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## Notch Mutation Effects on NICD Molecules Dimerization

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## Notch Mutation Effects on NICD Molecules Dimerization

### Abstract

The Notch signaling pathway plays important roles in developmental biology, Immune system, vascular system and variety of other systems. There is a great need to research more on how this pathway functions. The notch receptors located on the cell surface are activated when it interacts with a ligand that leads to the release of the Notch intracellular domain(NICD) that then translocate to the nucleolus and begins transcription. There are four notch proteins(NICDs) that contain an important Ankyrin domain for NICD homodimerization. The notch 4(NICD) is quite different in structure and how it performs compared to the rest of the group of notches and in published research performed by crow and Albig it was observed that notch4 (N4ICD) displayed a stronger dimerization activity. It is hypothesized that because it is disparate that it is able to dimerize far better than the other notches. Data collected from Crow and Albig found a site where 1-3 NICDs notches coded for a similar amino acid and N4ICD presented a different one. It was speculated that by converting the amino acid to the same one the other NICDs coded that it will convey if there is relation to its dimerization activity strength.



# Notch mutation effects on NICD molecules dimerization

M.Marquez, A.Albig

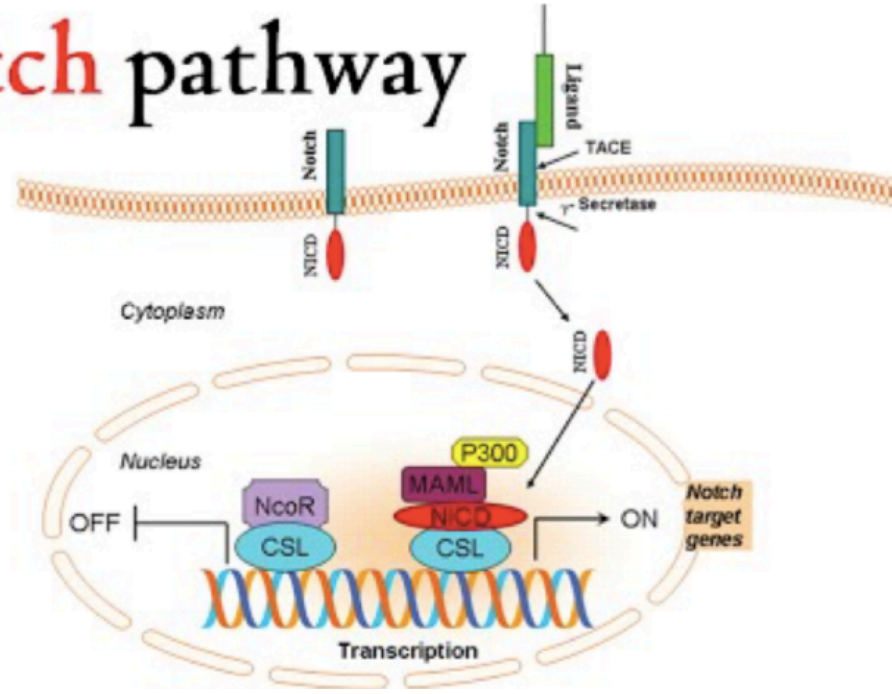
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## Abstract

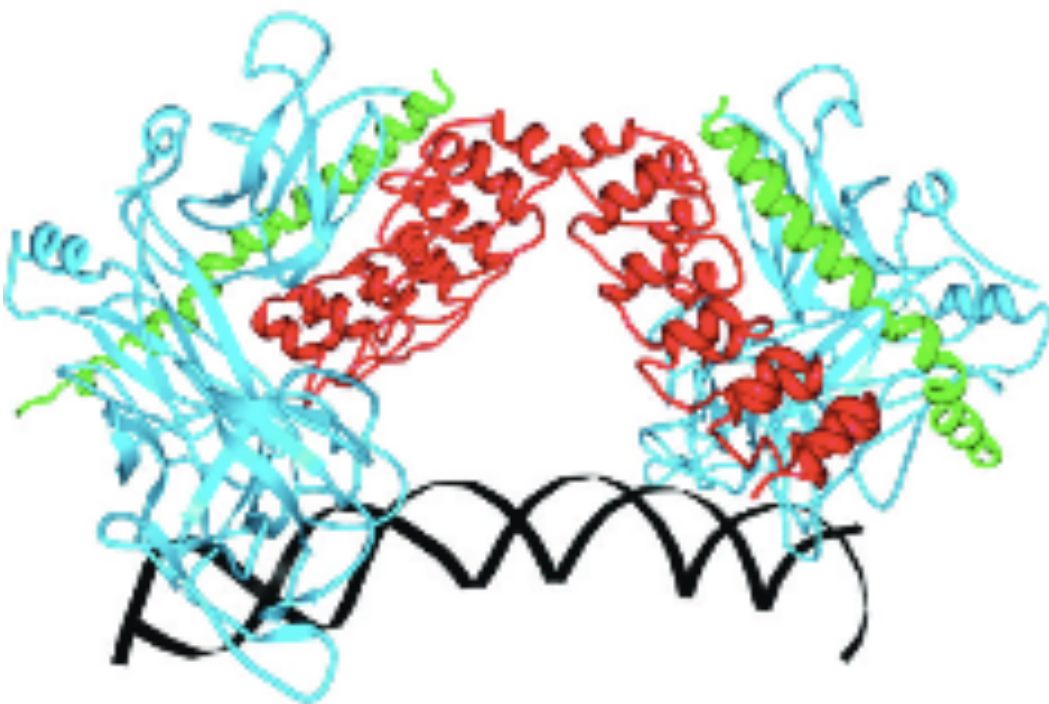
The Notch signaling pathway plays important roles in developmental biology, Immune system, vascular system and variety of other systems. The dysregulation of the notch signaling pathway has led to certain diseases, cancers and developmental malformations. The notch receptors located on the cell surface are activated when it interacts with a ligand that leads to the release of the Notch intracellular domain(NICD) that then translocate to the nucleolus and begins transcription. There are four notch proteins(NICDs) that contain an important Ankyrin domain for NICD homodimerization. The notch 4(N4ICD) is quite different in structure and how it performs compared to the rest of the group of notches and in published research performed by crow and Albig it was observed that notch4 (N4ICD) displayed a stronger dimerization activity. It is hypothesized that because it is disparate that it is able to dimerize far better than the other notches. Data collected from Crow and Albig found a site where 1-3 NICDs notches coded for a similar amino acid and N4ICD presented a different one. It was speculated that by converting the amino acid to the same one the other NICDs coded that it will convey if there is relation to its dimerization activity strength.

## Notch Signaling Background

### Notch pathway



Crystal Structure of N1ICD domain (Red) with MAML (Green) and CSL(Blue) Bound to DNA(black)

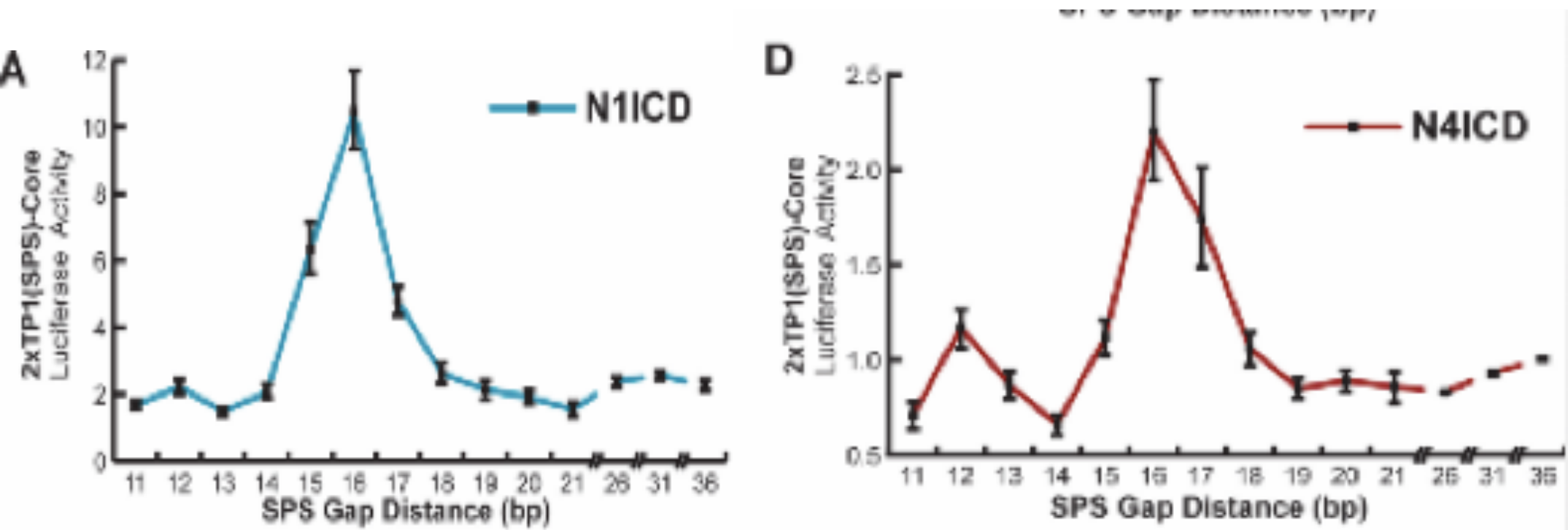


## Notch proteins structure



- Ankyrin domain important for homodimerization
- Notch1&2 (similar)
- Notch 3 (different)
- Notch 4 (most divergent)
- Notch share similar promoter preferences but variable transcriptional strengths

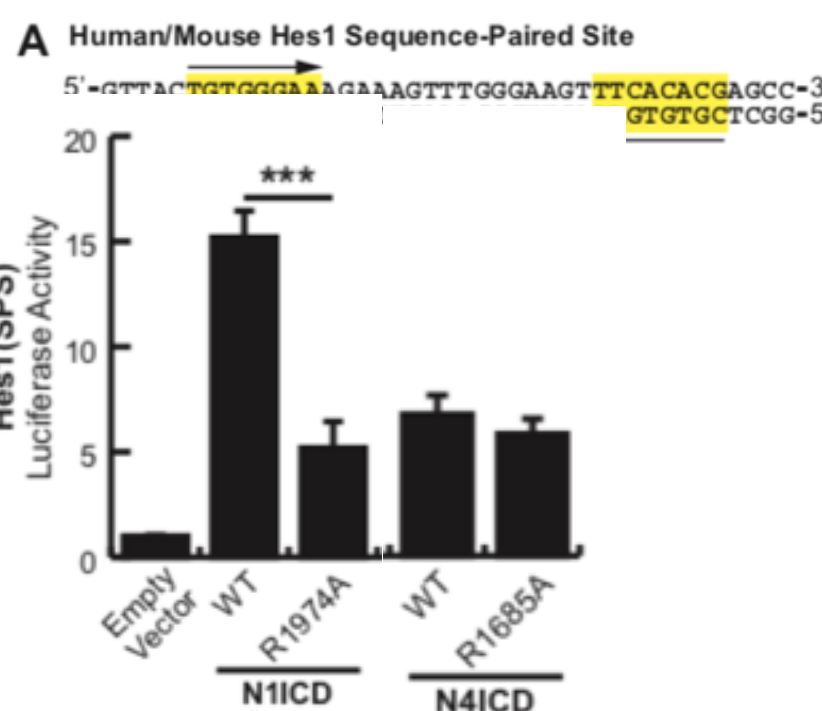
## Background Data 1 Dimerization of NICD molecules



- 16 nucleotide gap preference for transcription activation
- when it goes past 16 the transcription drops
- correlative evidence that they are forming dimers

## Background Data 2

Crow and Albig: Figure 3



- N1ICD mutation cut transcription in half
- N4ICD mutation showed no significant change

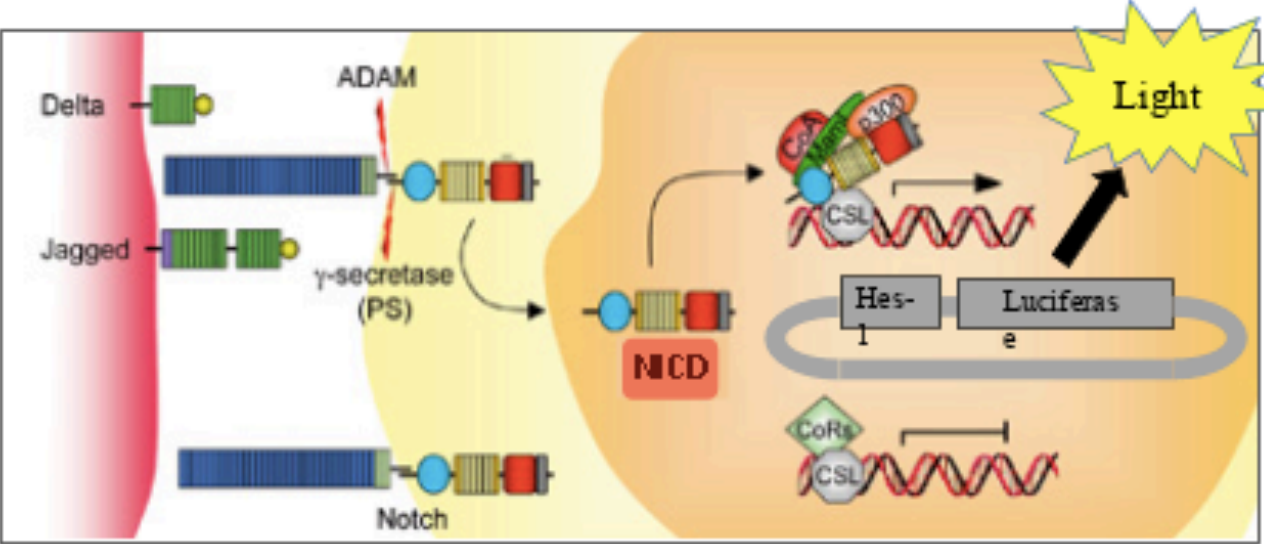
	K1946	K1950
N1ICD	A	A
N2ICD	A	A
N3ICD	A	A
N4ICD	A	A

	R1983	R1985
N1ICD	L	L
N2ICD	L	L
N3ICD	L	L
N4ICD	L	L

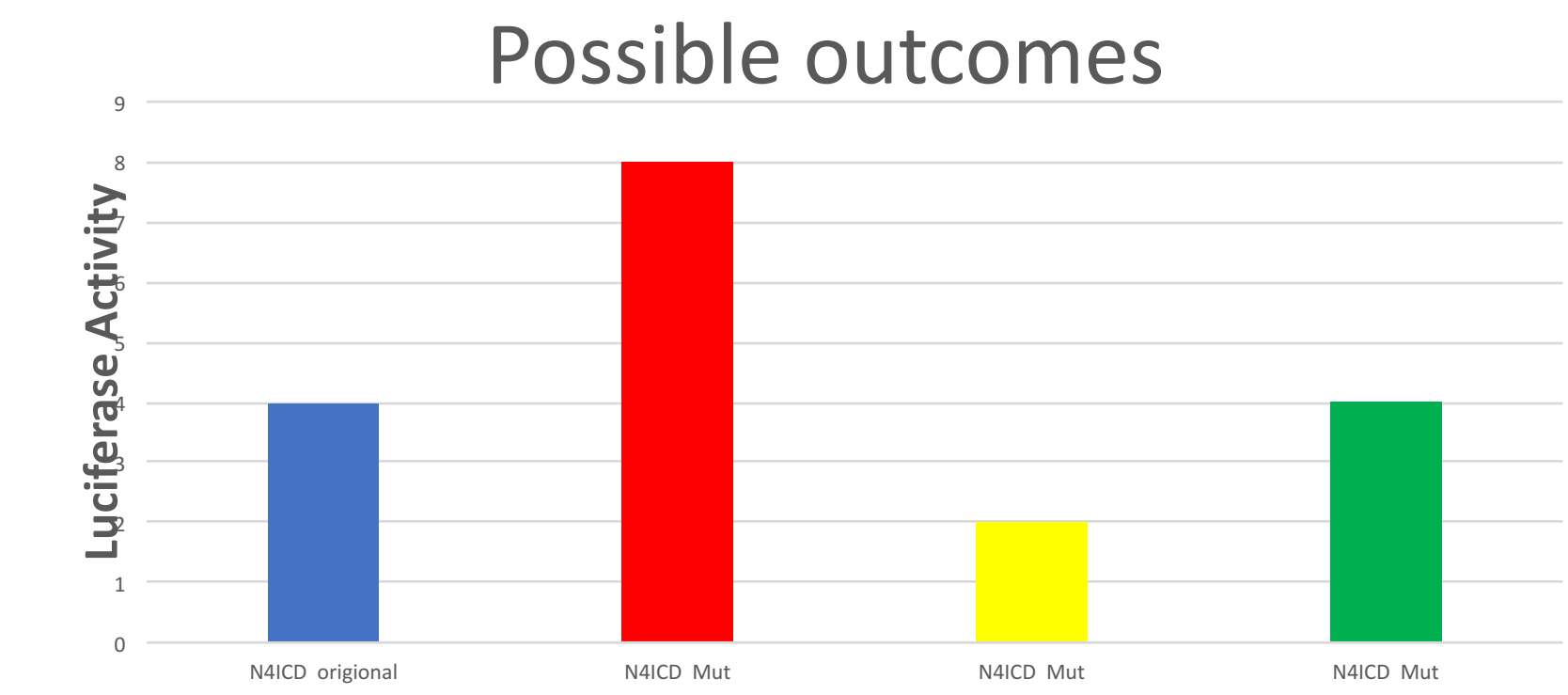
- All mutated 1-3 NICDs code for amino acid "K" and N4ICD code for "R"

## Experimental approach Luciferase activity



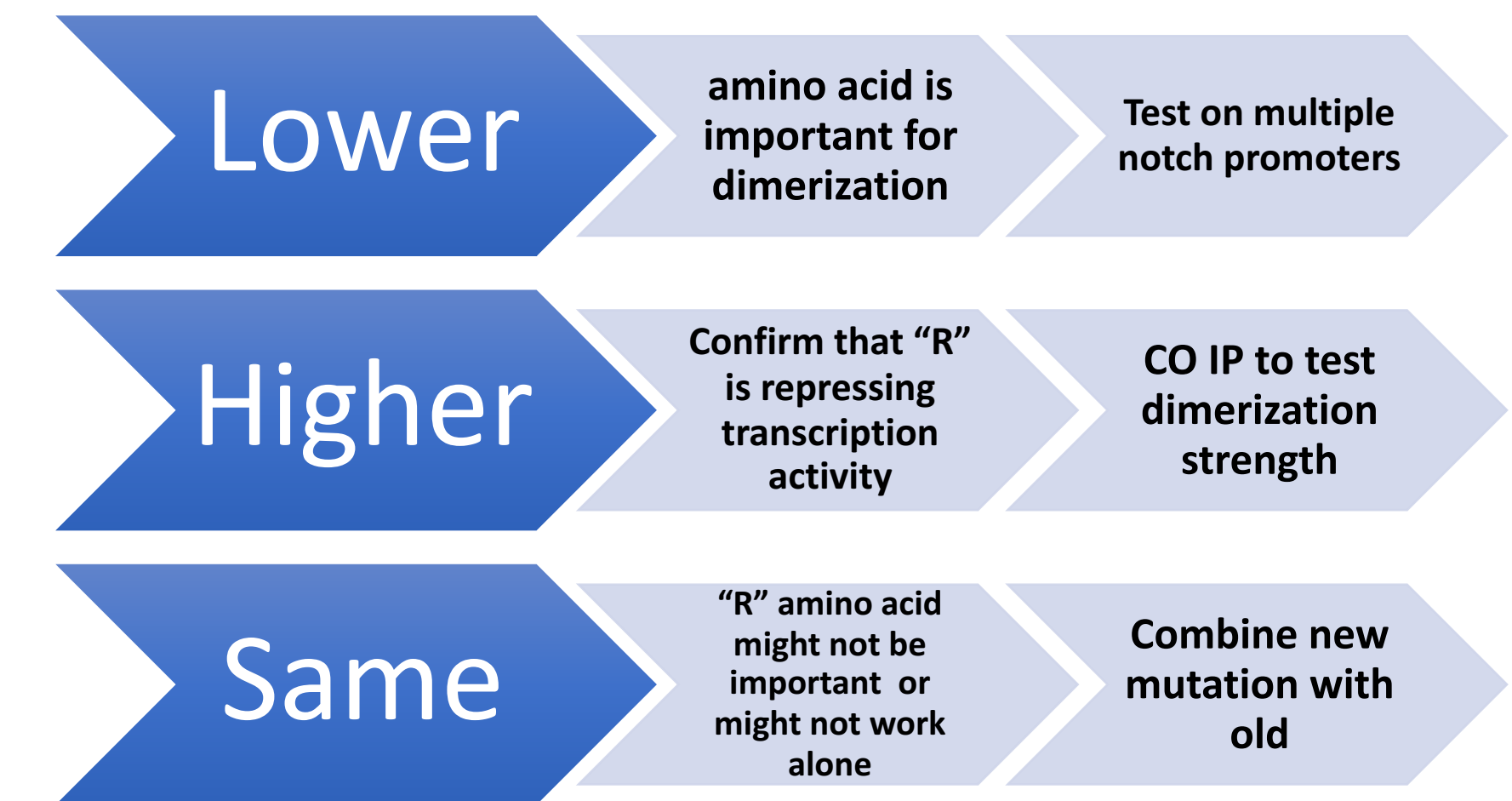
- DNA inserted to plasmid, plasmid contains enzyme for luciferase
- luciferase assay to determine strength of transcriptional activity

## Results



- [BLUE]- Original NICD
- 1 Possible outcome [RED]-NICD mutation with a Higher transcription activity
- 2 Possible outcome [Yellow]- NICD mutation with a Lower transcription activity
- 3- Possible outcome [Green]- NICD mutation transcription activity stayed the same

## Next Steps



## CONCLUSION

- notch involved in all multicellular cells
- irregular signaling result in developmental malformations, diseases and cancers
- Better understanding of the basic function/ mechanisms may give insight on how to produce treatments to diseases that are related to notch dysregulation

## References and Acknowledgements

The National Institute of General Medical Sciences to A. Albig (2R15GM102852-02) and from grants NIH/NIGMS P20GM103408 and P20 GM109095.

The National Institutes of General Medical Sciences of the National Institutes of Health under Award No.

R25GM123927.

Notch family members follow stringent requirements for intracellular domain dimerization at sequenced-paired sites Crow JJ, Albig AR