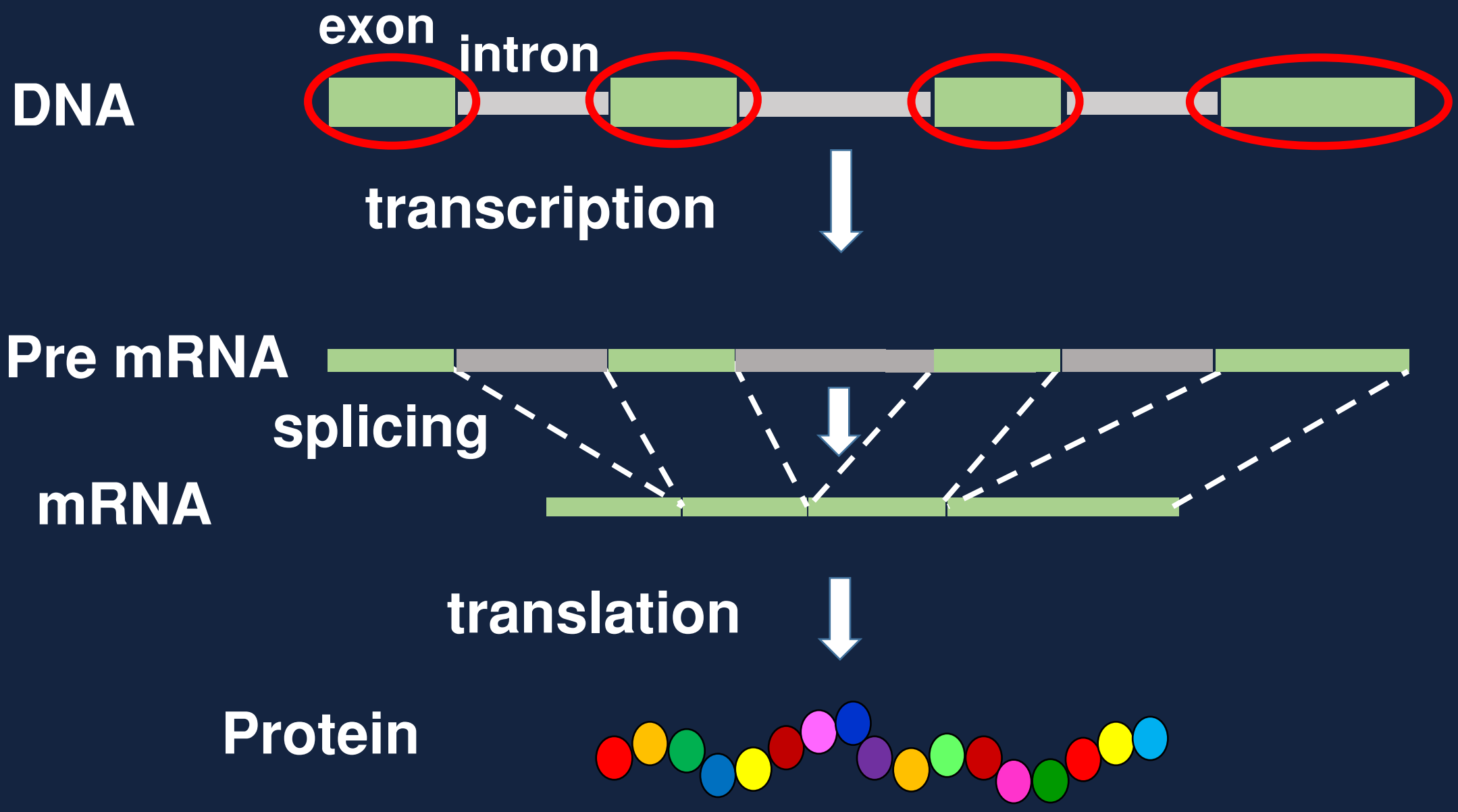
Isoform A



Isoform B



From DNA to mRNA to Protein



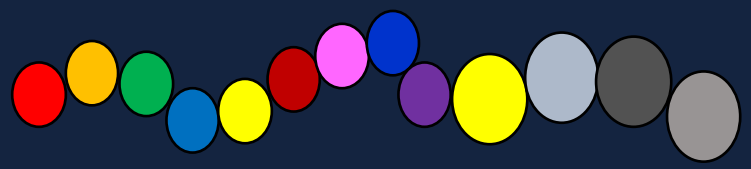
DNA diagnostics – step 1

Normal

Early Stop

Shorter or no protein

Code shift: Splice Defect, DNA missing, Additional DNA



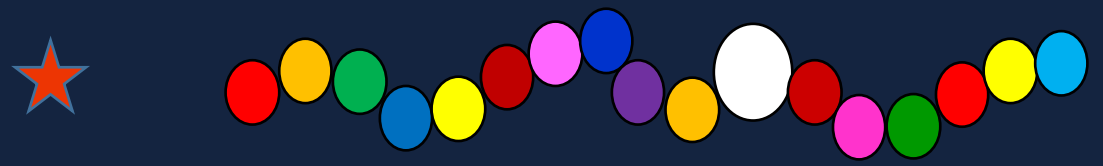
Protein partly normal partly abnormal

DNA missing no code shift

Protein part missing

Change of 1 amino acid: effect?

Change in 1
Building block

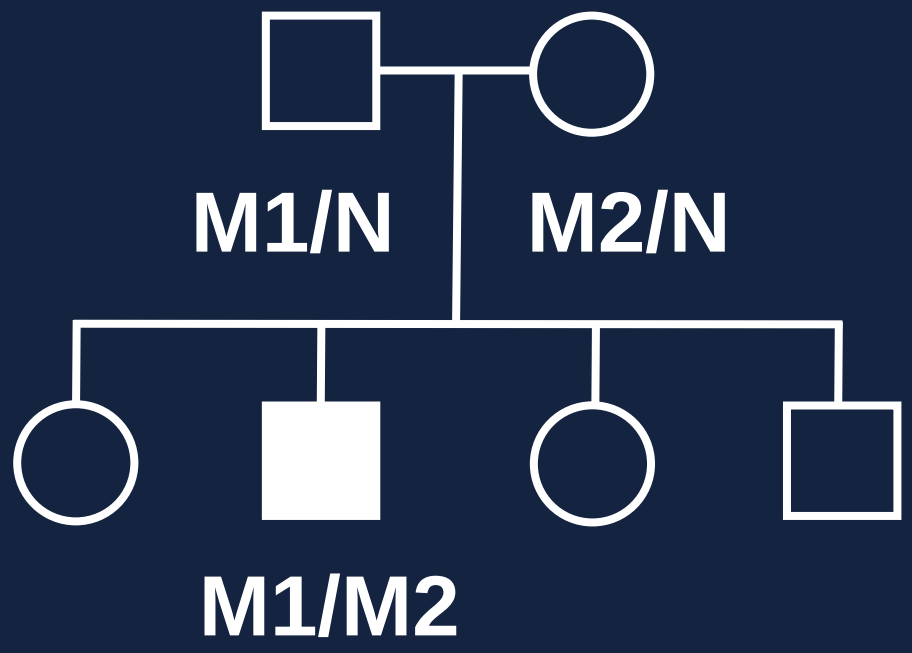


Common in Usher syndrome cases and common in the general population

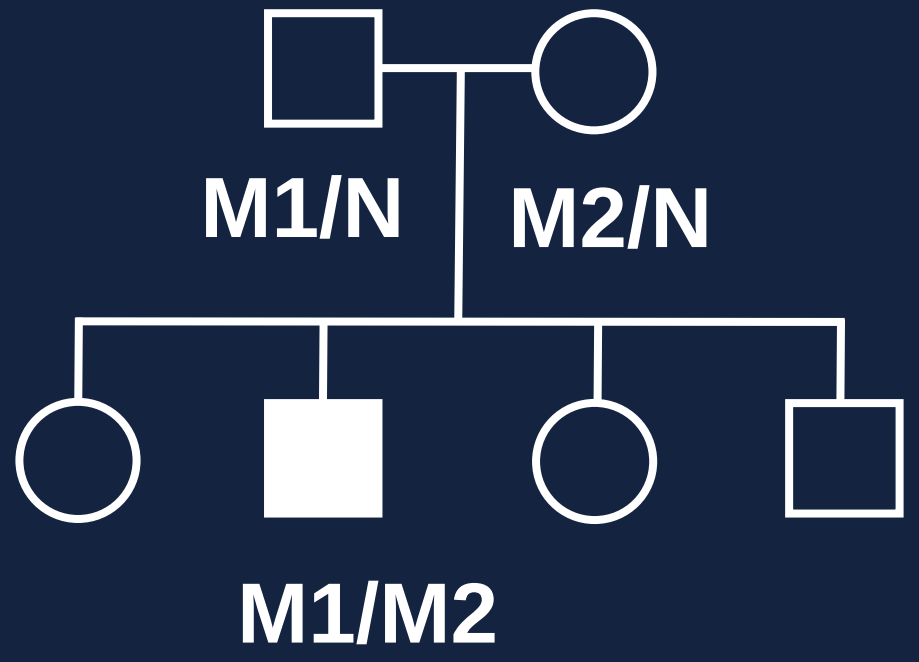
How to determine that these changes are likely to be deleterious?

- Big change in the chemical characteristics?
- Affects an amino acid that is conserved in evolution?
- Is predicted to change the structure of the protein
- Previously found in a person with Usher syndrome
- Very rare in the general population
- Guidelines by ACMG, expert evalulation teams
- Test family members

Testing family members



Segregation with USH

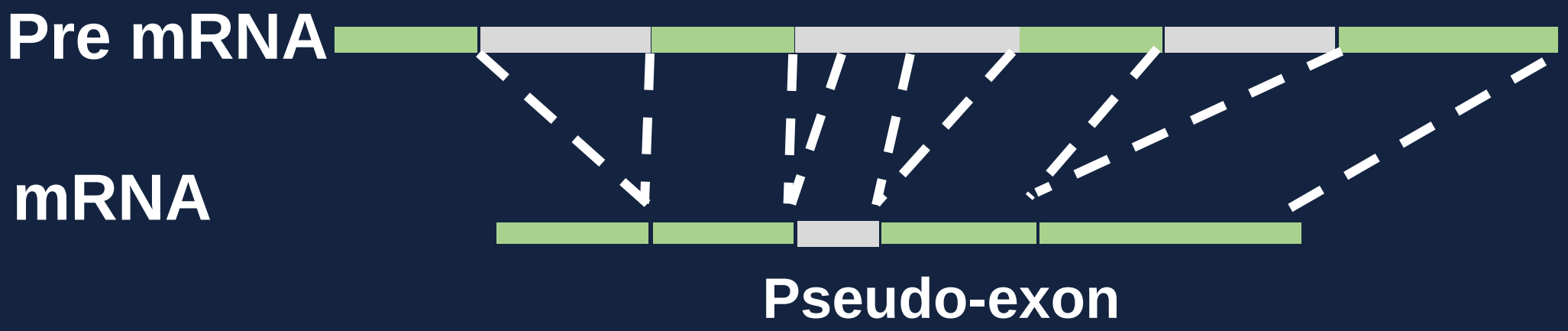


No segregation with USH

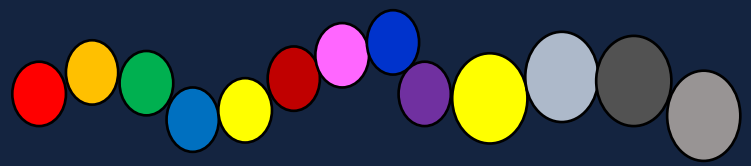
M = Mutation
N = Normal

Variants in non-coding DNA

Tests needed to prove the deleterious effect



code shift
or code changes



Summary

- Protein coding regions of the USH2A gene and flanking regions are analyzed first in DNA diagnostics
- DNA Changes that lead to the change of only 1 amino acid in the USH2A protein are often difficult to interpret
- The ‘next step’ in DNA-diagnostics is the analysis and interpretation of variants in non-coding DNA