

# Novel promoters and coding first exons in *DLG2* linked to developmental disorders and intellectual disability

**Claudio Reggiani**

Université Libre de Bruxelles, Bruxelles, Belgium

Interuniversity Institute of Bioinformatics in Brussels, Bruxelles, Belgium

Online Journal Club

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Hôpital Universitaire  
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# Biology

Reggiani et al. *Genome Medicine* (2017) 9:67  
DOI 10.1186/s13073-017-0452-y

Genome Medicine

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Biology

Computer  
science

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Genome Medicine

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 CrossMark

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Biology

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Clinics

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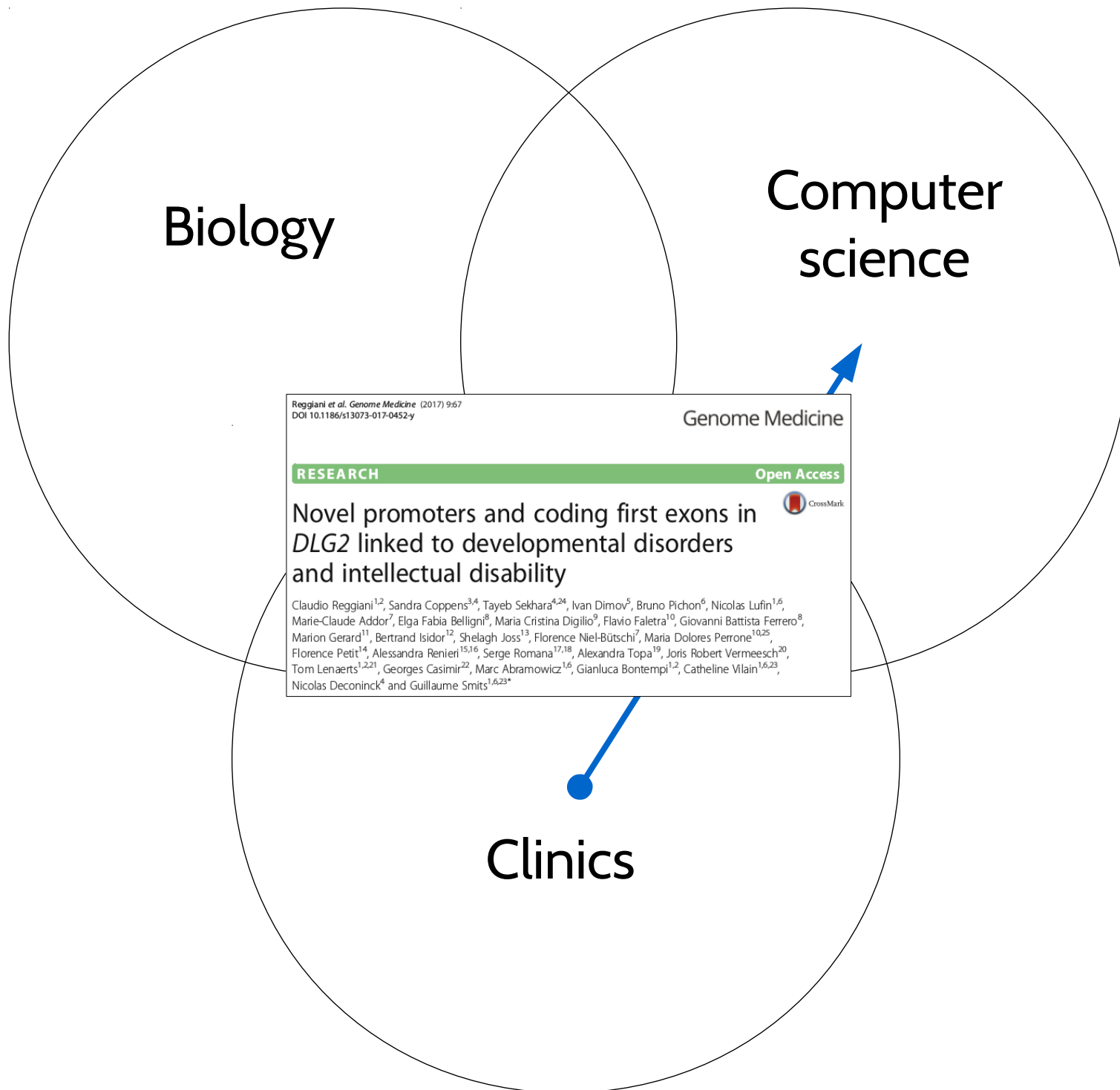
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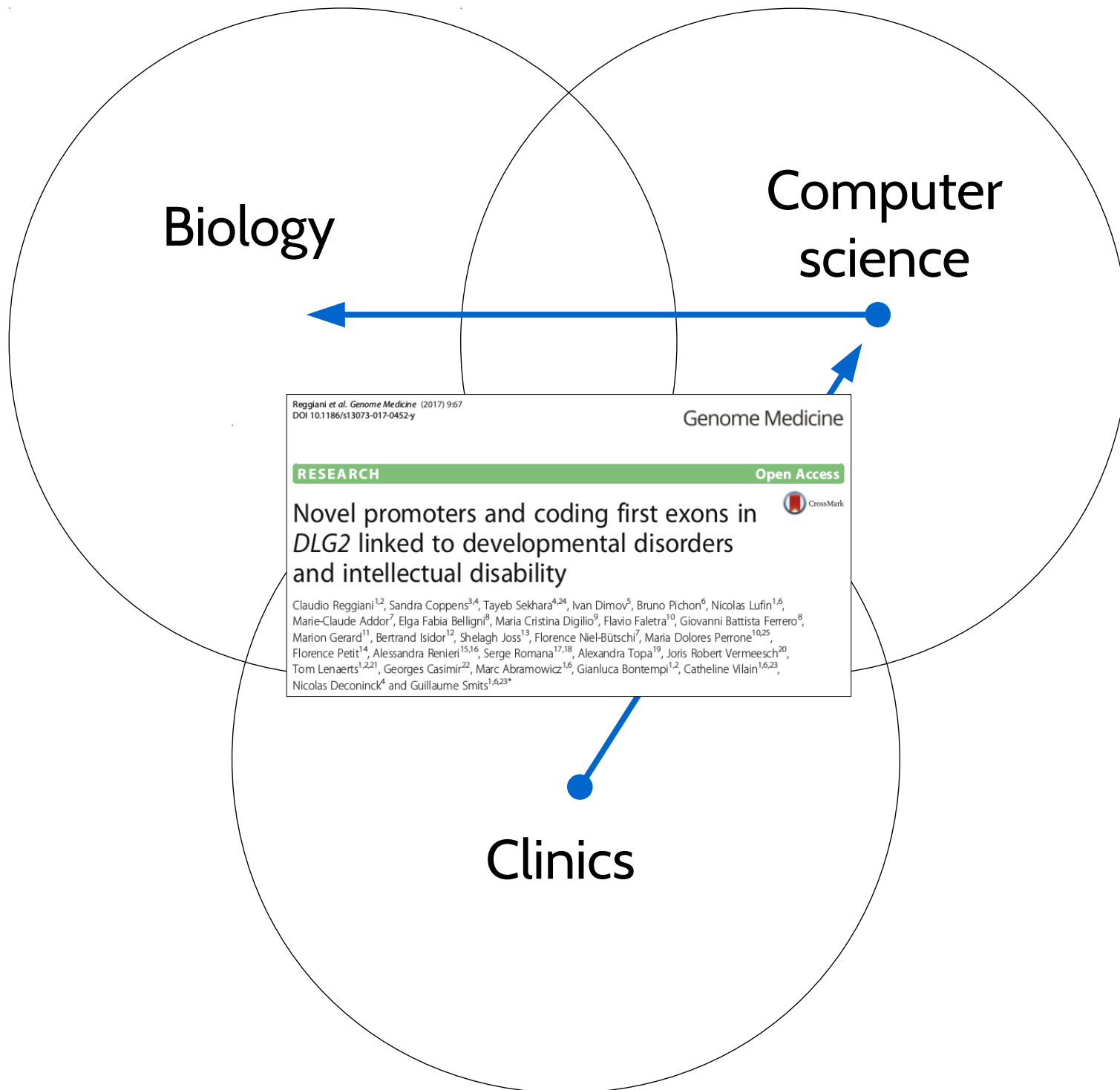
RESEARCH Open Access

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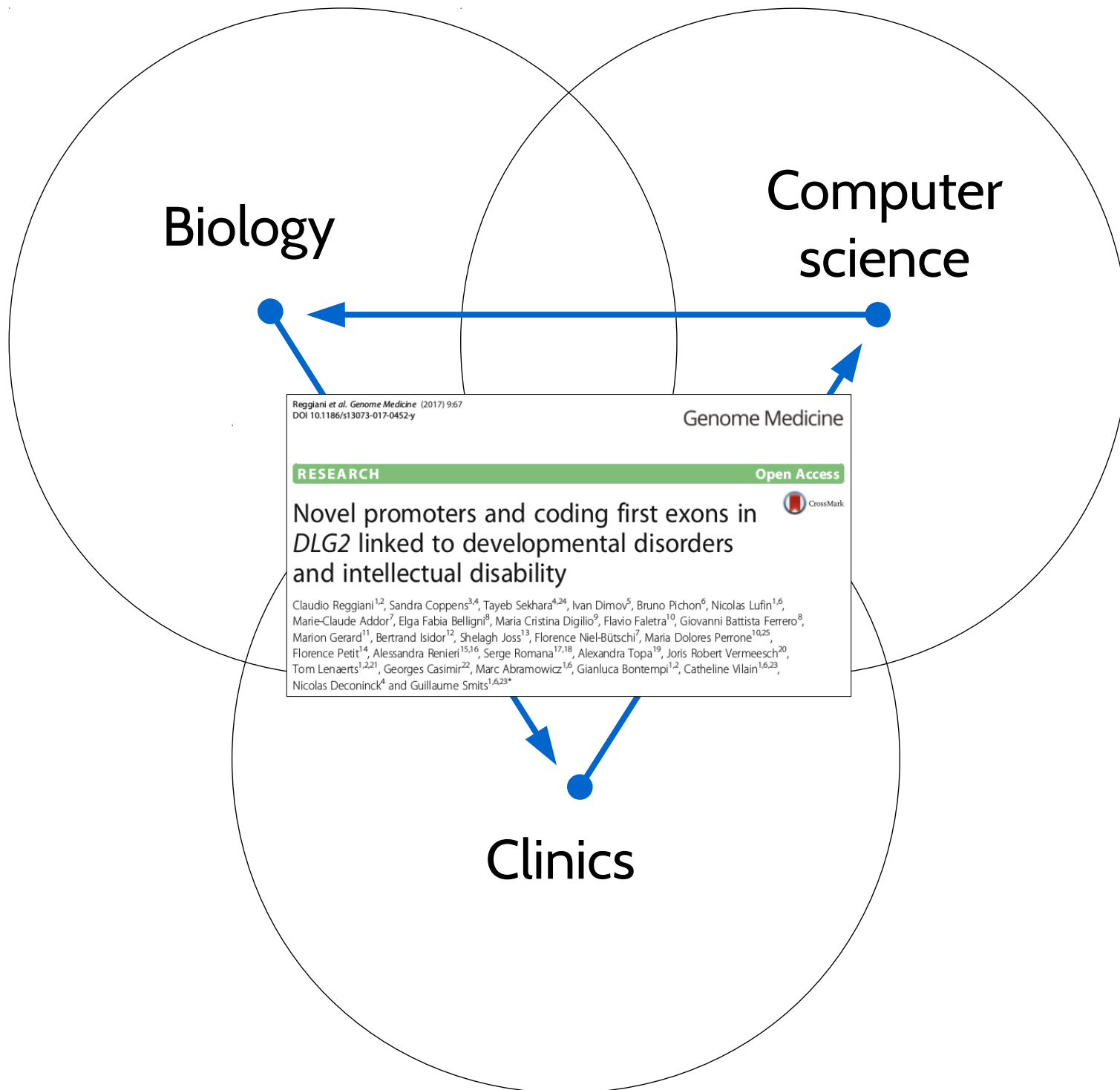
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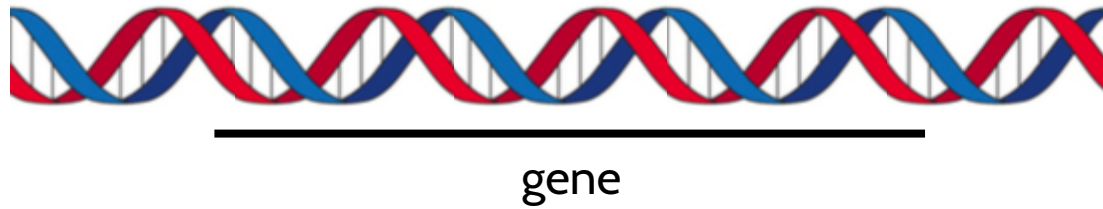




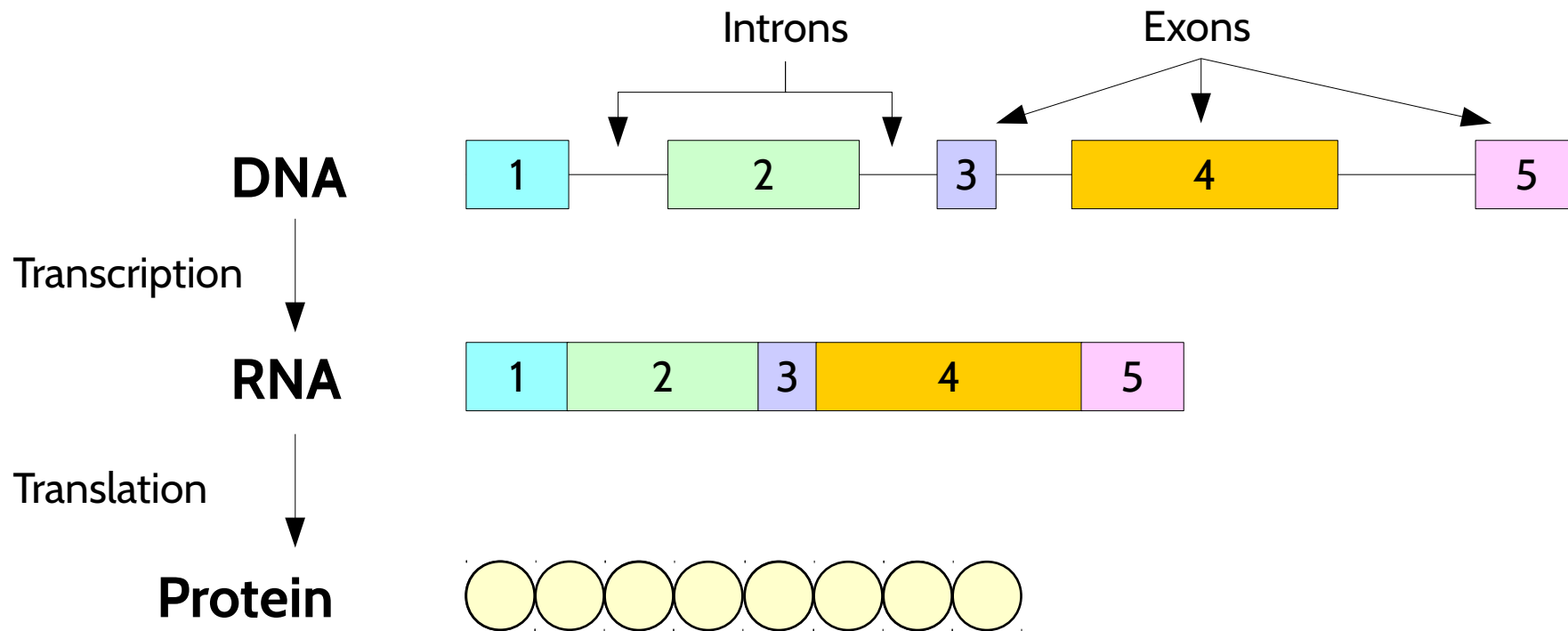
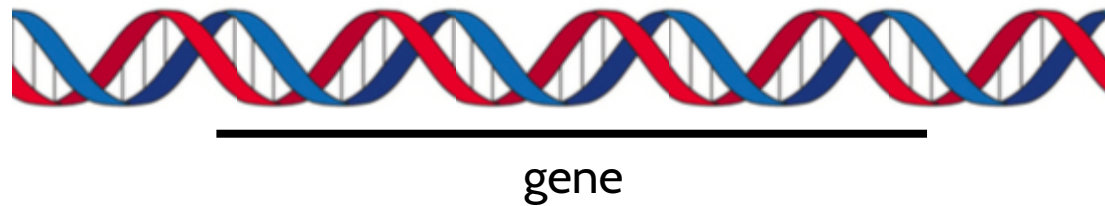
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(biology)

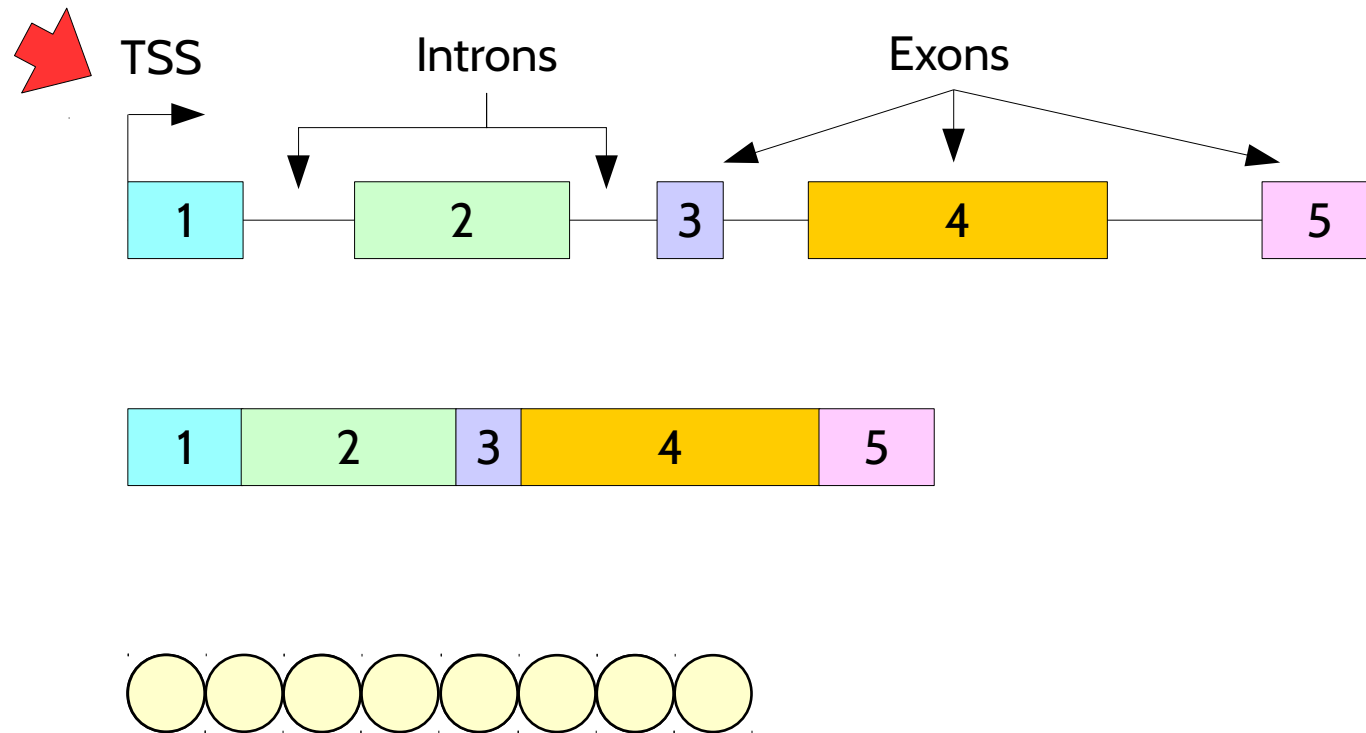
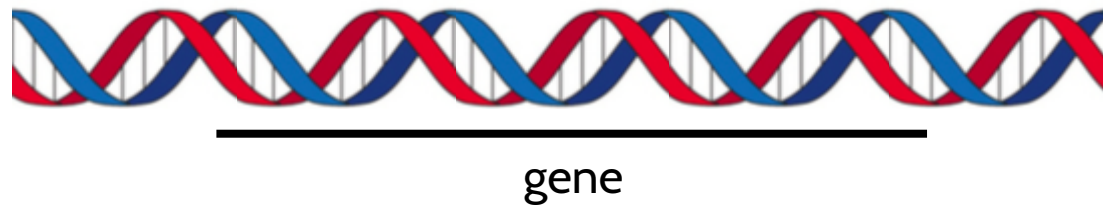
# Gene model and isoforms



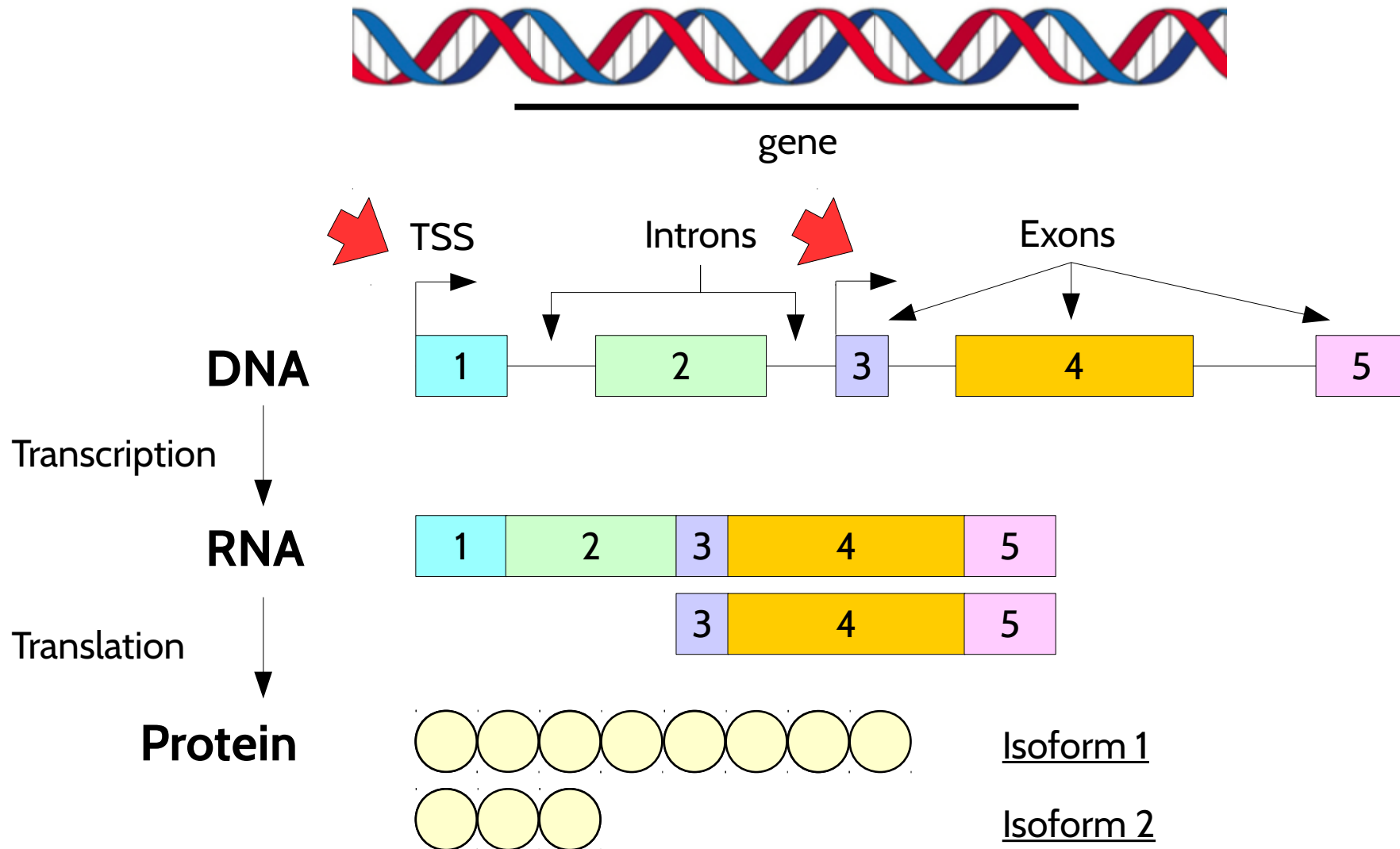
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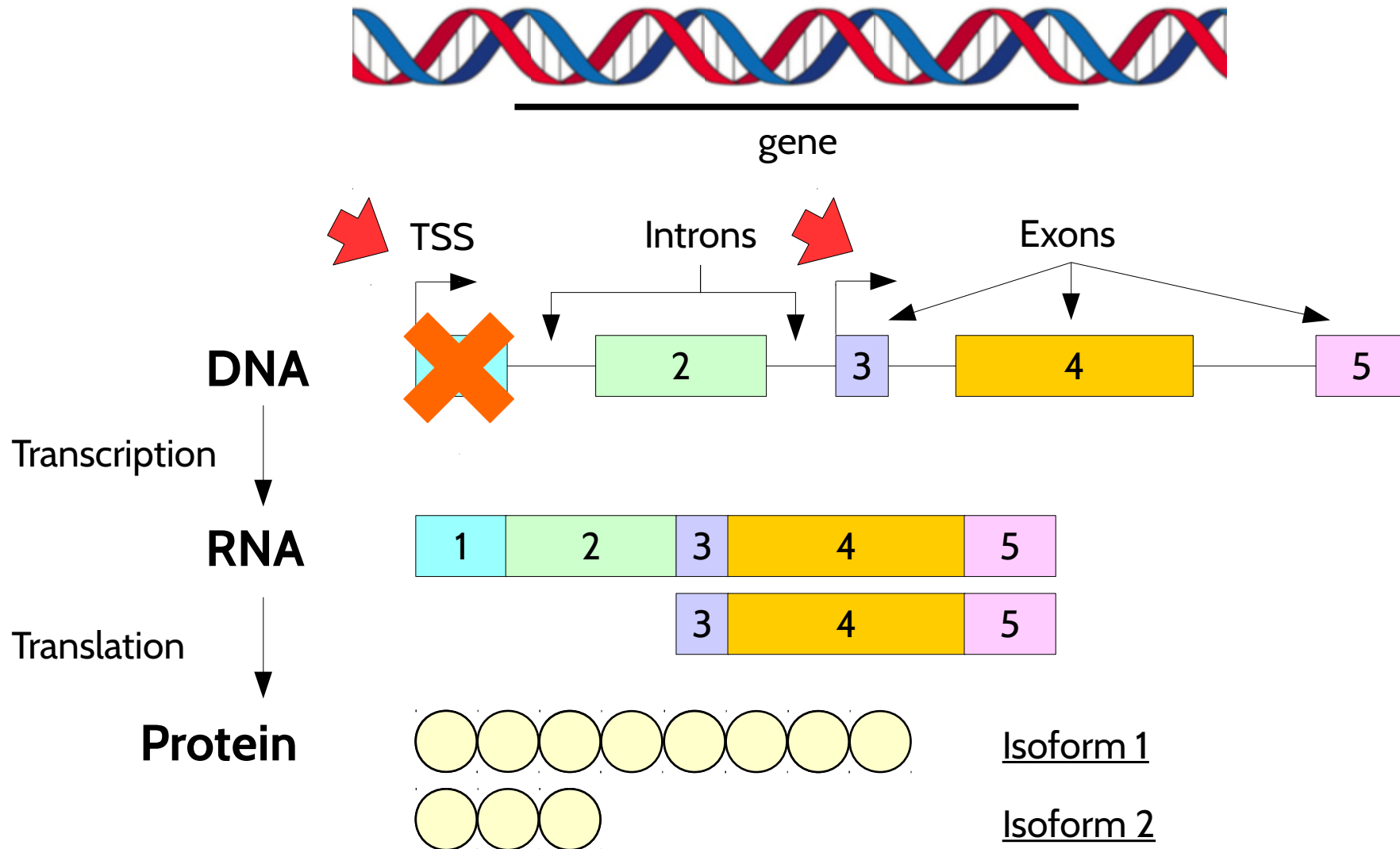
# Gene model and isoforms



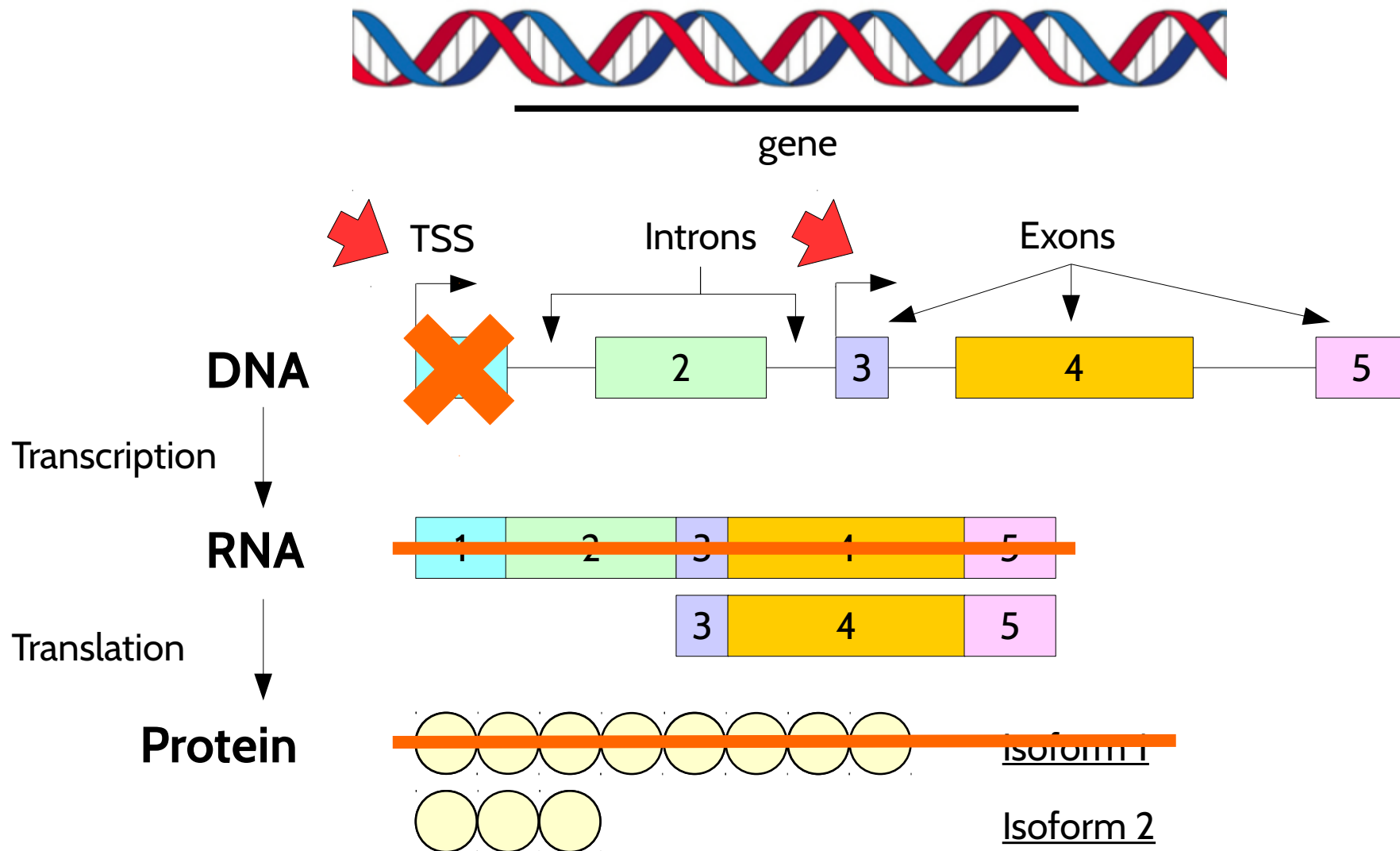
# Gene model and isoforms



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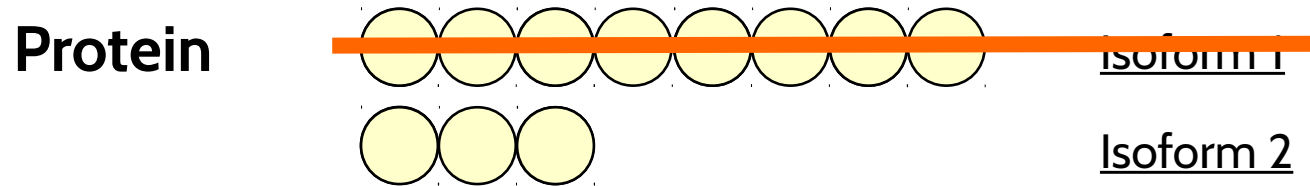


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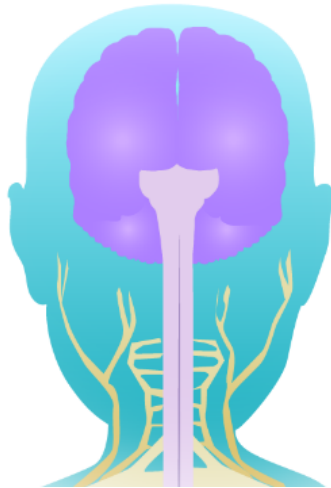
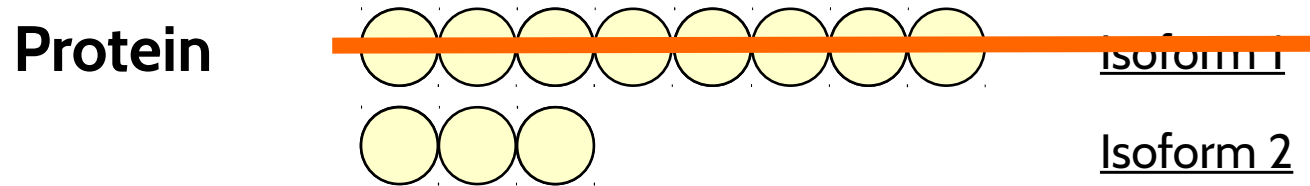




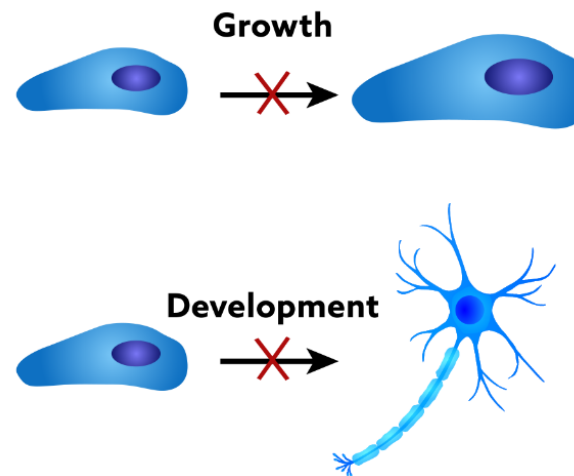
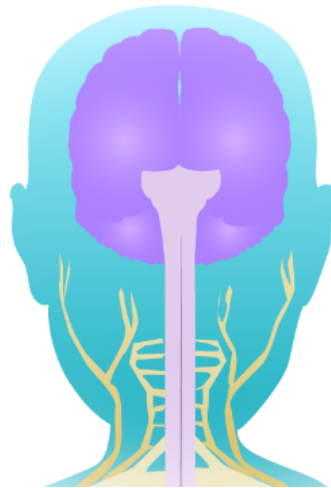
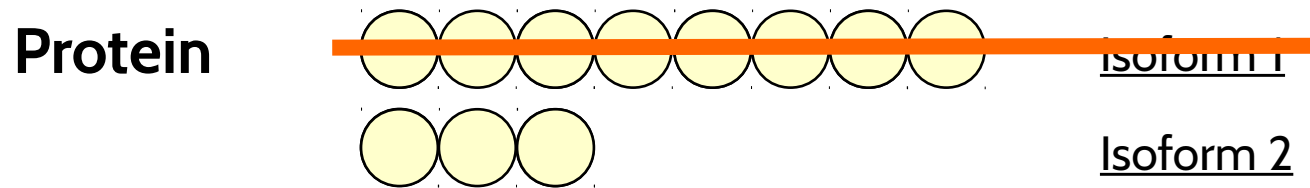
# Gene model and isoforms



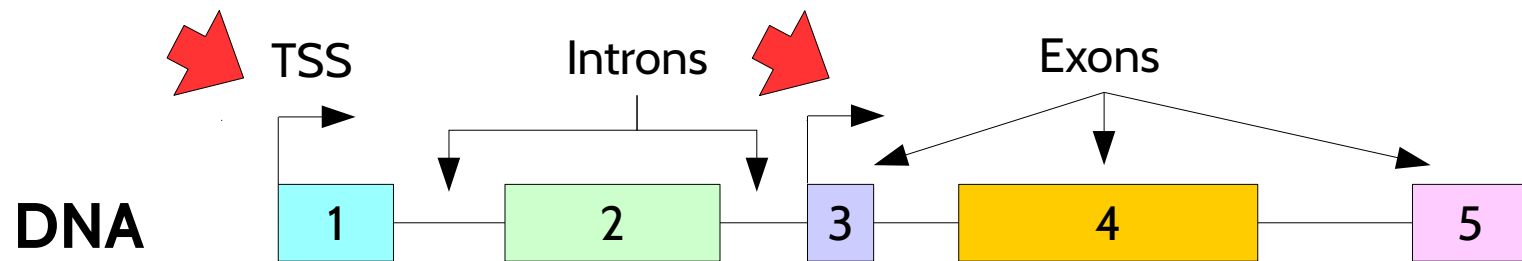
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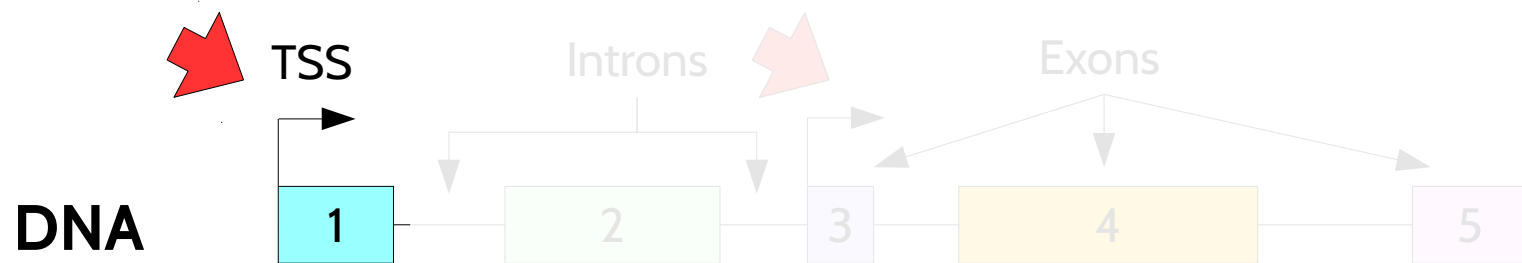
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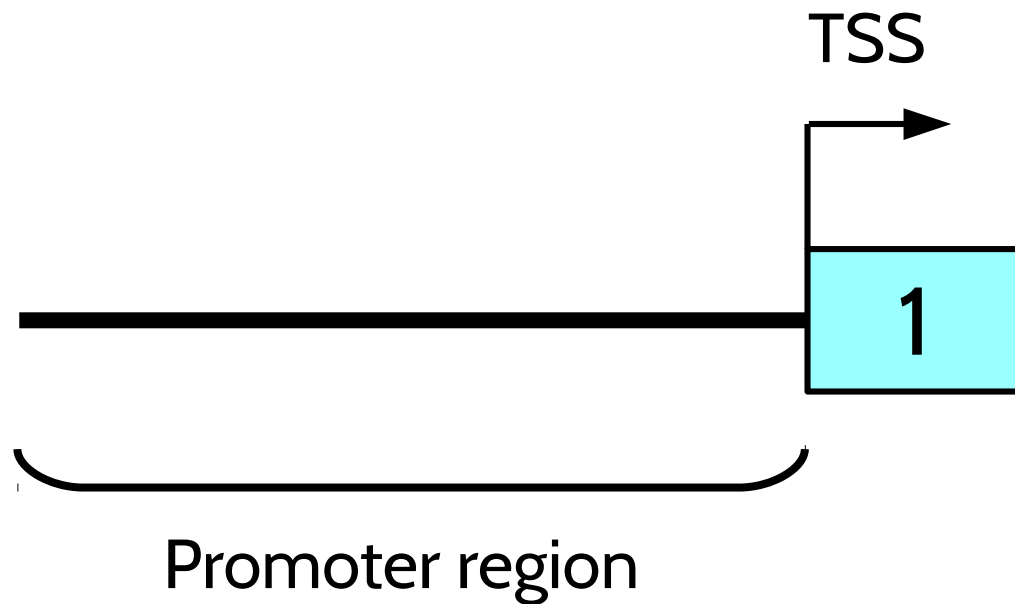
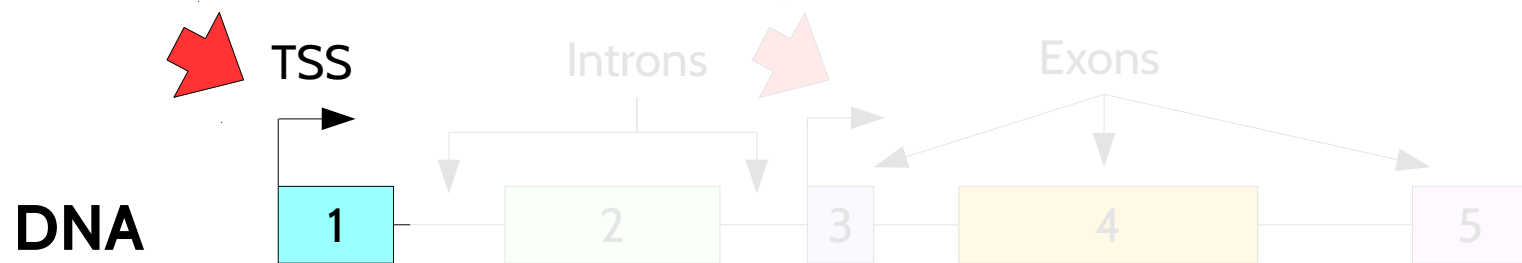
# Promoter regions



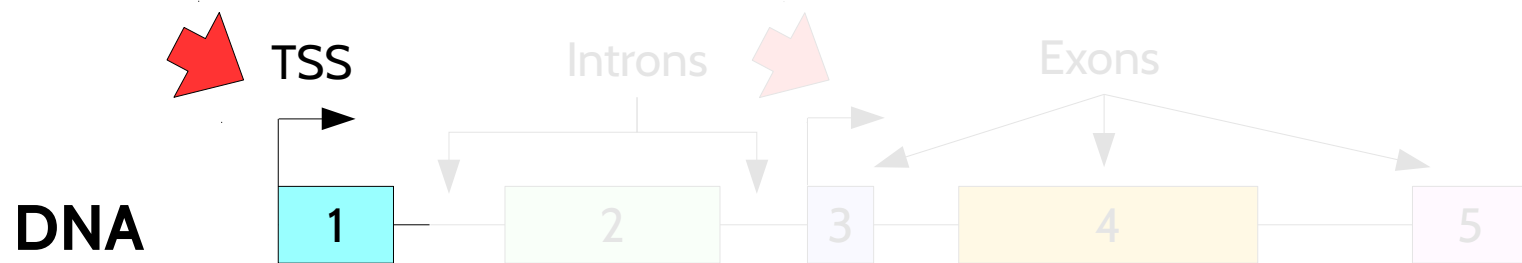
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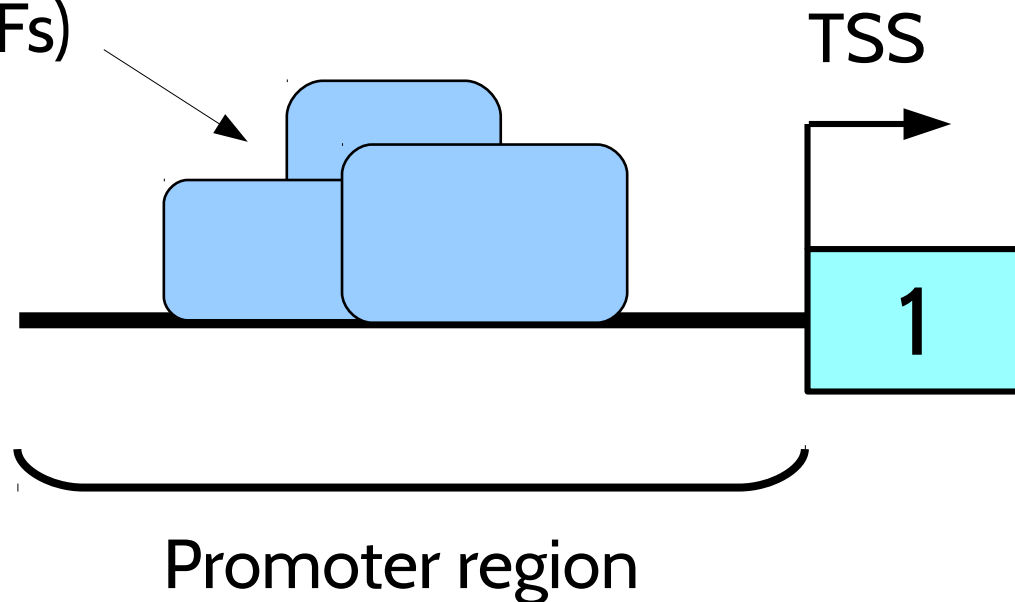
# Promoter regions



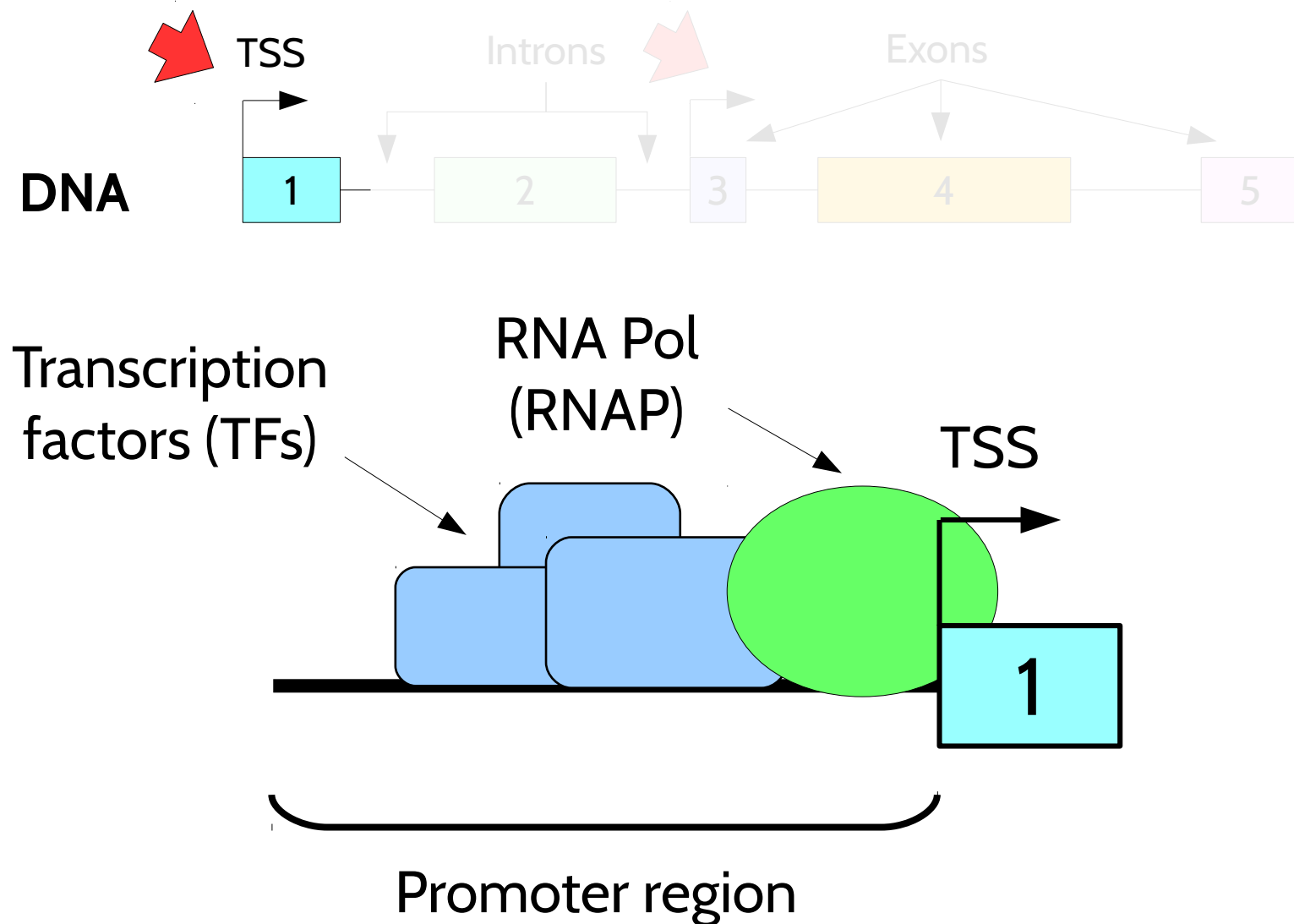
# Promoter regions



Transcription  
factors (TFs)

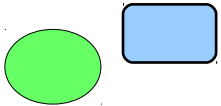


# Promoter regions

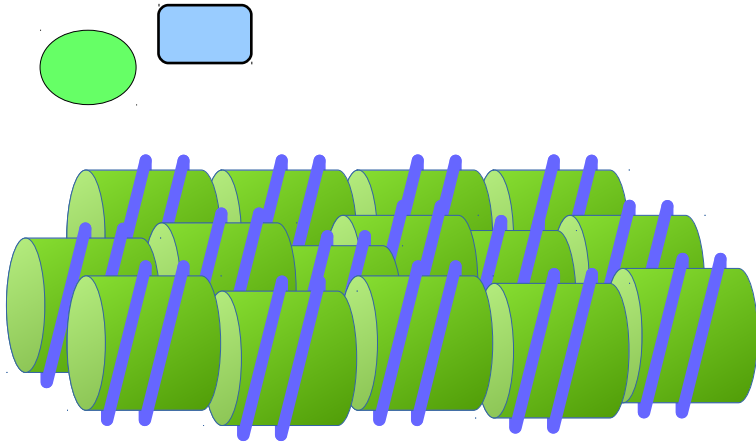




# Epigenetic mechanisms

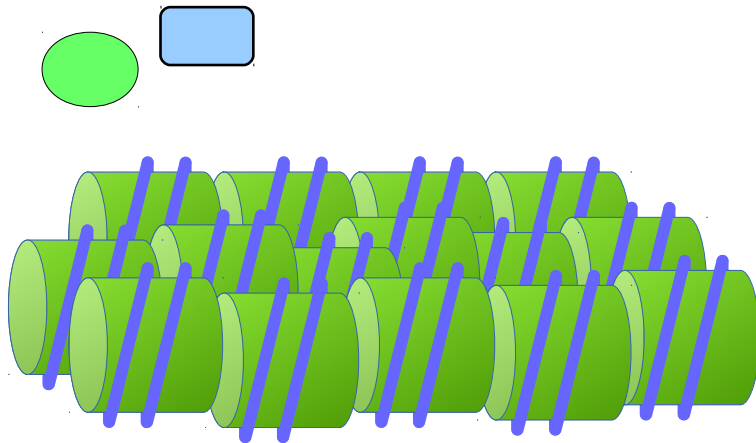
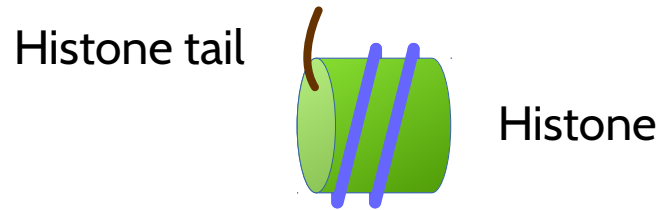


# Epigenetic mechanisms



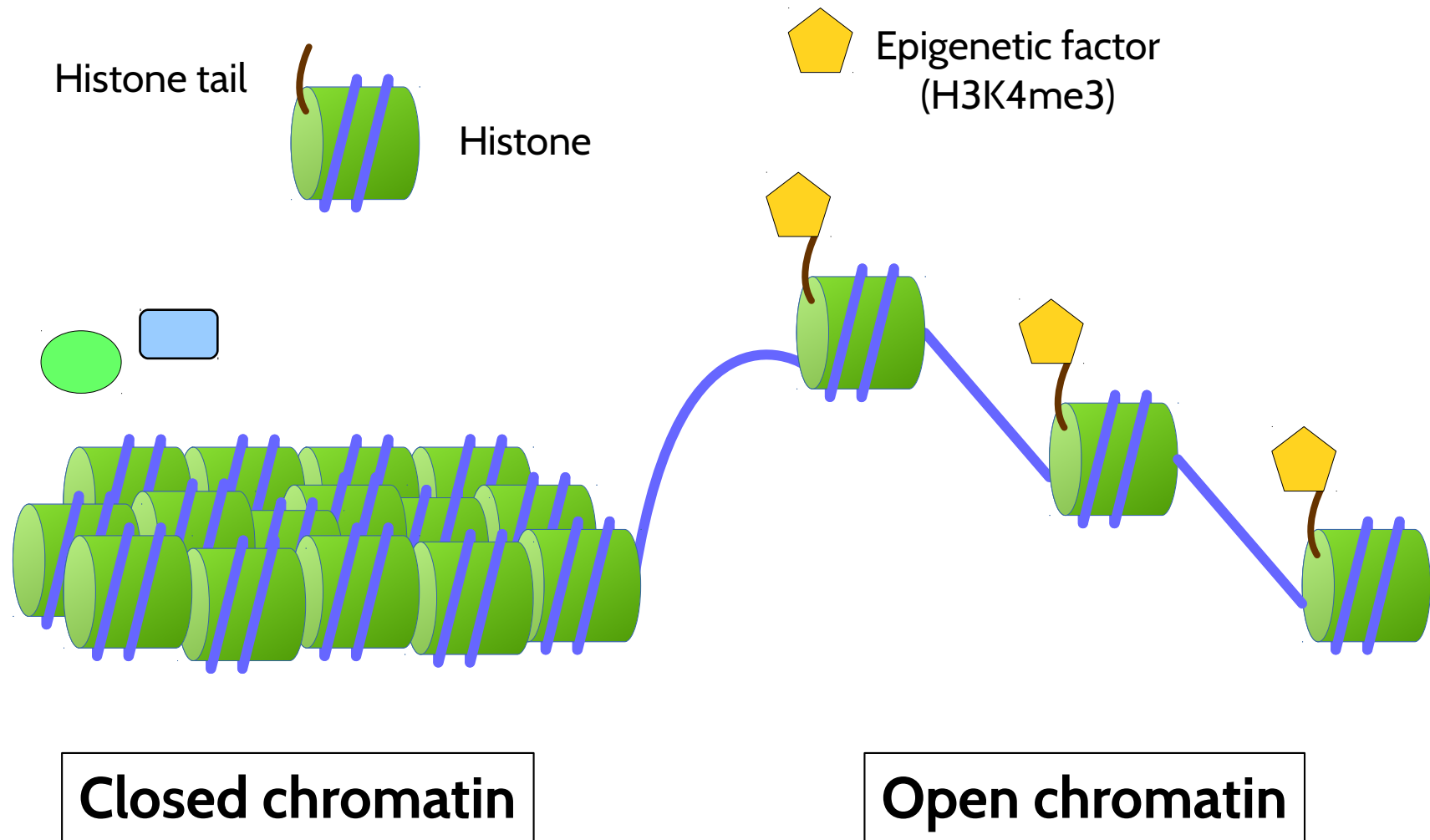
**Closed chromatin**

# Epigenetic mechanisms

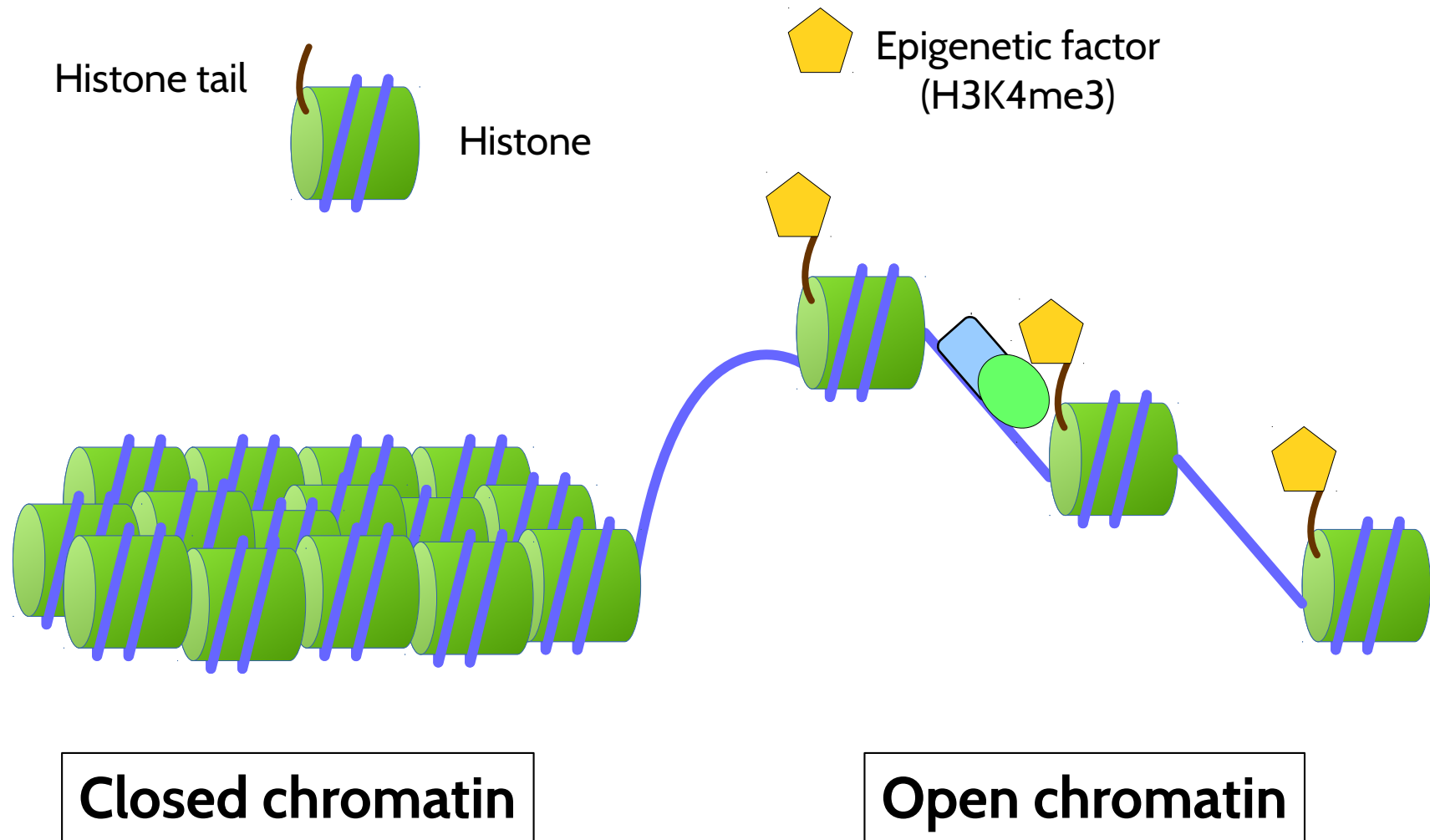


**Closed chromatin**

# Epigenetic mechanisms



# Epigenetic mechanisms



# Background (clinics)

# Copy Number Variation

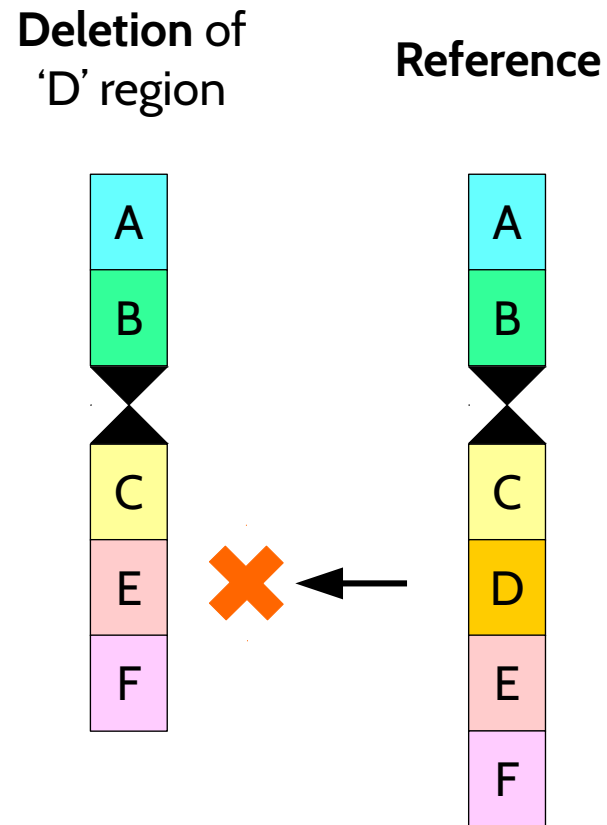
# Copy Number Variation

Reference

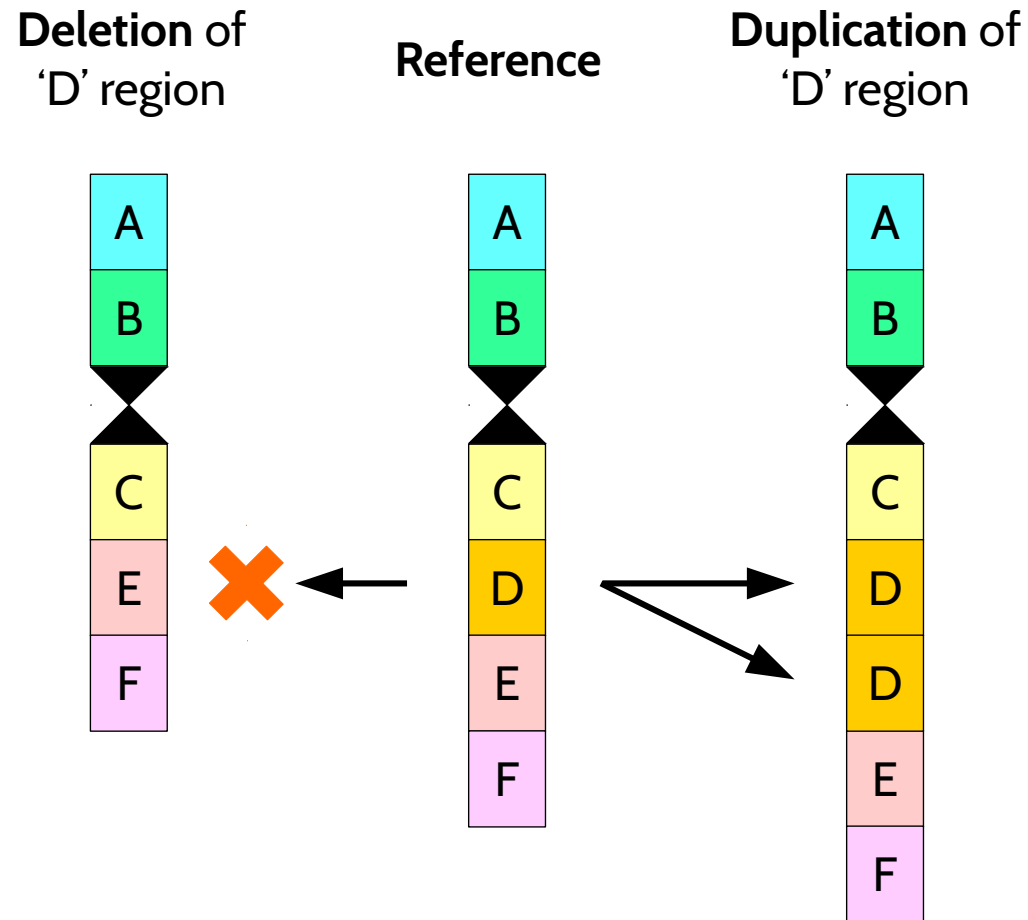




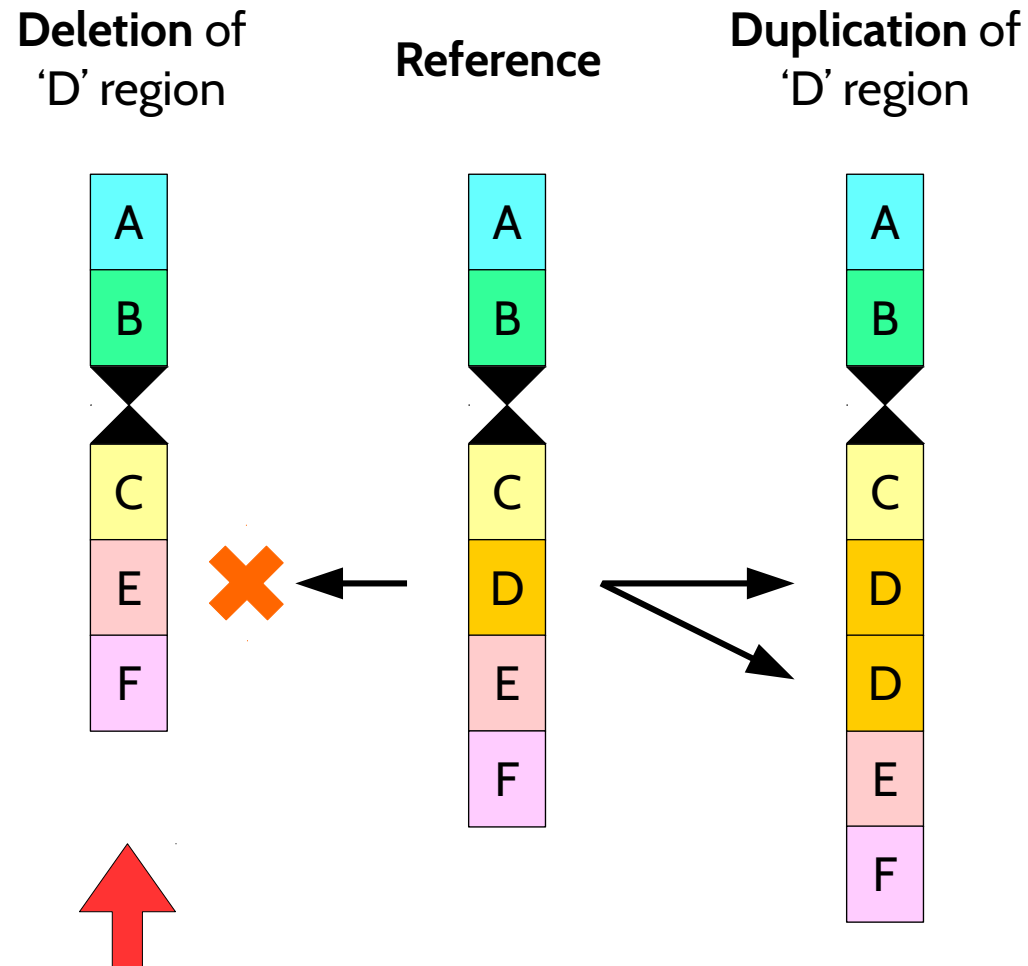
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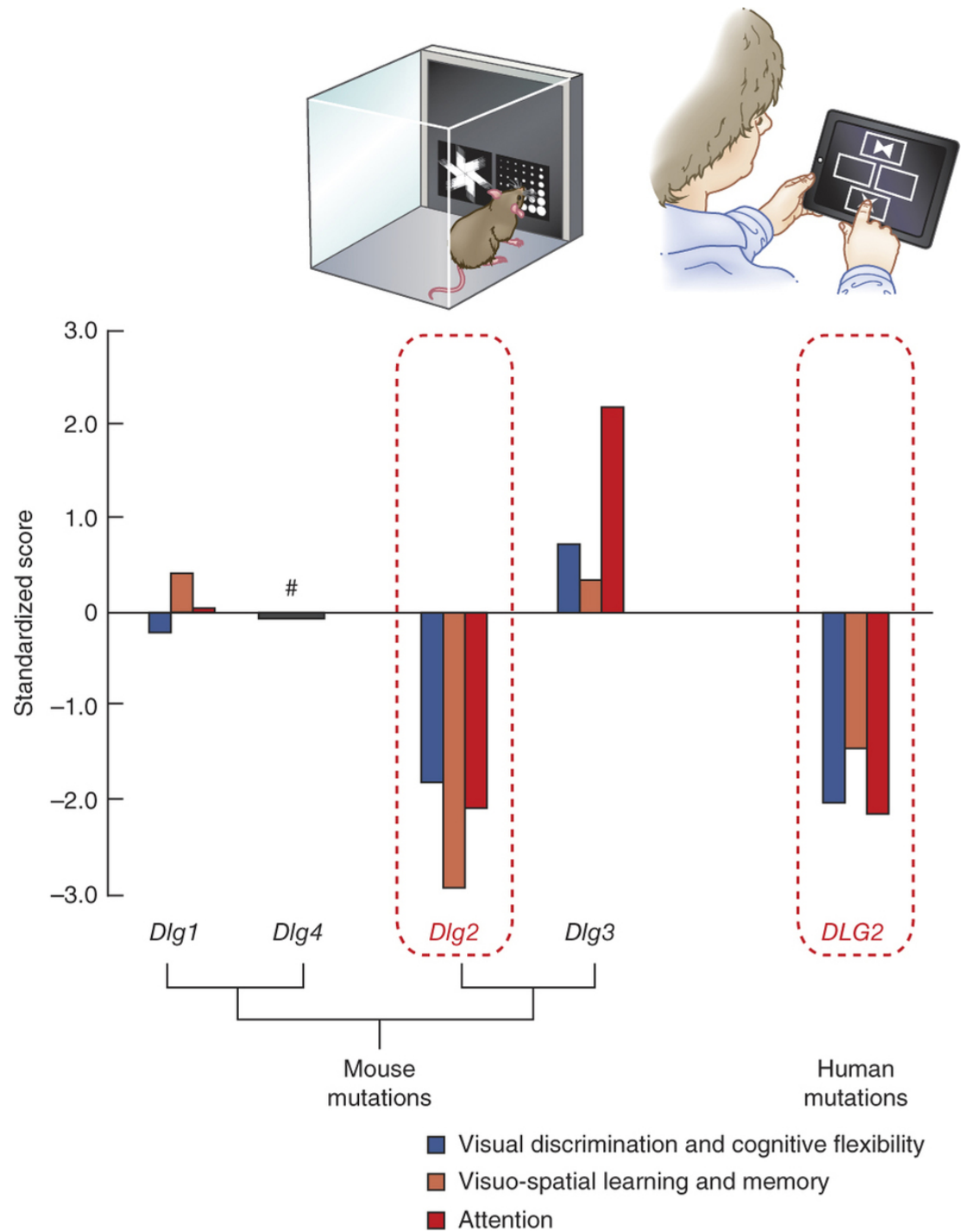
# *DLG2* gene

# DLG2 gene

Location: 11q14.1 (2.1Mb)

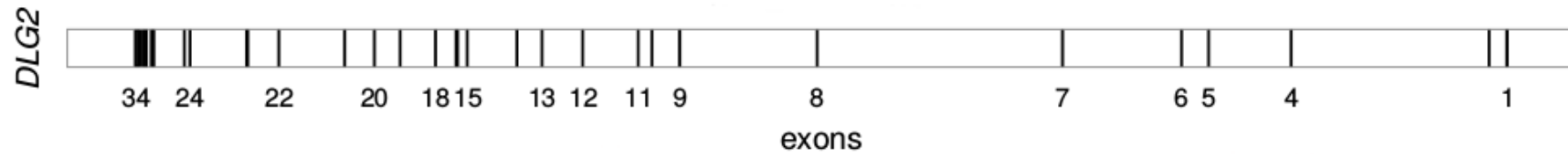
## Role

- complex learning
- cognitive flexibility
- attention

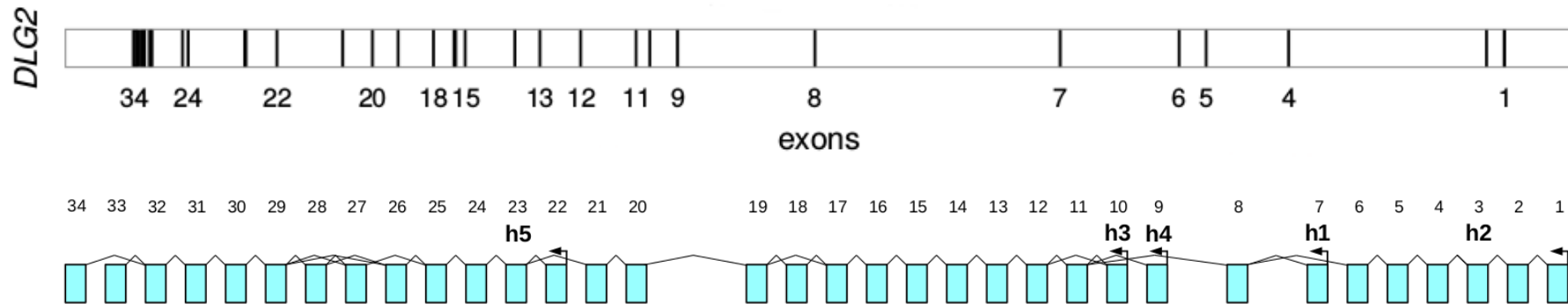


# How the investigation began

# *DLG2* patients

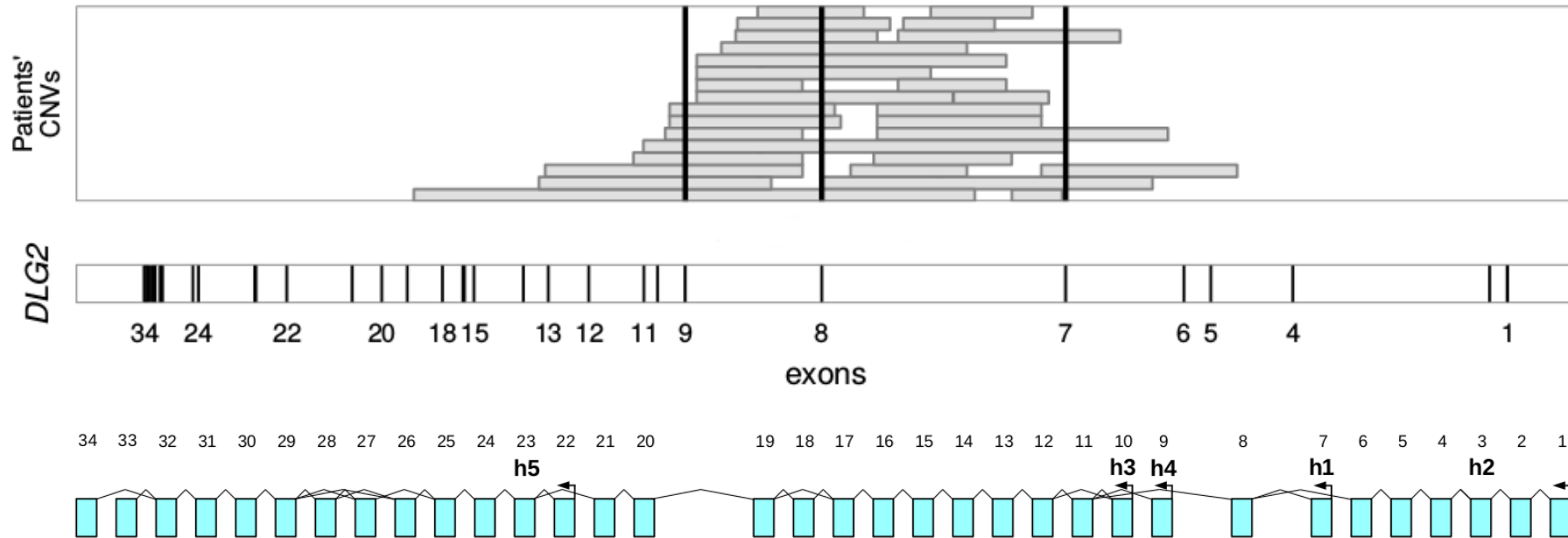


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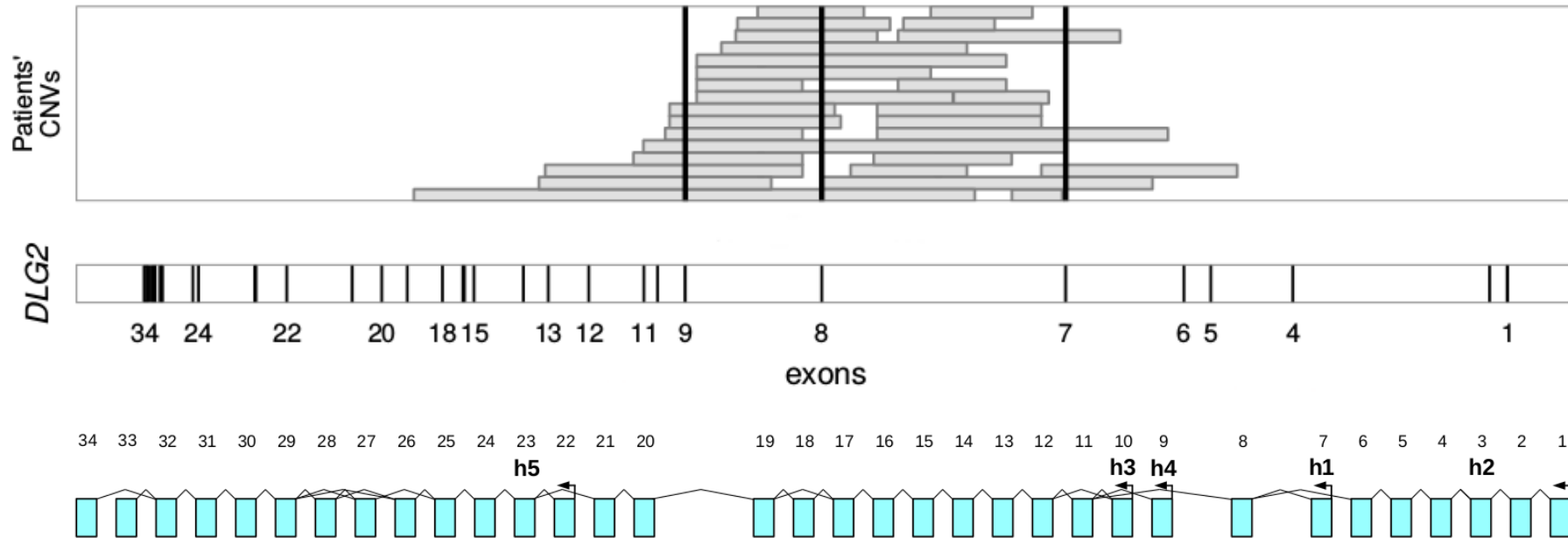




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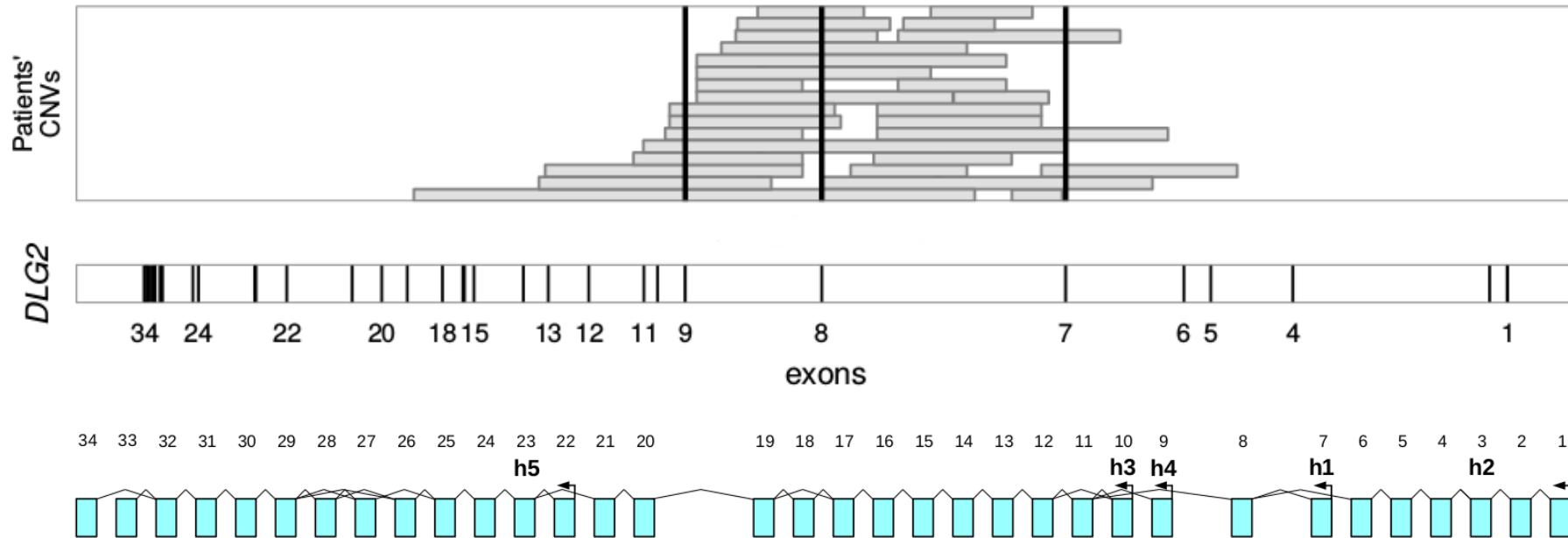


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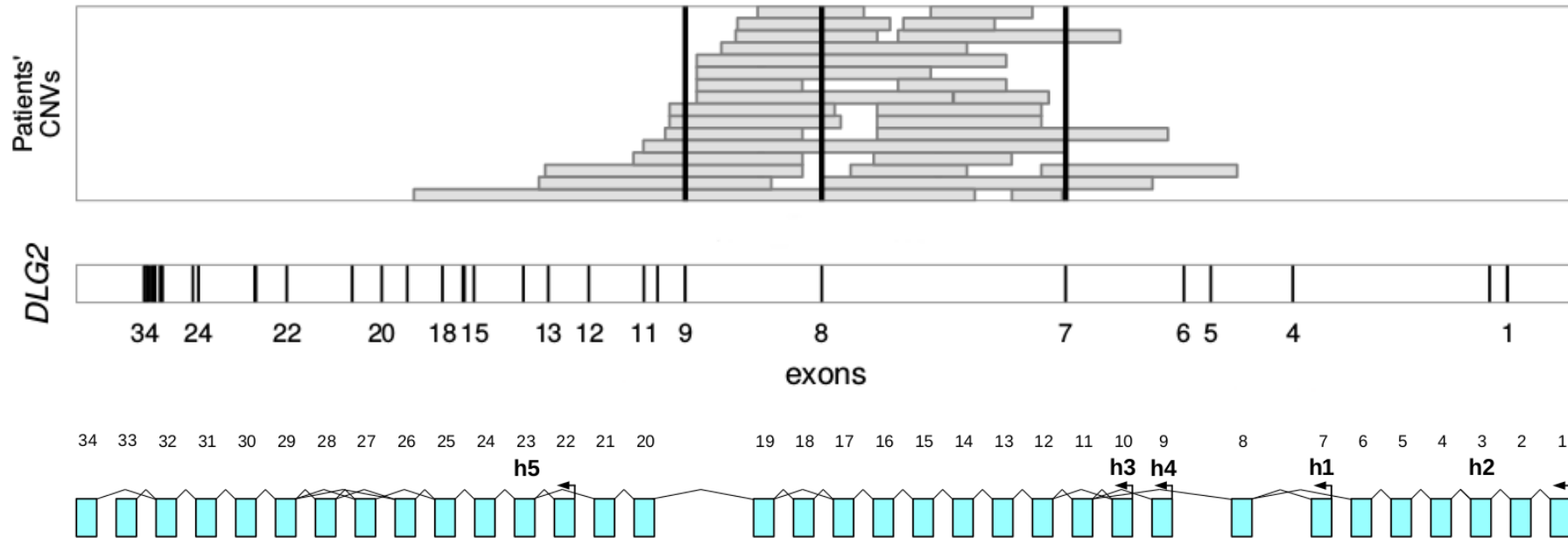
- 29 patients in the *DLG2* 7-9 region from DECIPHER, ULB, Literature

# DLG2 patients



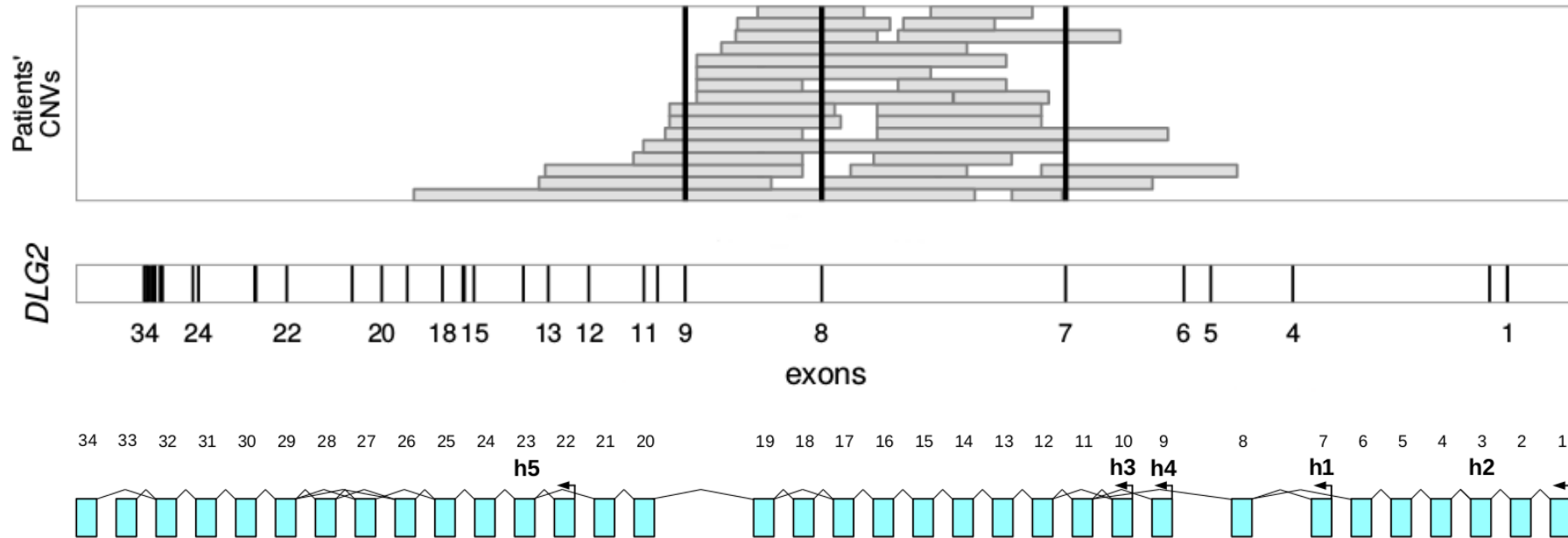
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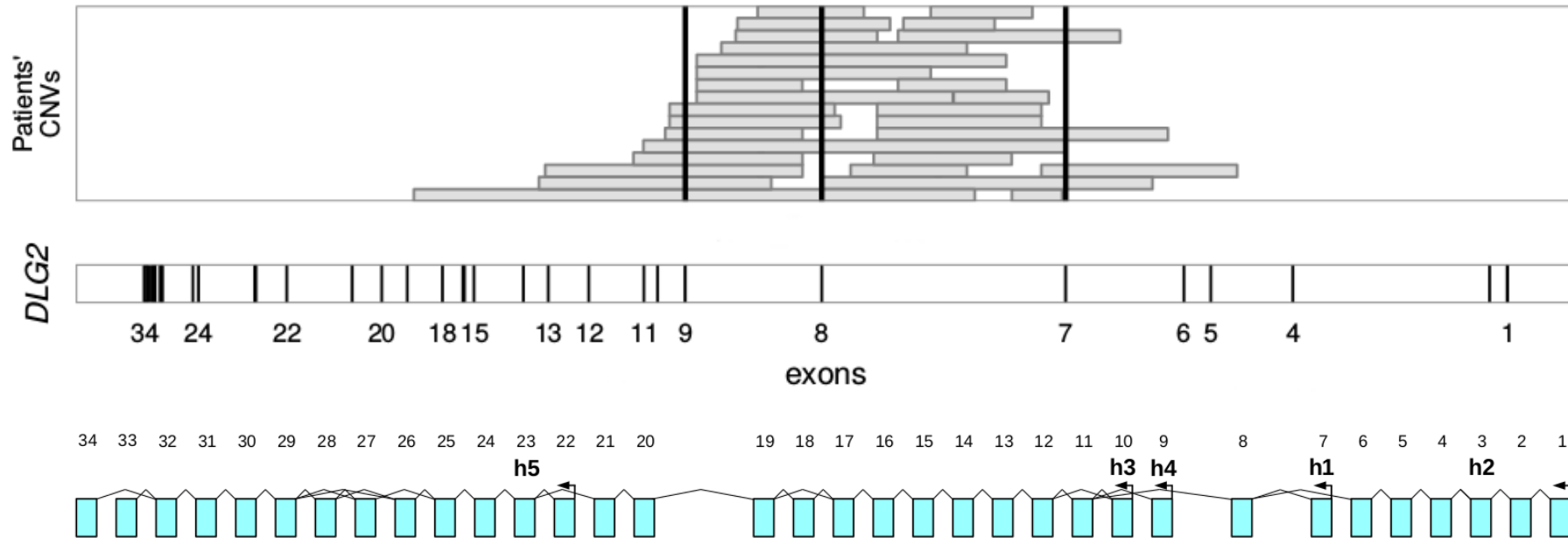
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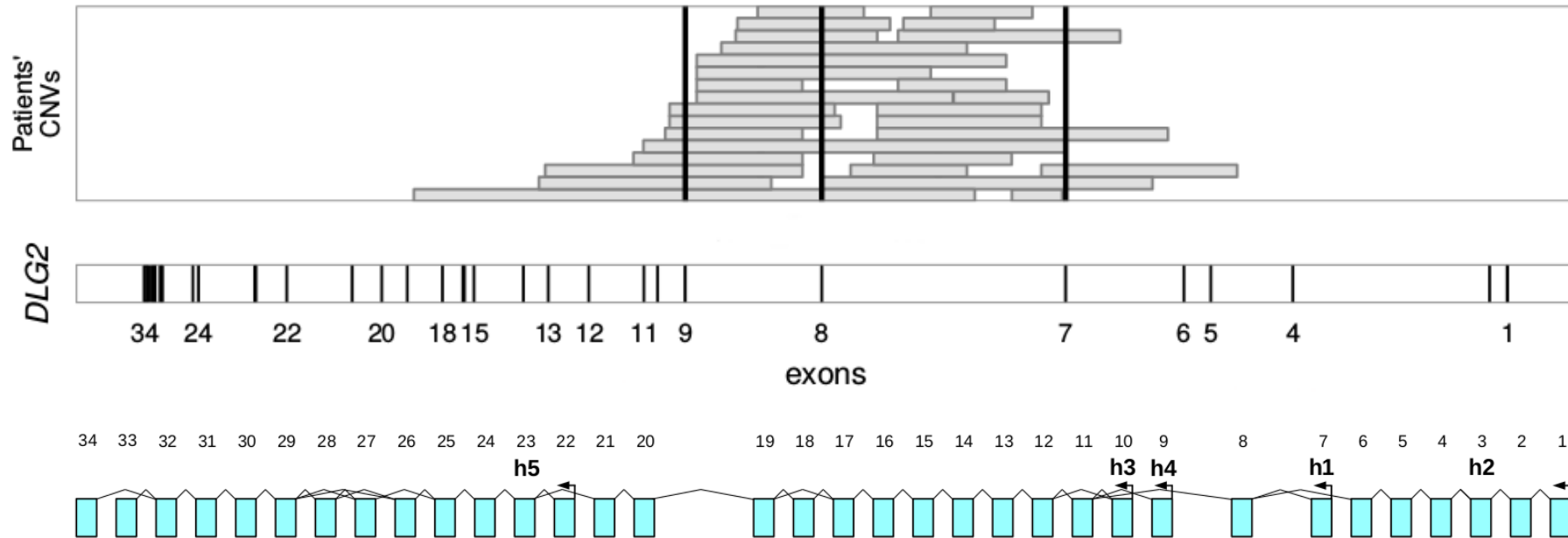
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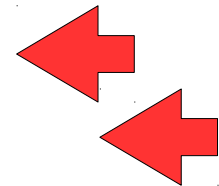


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# Integrative analysis of multi-omics data



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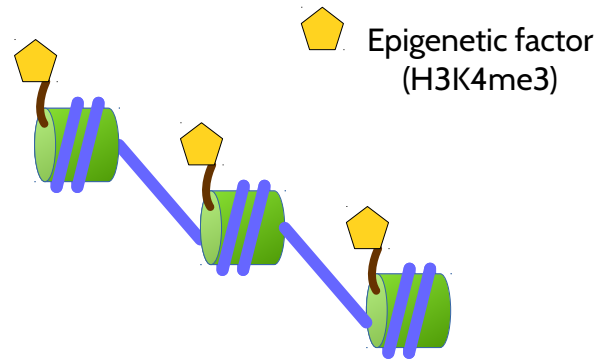
*Novel promoters and coding first exons in DLG2 linked to developmental disorders and intellectual disability*

# Integrative analysis of multi-omics data

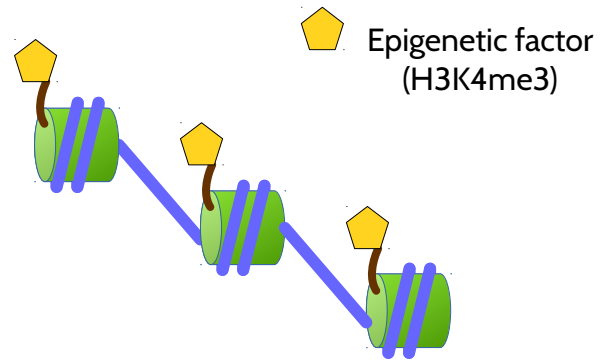
*Novel promoters and coding first exons in DLG2 linked to developmental disorders and intellectual disability*



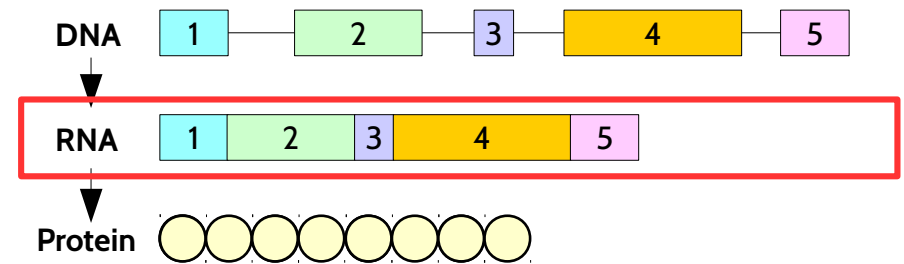
# Histone Modification H3K4me3



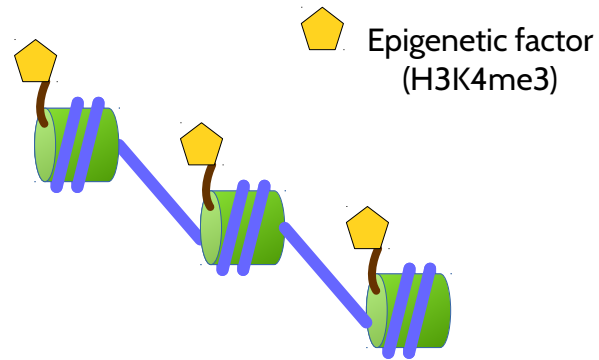
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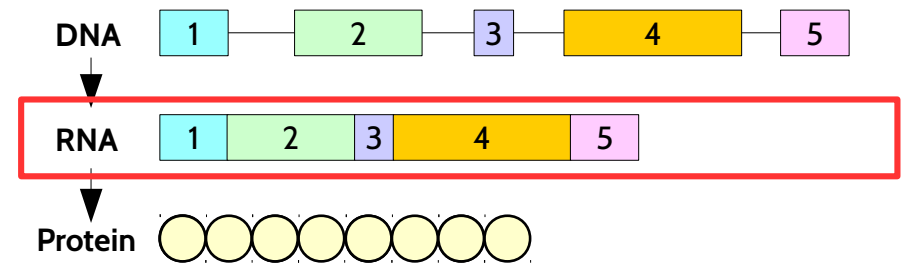
# Transcription, RNA



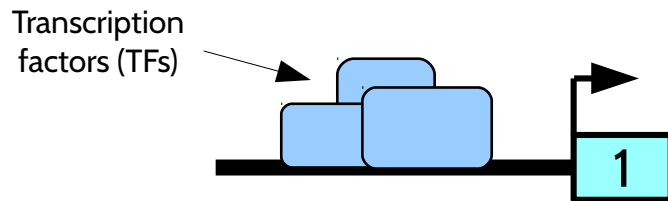
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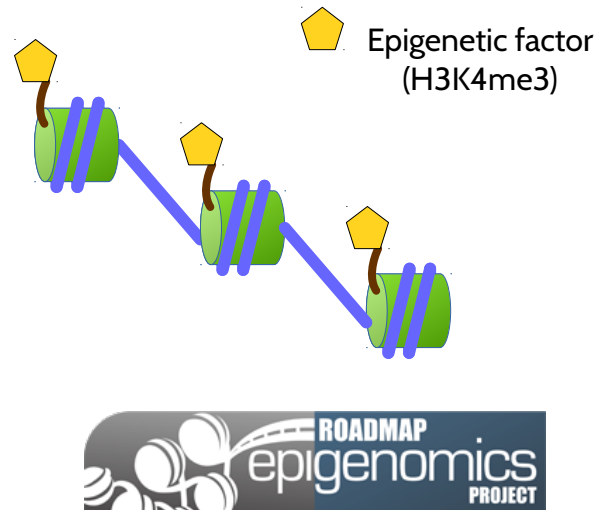
## Transcription, RNA



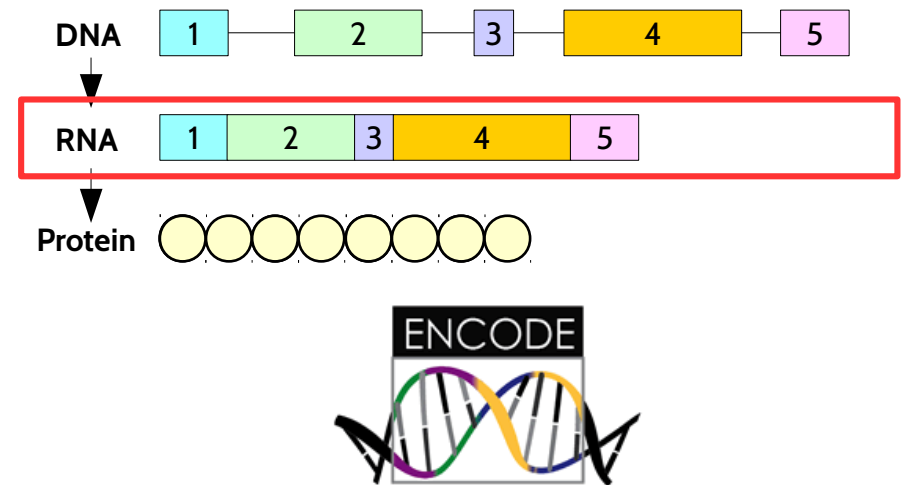
## Transcription Factor Binding Sites



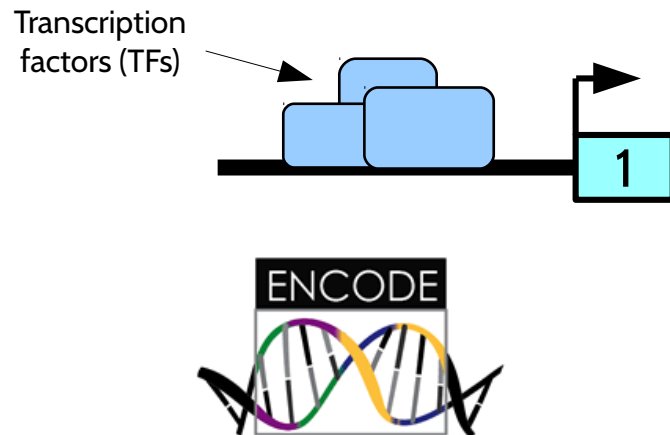
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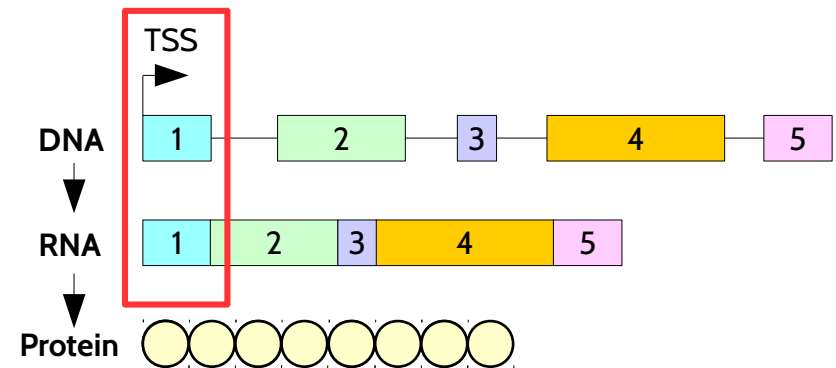
## Transcription, RNA



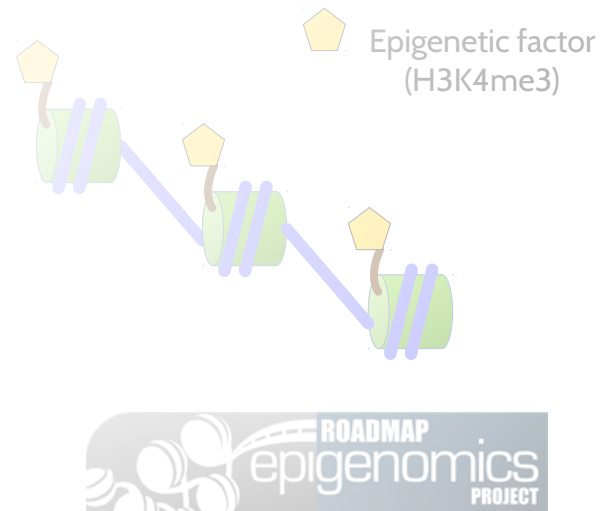
## Transcription Factor Binding Sites



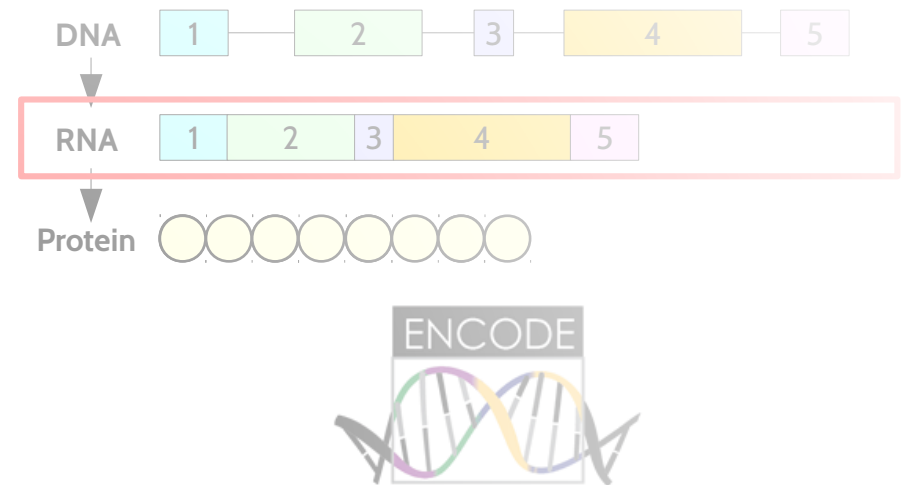
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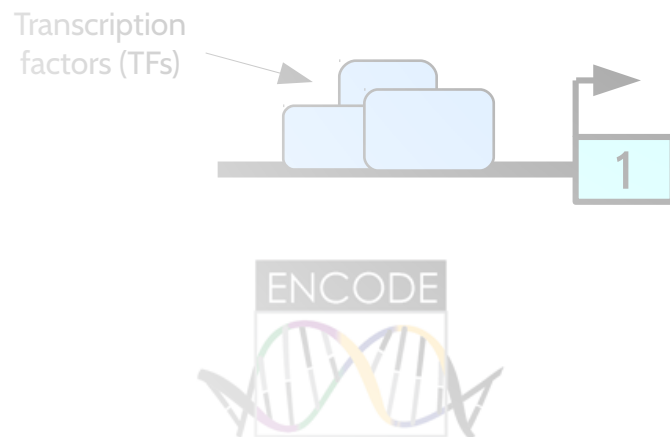
## Histone Modification H3K4me3



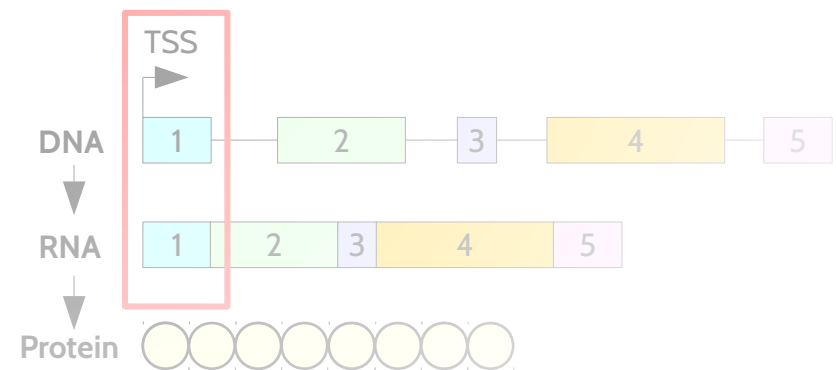
## Transcription, RNA



## Transcription Factor Binding Sites

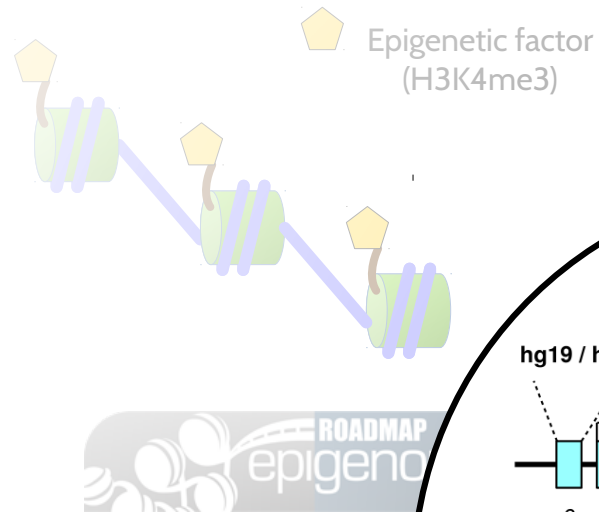


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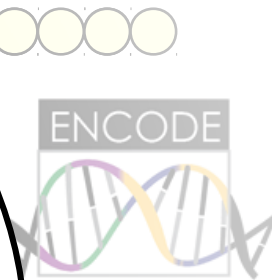
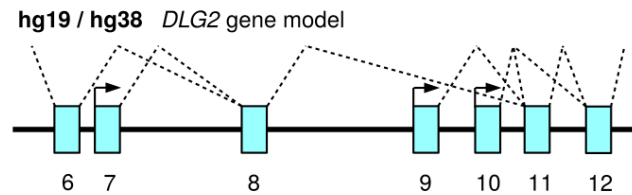
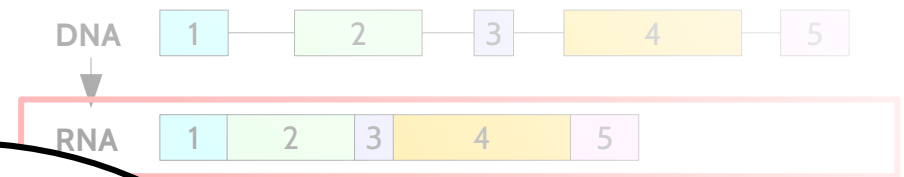




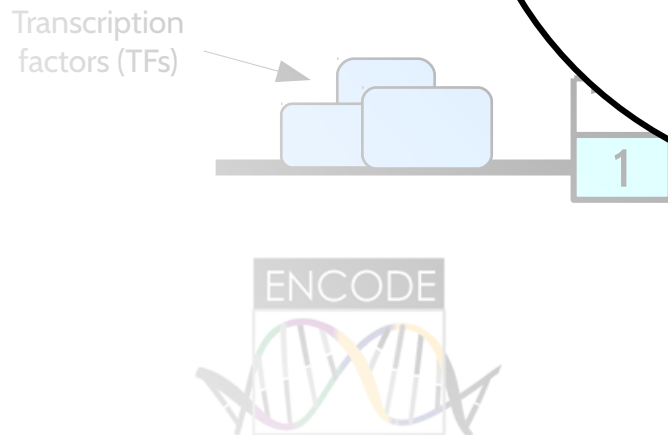
# Histone Modification H3K4me3



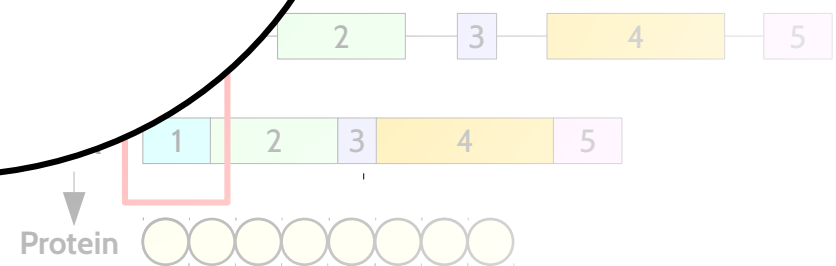
# Transcription, RNA



# Transcription Factor

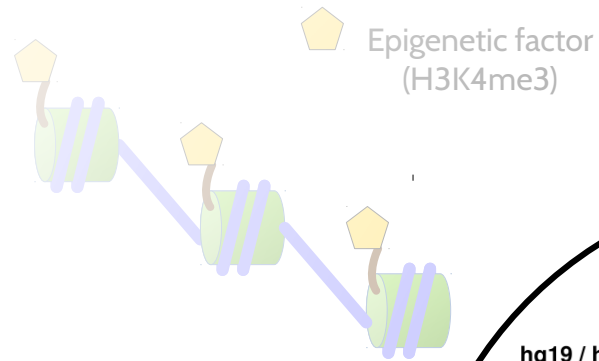


# on of TSS (CAGE)



# Histone Modification H3K4me3

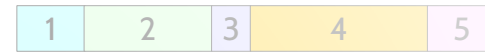
# Transcription, RNA



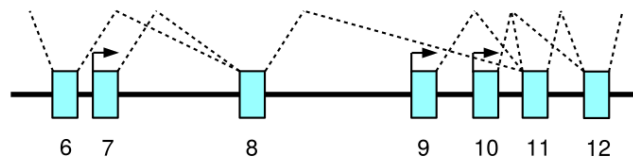
DNA



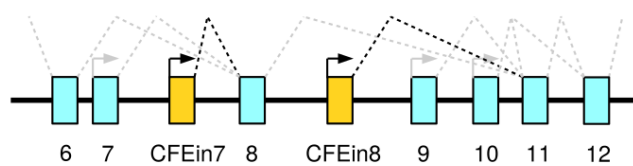
RNA



hg19 / hg38 *DLG2* gene model



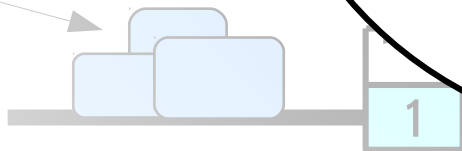
New *DLG2* gene model



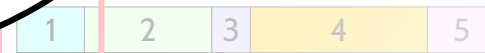
# Transcription Factor

# on of TSS (CAGE)

Transcription factors (TFs)

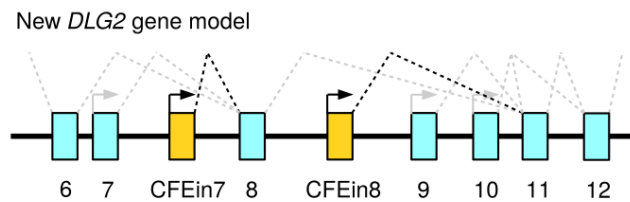
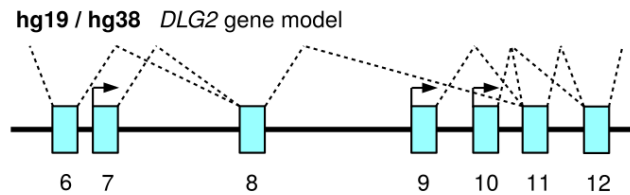
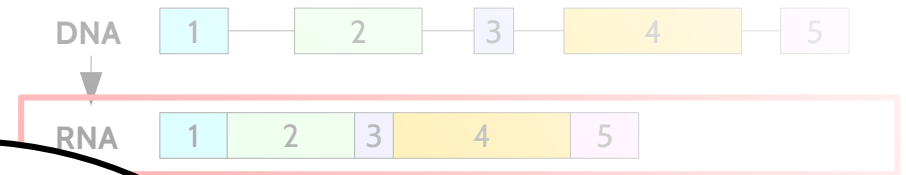
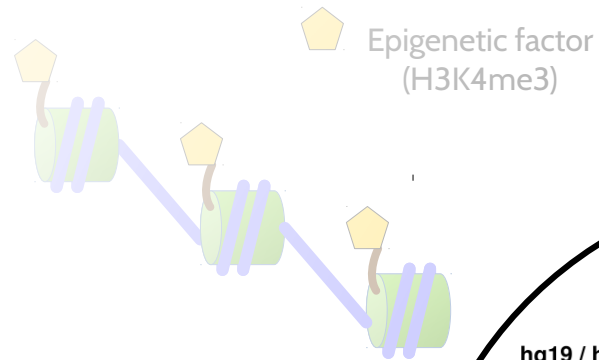


Protein



# Histone Modification H3K4me3

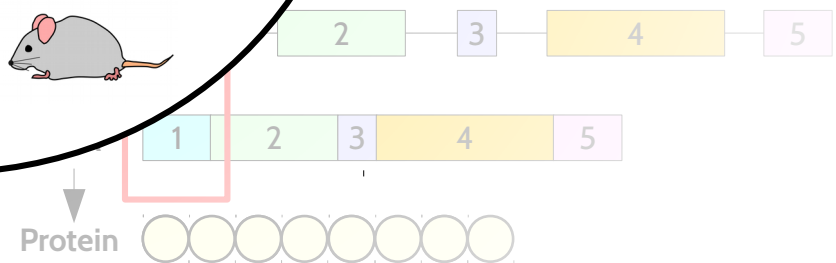
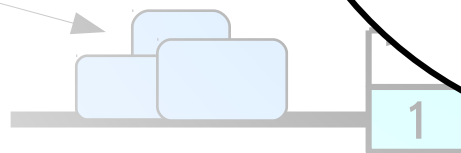
# Transcription, RNA



# Transcription Factor

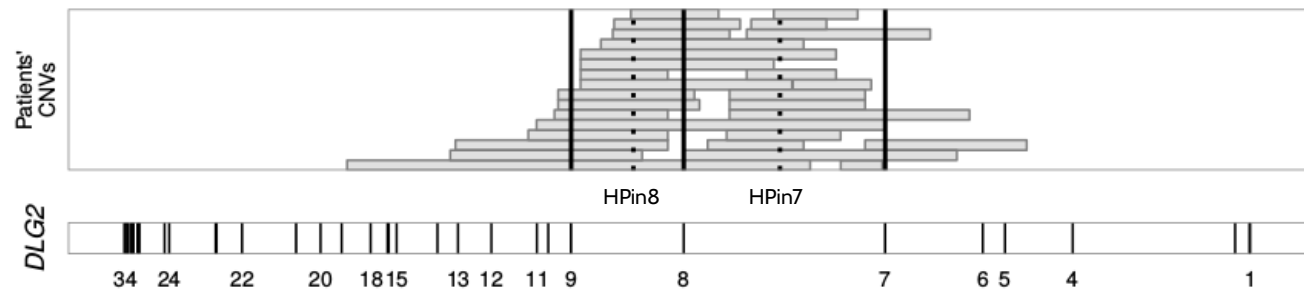
# on of TSS (CAGE)

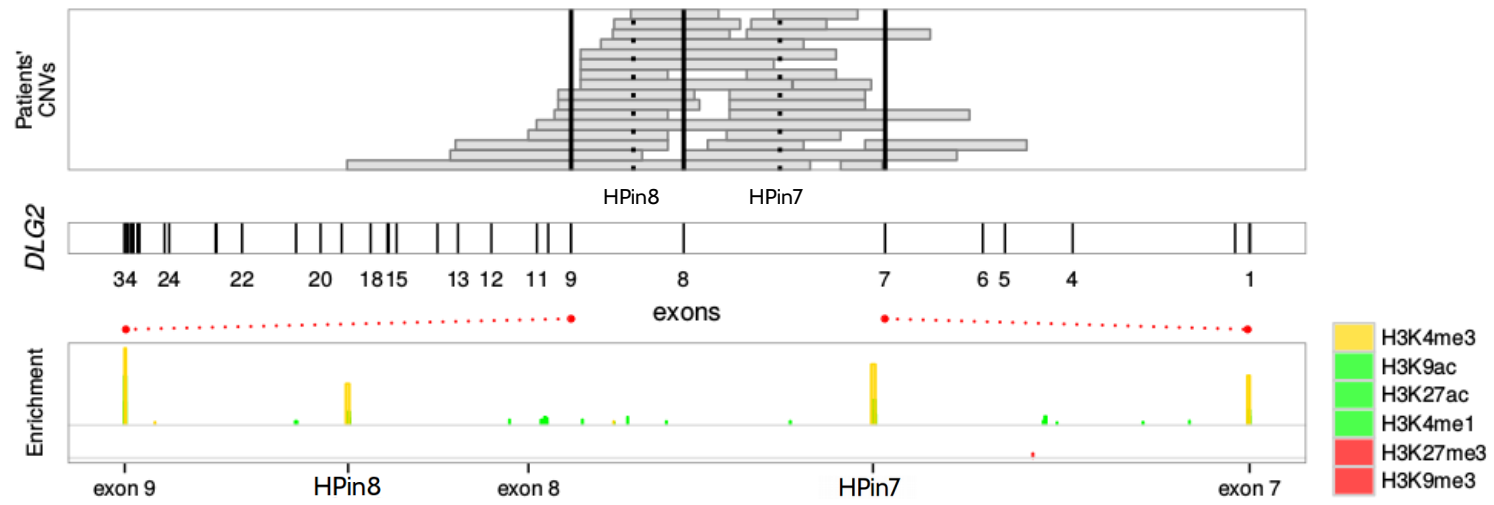
Transcription factors (TFs)

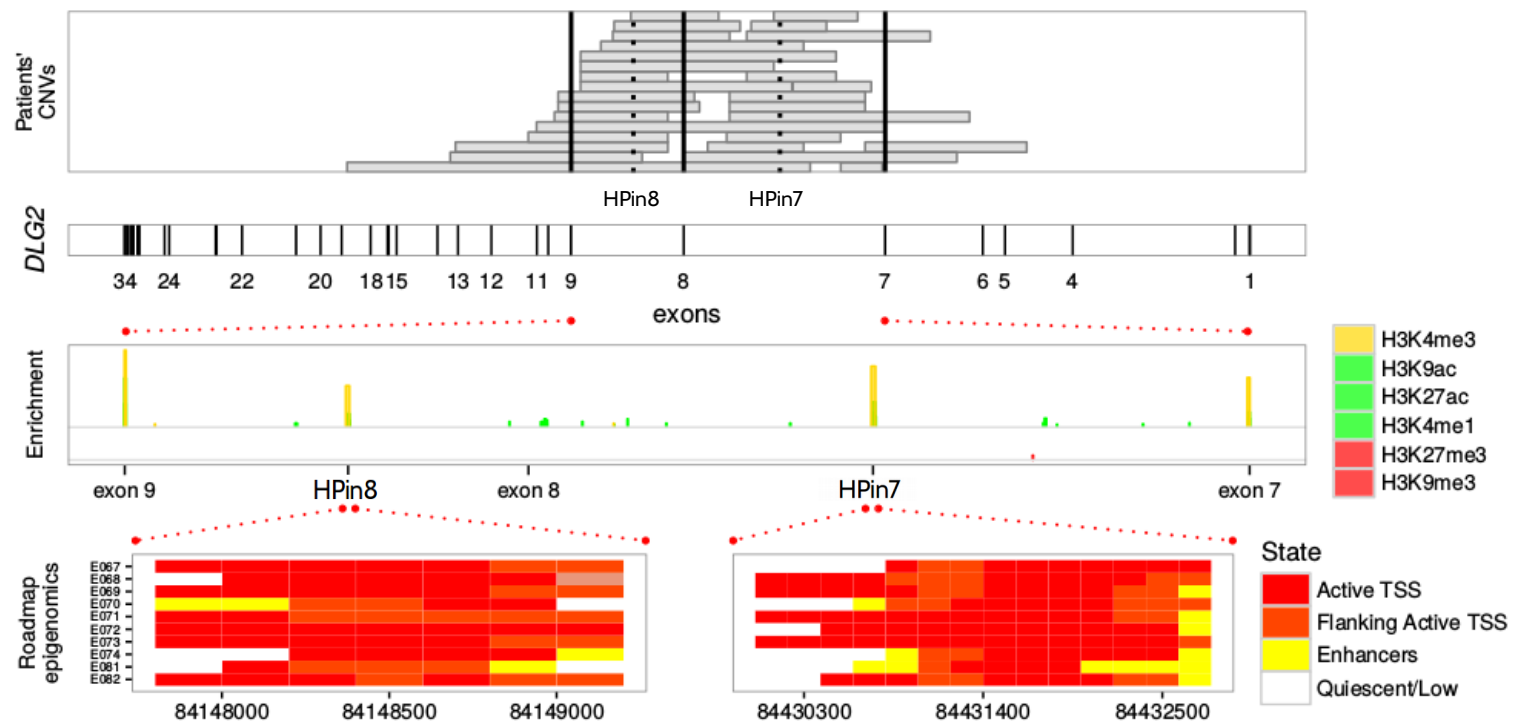


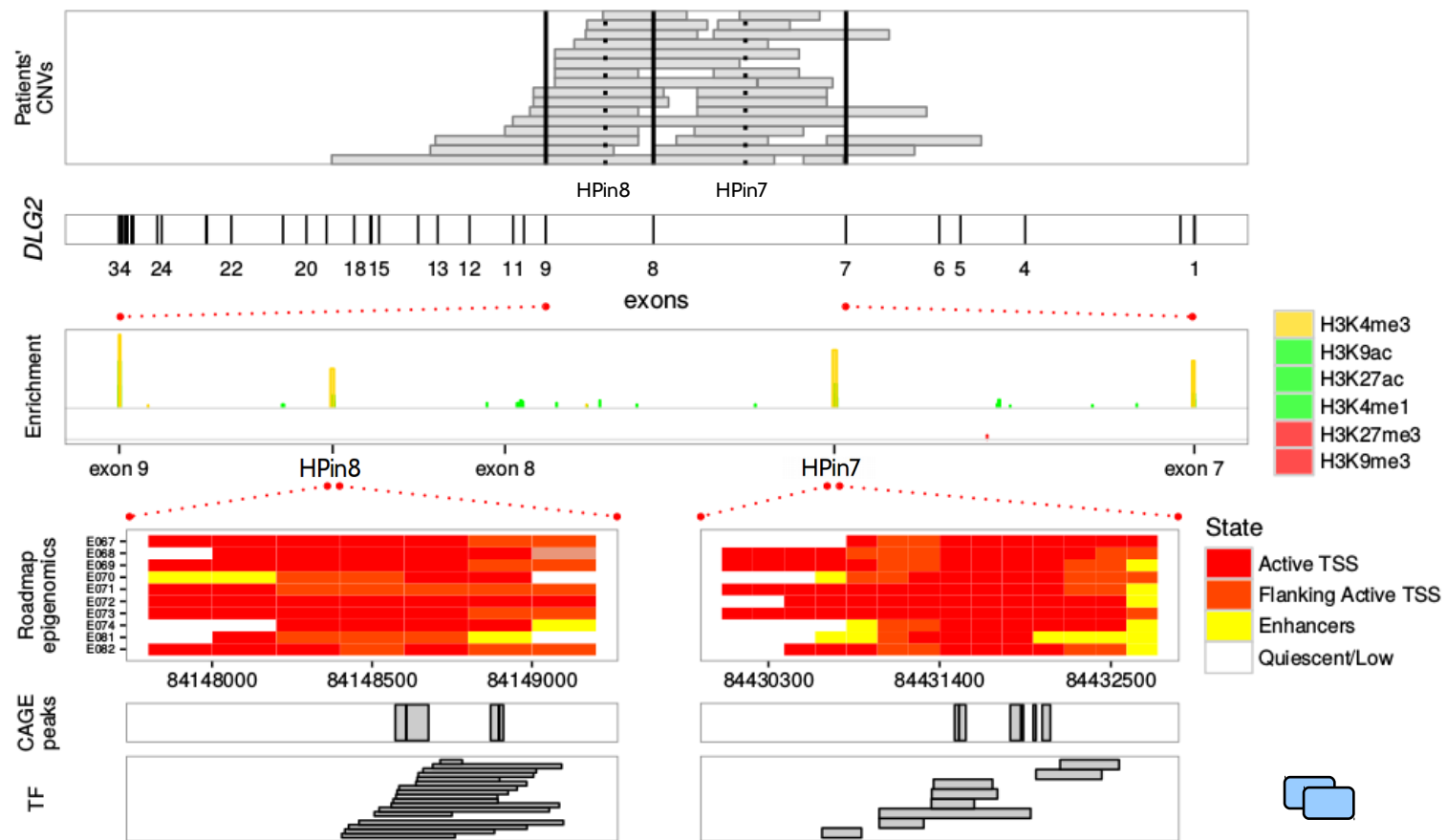
# Integrative analysis of multi-omics data (part II)

*Novel promoters and coding first exons in DLG2 linked to  
developmental disorders and intellectual disability*



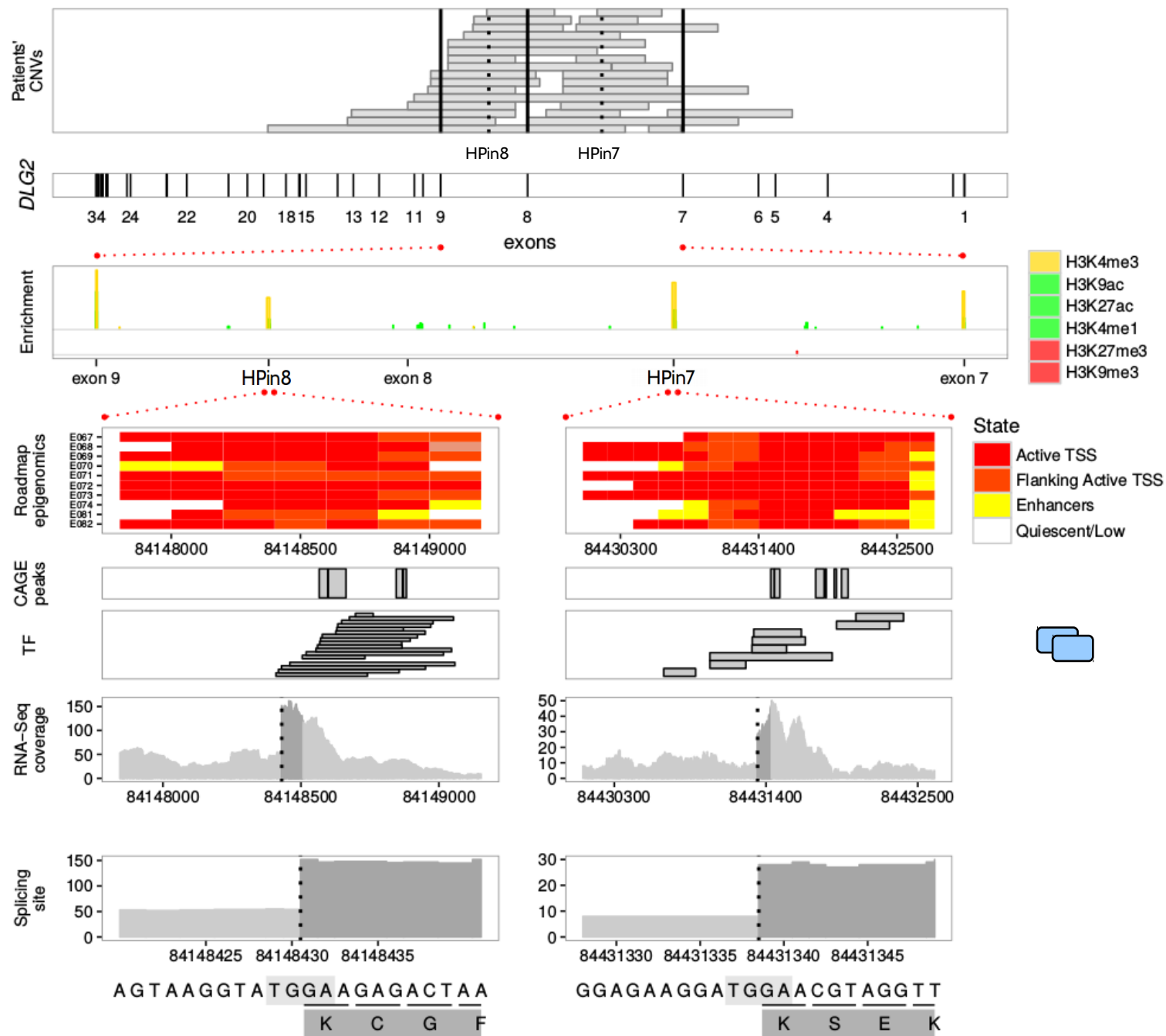


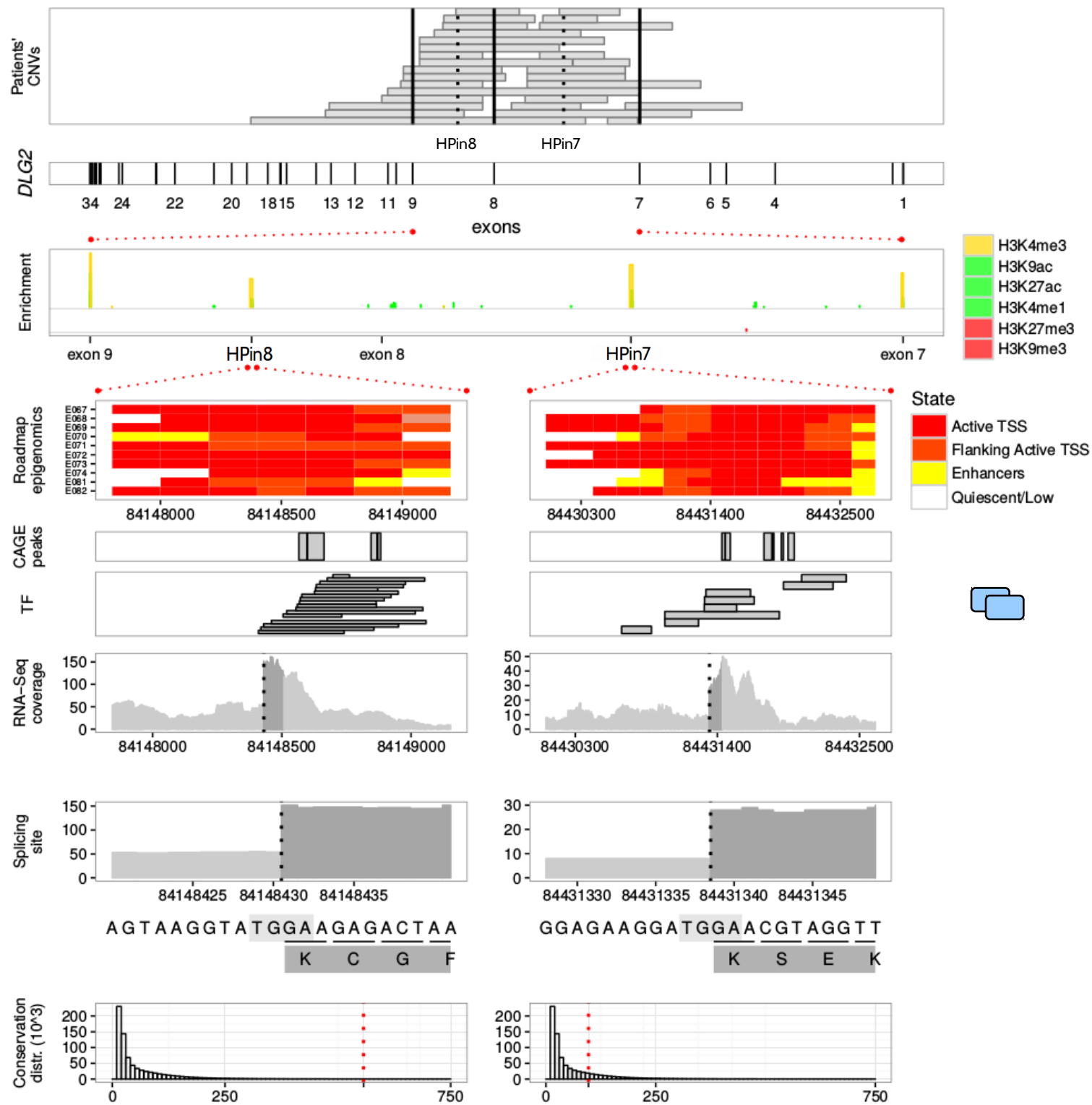




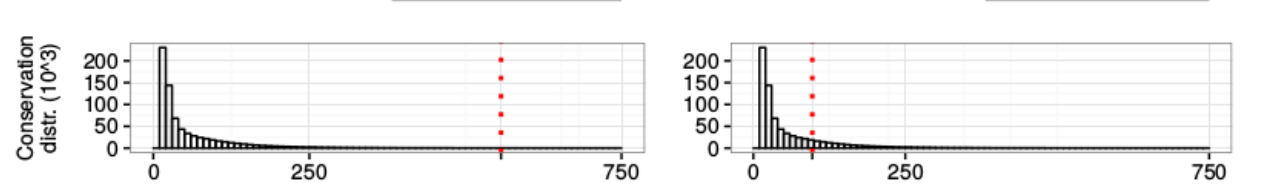
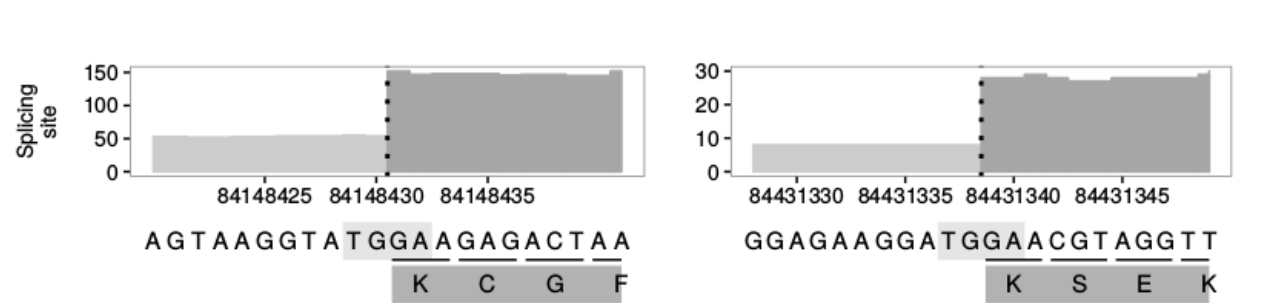
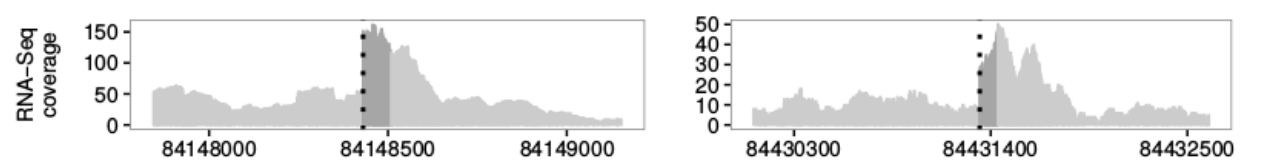
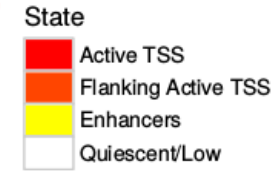
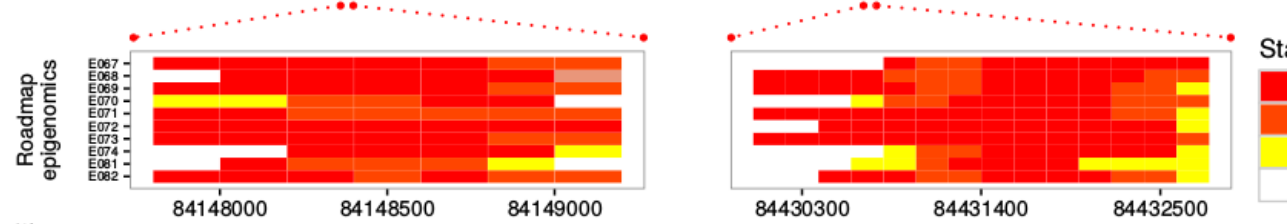
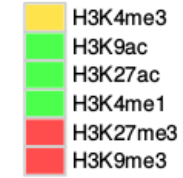
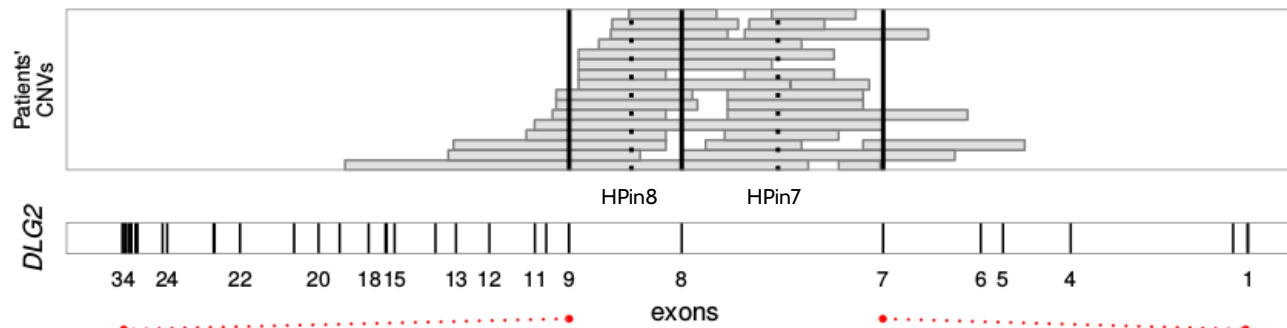








DECIPHER  
ULB  
Literature

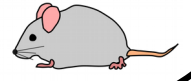
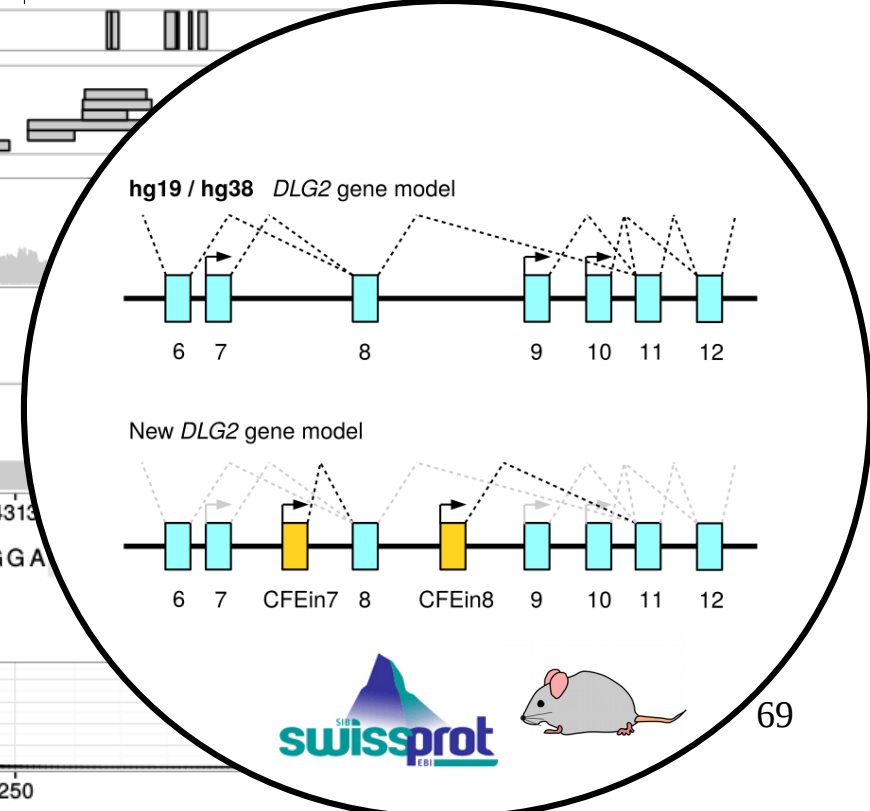
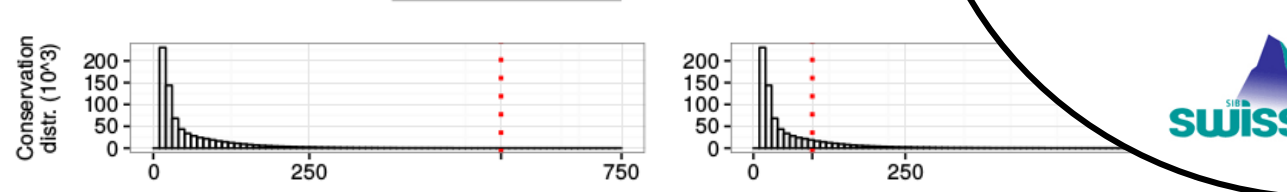
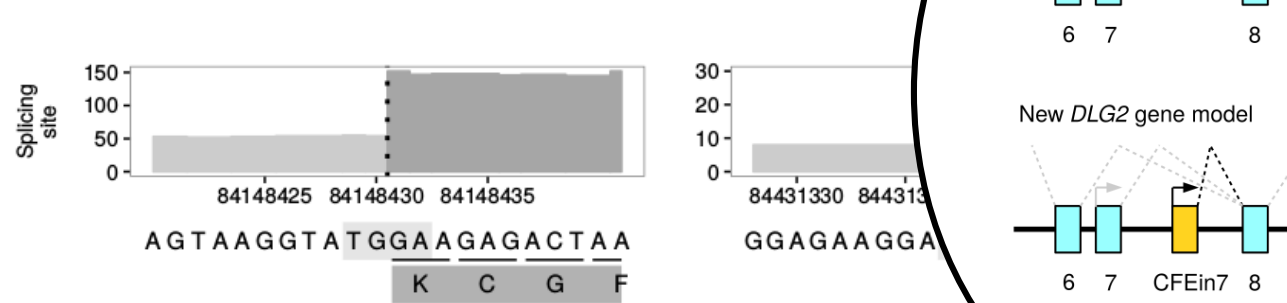
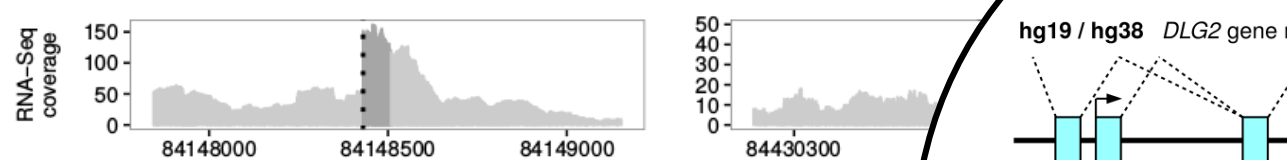
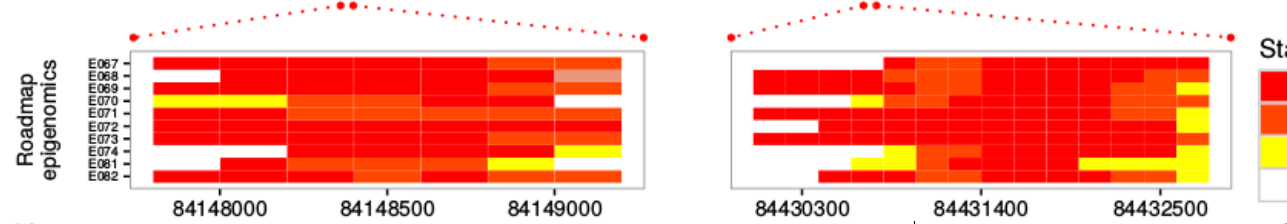
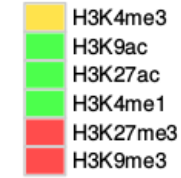
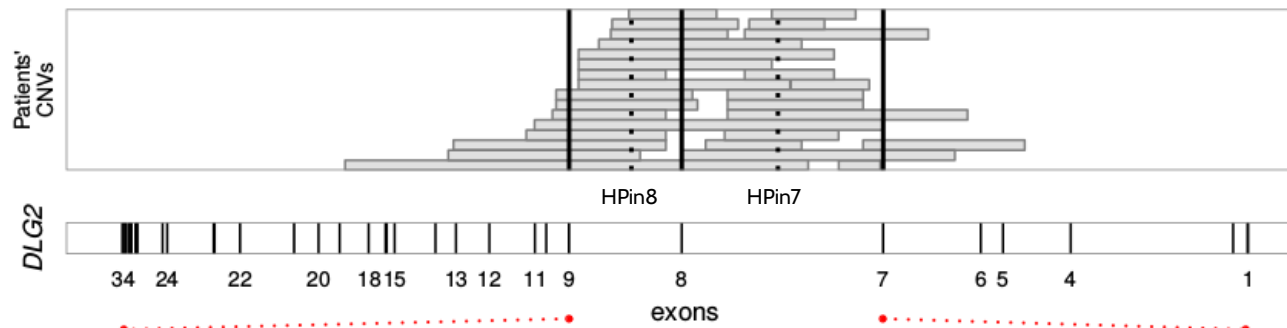


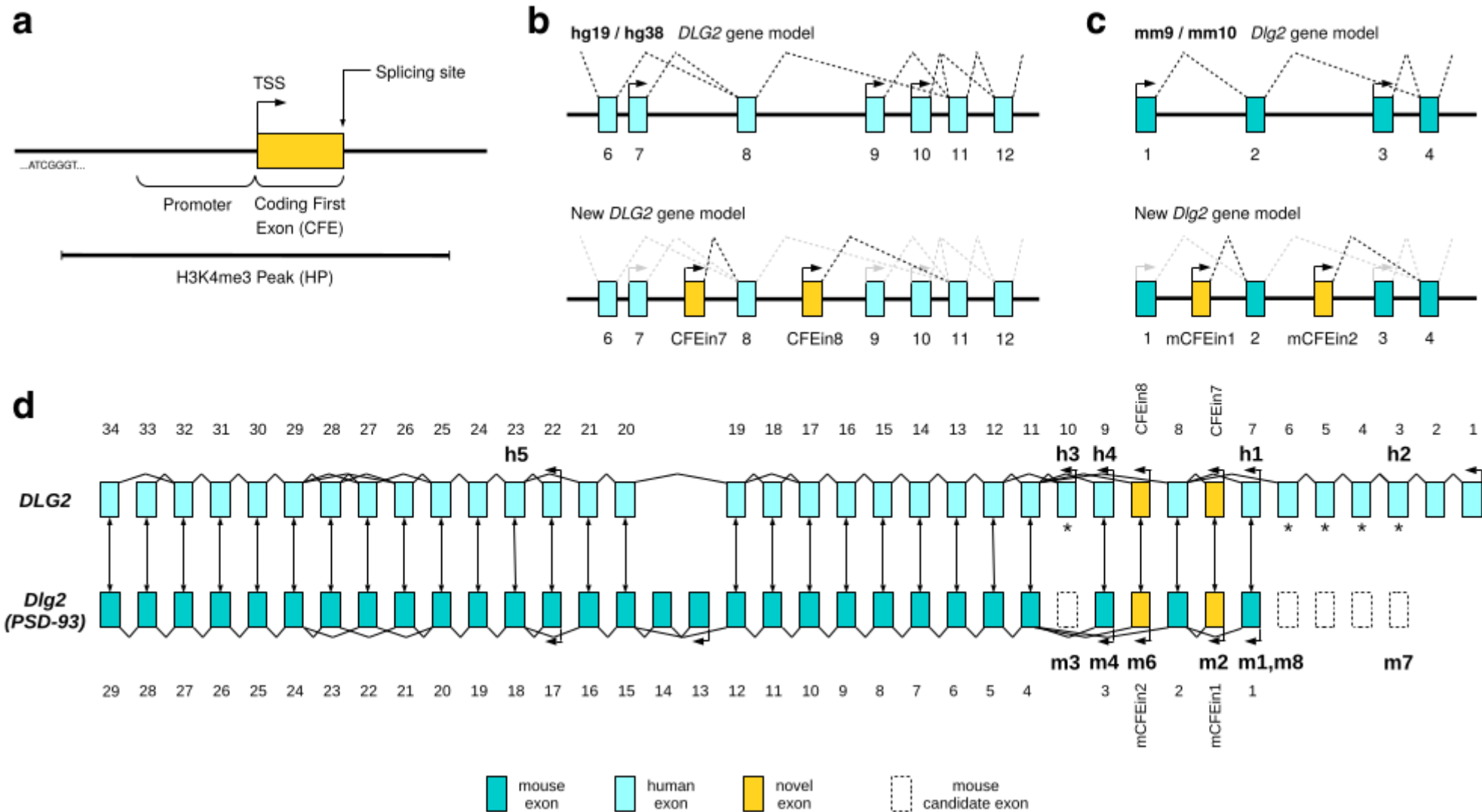
Roadmap  
Epigenomics

FANTOM5

ENCODE  
(fetal brain)

DECIPHER  
ULB  
Literature

















# Statistical analysis

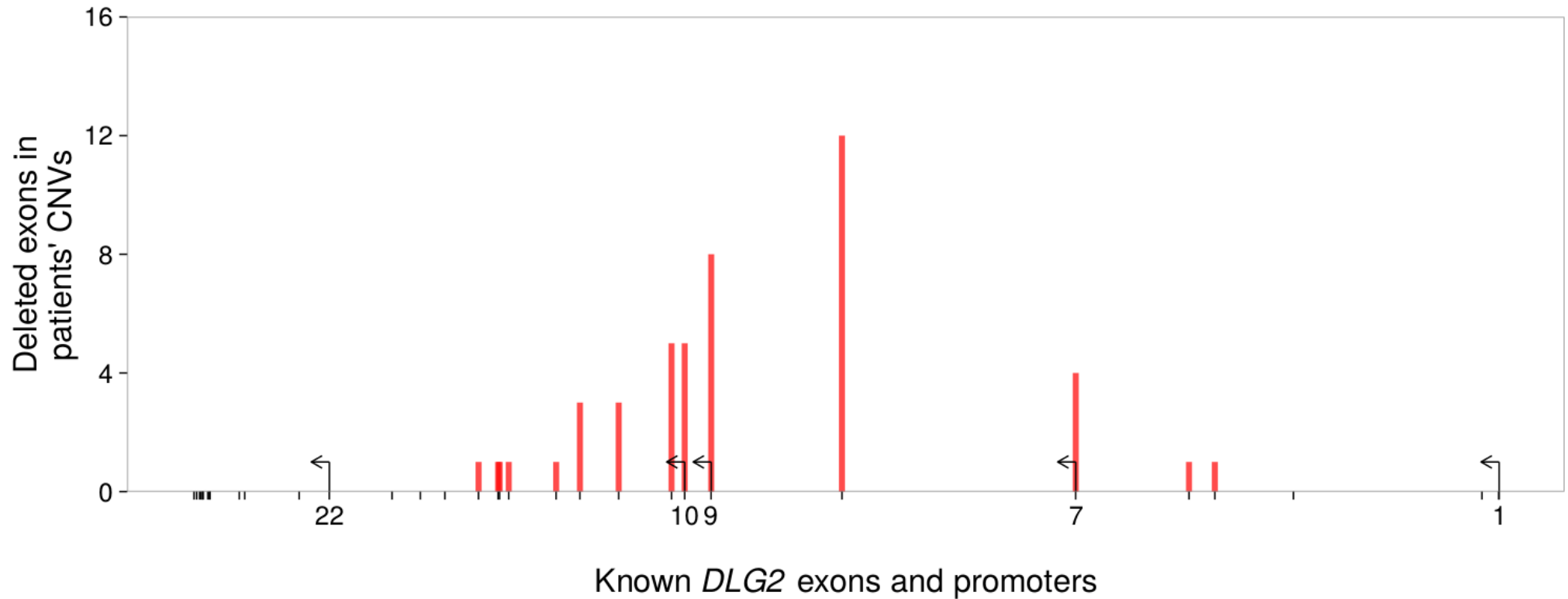
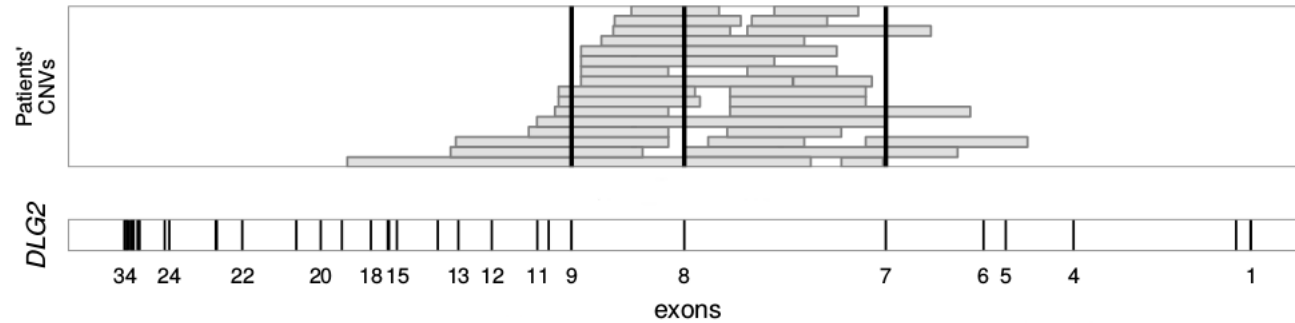
# Statistical analysis

*Novel promoters and coding first exons in DLG2 linked to developmental disorders and intellectual disability*

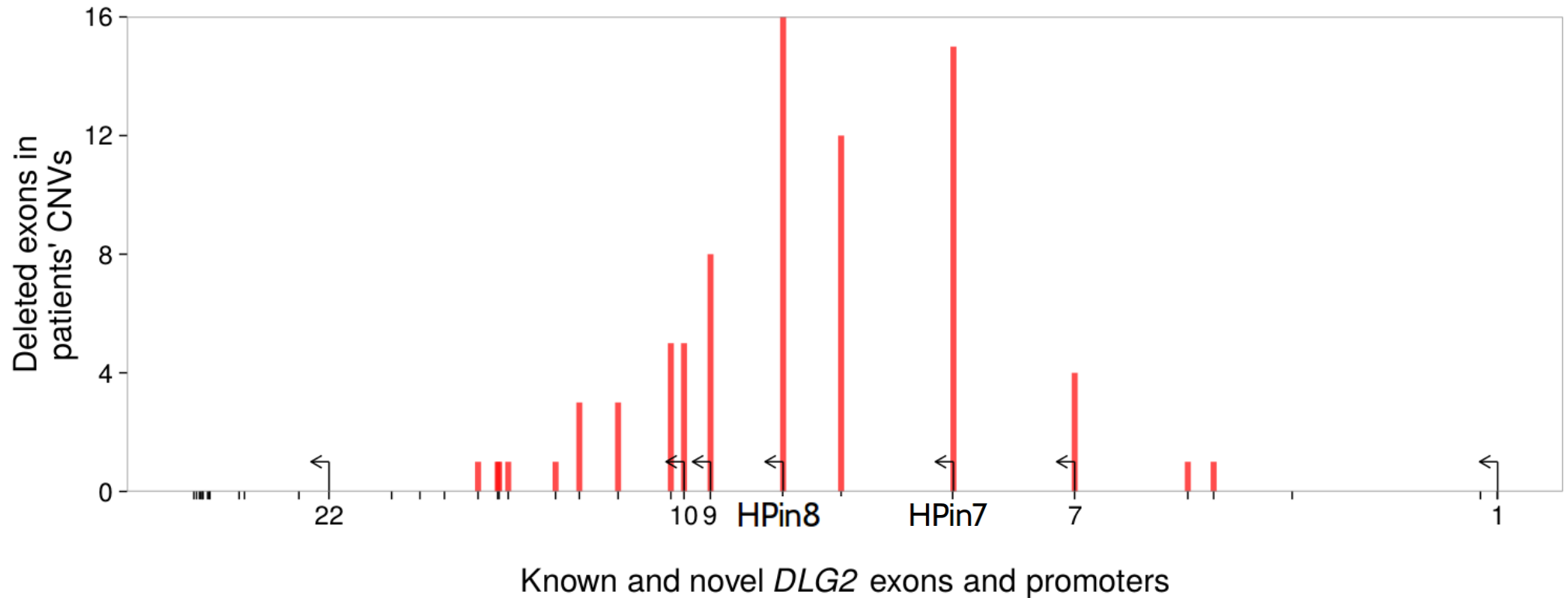
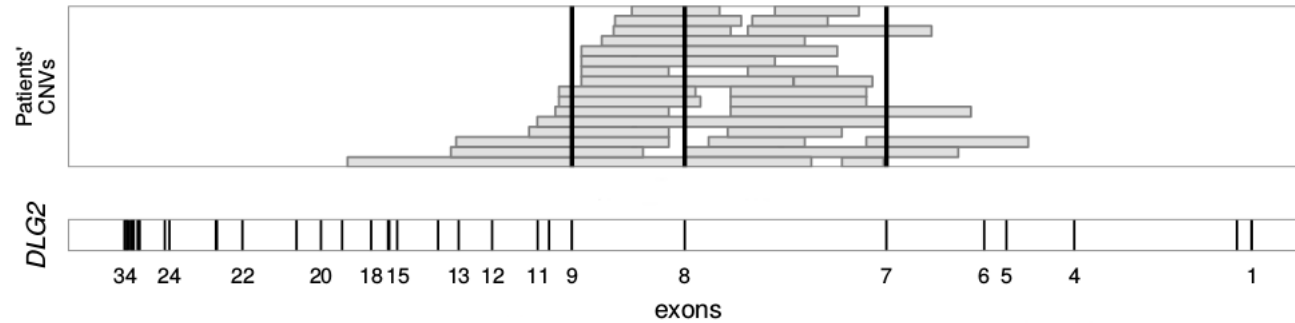
# Statistical analysis

*Novel promoters and coding first exons in DLG2 linked to developmental disorders and intellectual disability*

# Old *DLG2* gene model



# New *DLG2* gene model





# Statistical analysis

- DECIPHER (cases) vs DGV (control)
  - on exons 7,8,9: enrichment of cases pv.  $6 \times 10^{-04}$
  - on HPs: enrichment of cases, pv.  $8 \times 10^{-07}$

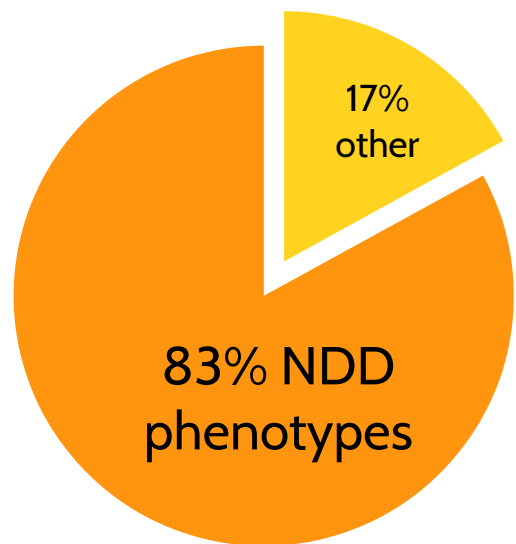
# Statistical analysis

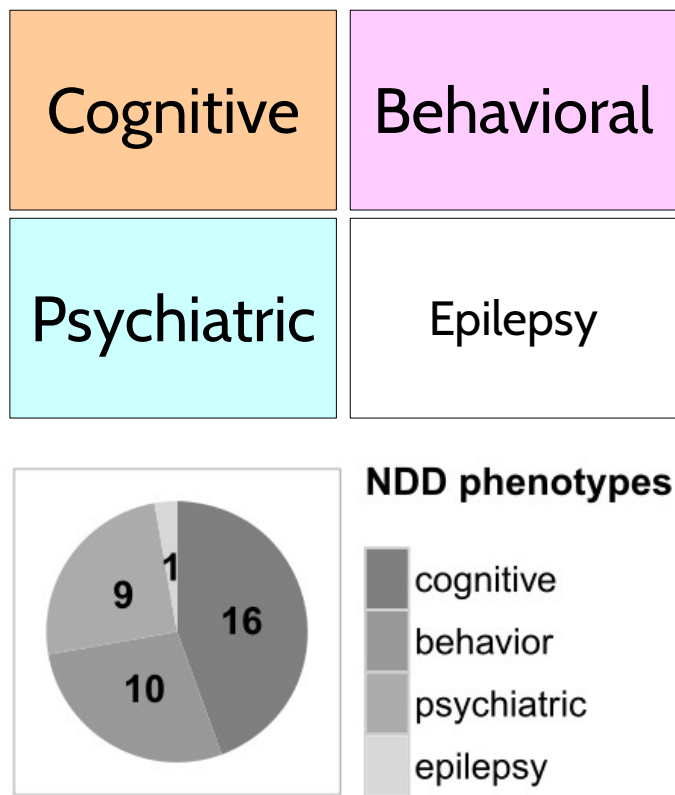
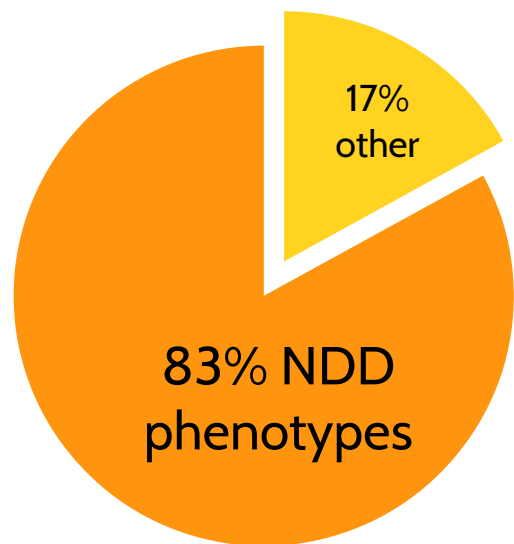
- DECIPHER (cases) vs DGV (control)
  - on exons 7,8,9: enrichment of cases pv.  **$6 \times 10^{-04}$**
  - on HPs: enrichment of cases, pv.  **$8 \times 10^{-07}$**
- GDD/ID cases vs GDD/ID control
  - on exons 7,8,9: enrichment of cases pv. **0.38**
  - on HPs: enrichment of cases, pv.  **$4 \times 10^{-04}$**

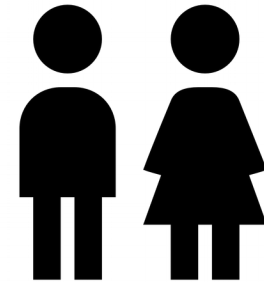
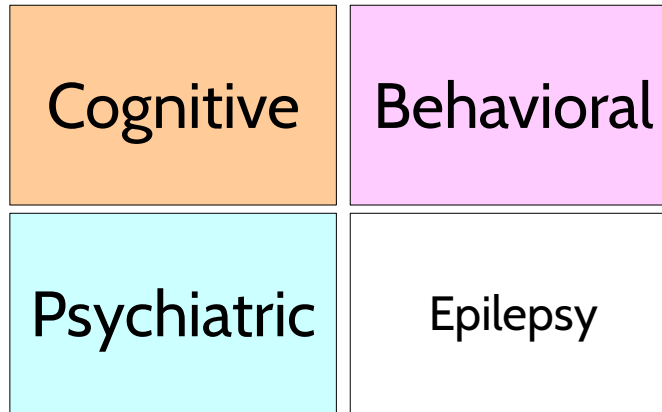
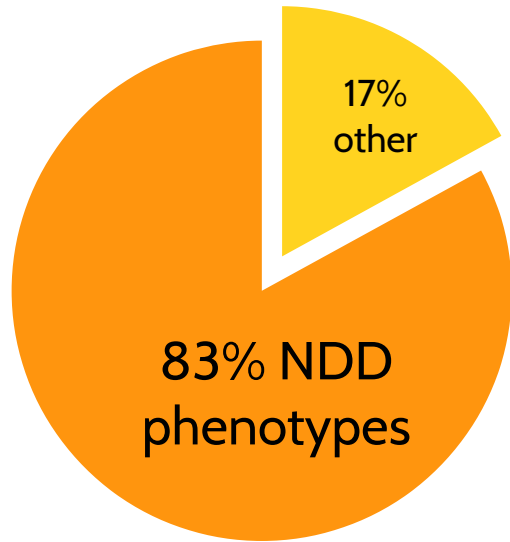
# Statistical analysis

- DECIPHER (cases) vs DGV (control)
  - on exons 7,8,9: enrichment of cases pv.  **$6 \times 10^{-04}$**
  - on HPs: enrichment of cases, pv.  **$8 \times 10^{-07}$**
- GDD/ID cases vs GDD/ID control
  - on exons 7,8,9: enrichment of cases pv. **0.38**
  - on HPs: enrichment of cases, pv.  **$4 \times 10^{-04}$**
- WG analysis (DECIPHER + DGV + GDD/ID)
  - 11 novel promoters detected in introns
  - HPin7 and HPin8 resulted statistical significant

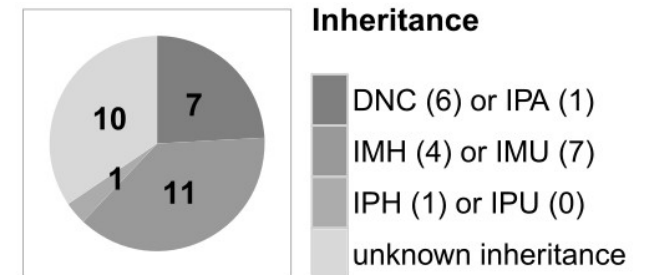
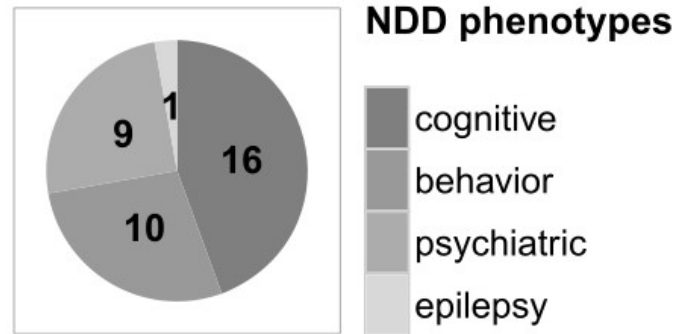
# Clinical considerations

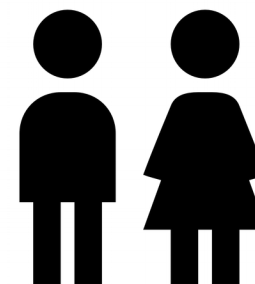
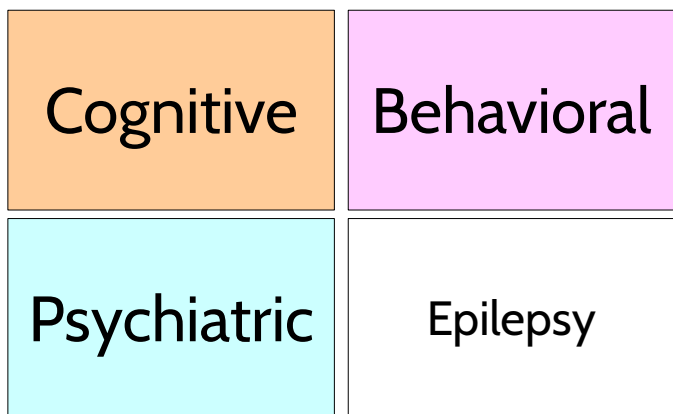
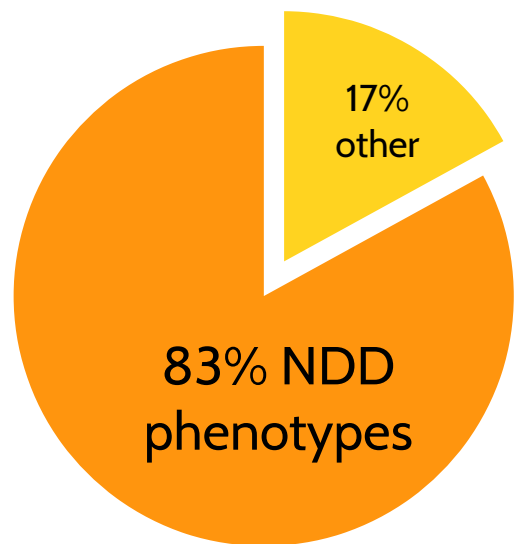




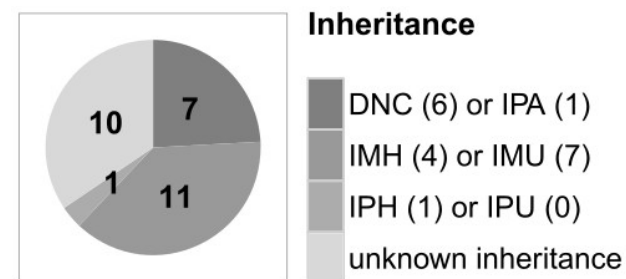
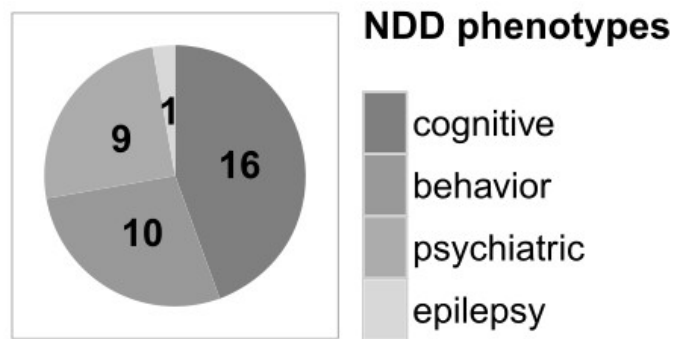


Male / Female ratio = 3.7  
(11 to 3, 10 unknown)





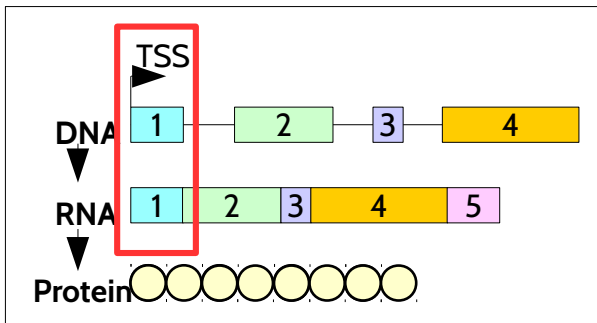
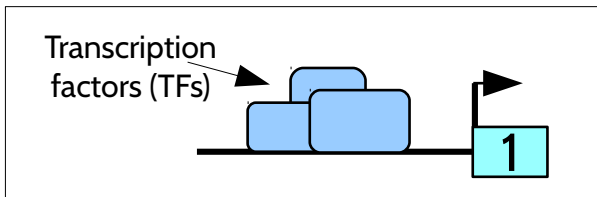
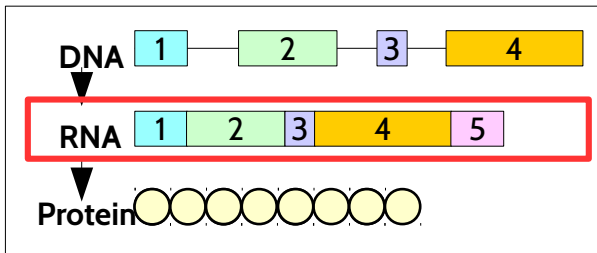
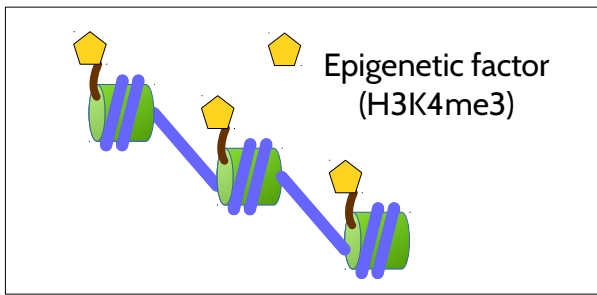
Male / Female ratio = 3.7  
(11 to 3, 10 unknown)

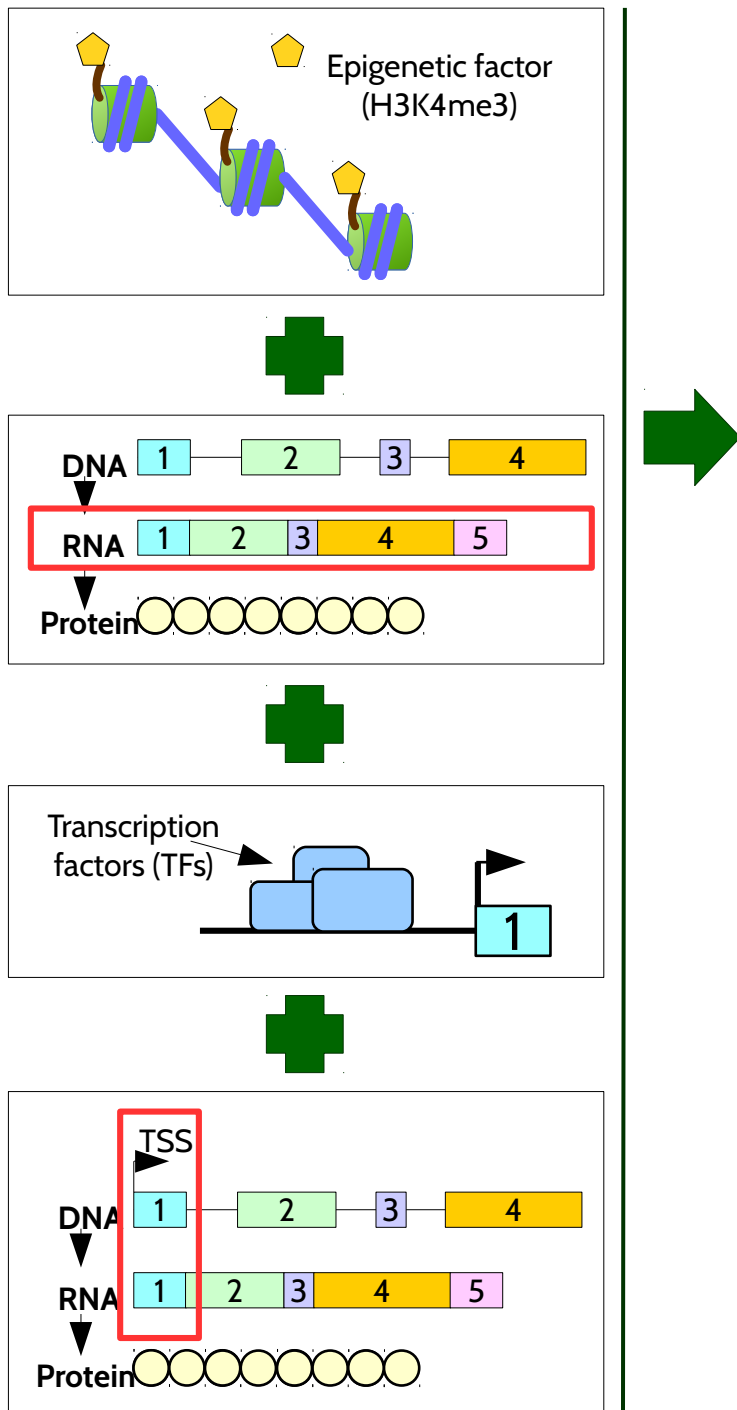


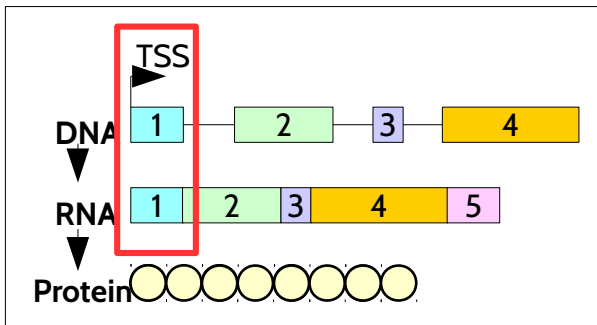
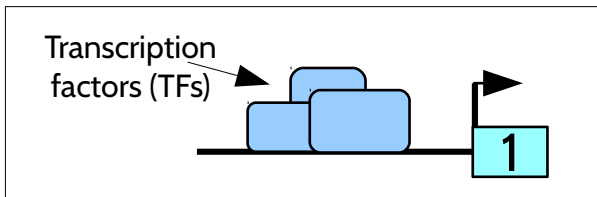
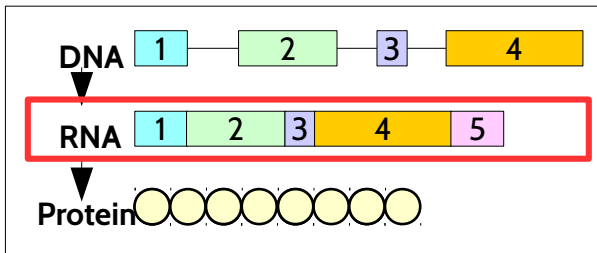
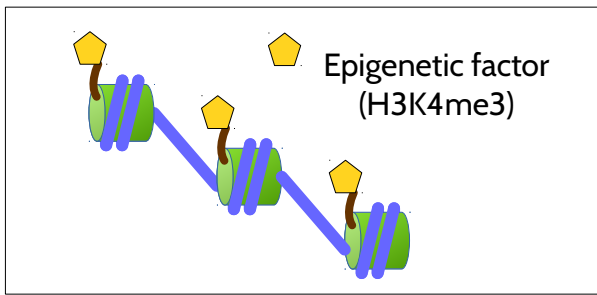
***DLG2* HP deletion as NDD risk factor**



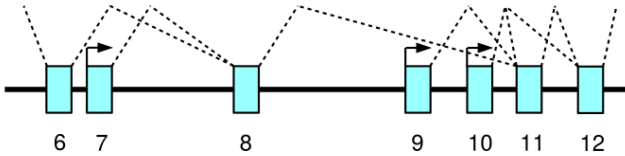
# Conclusions



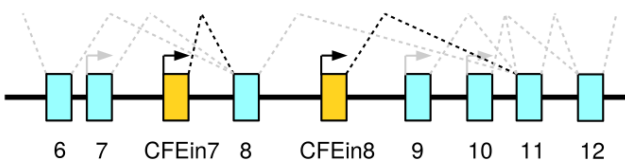


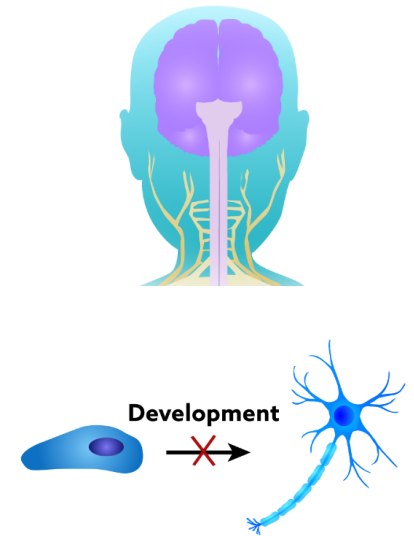
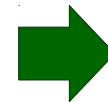
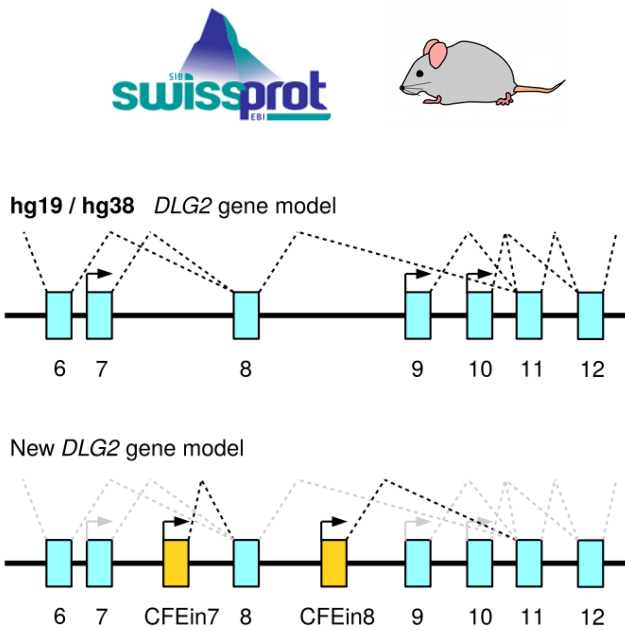
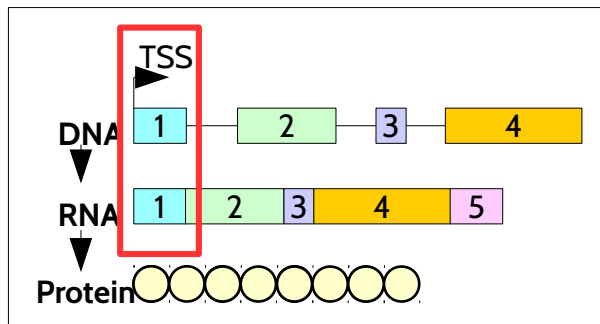
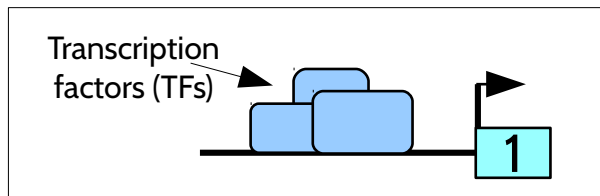
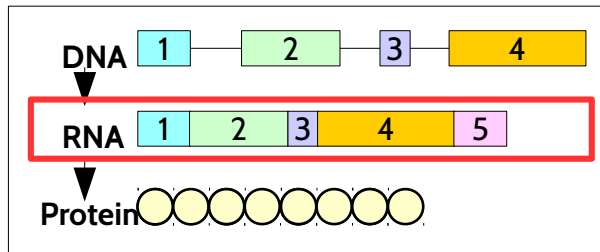
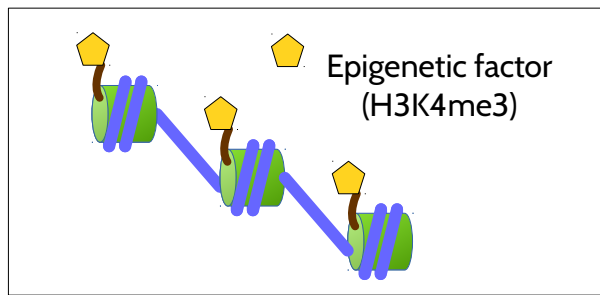


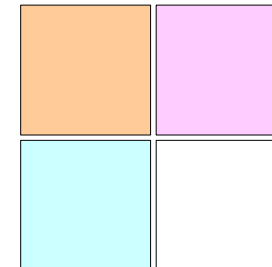
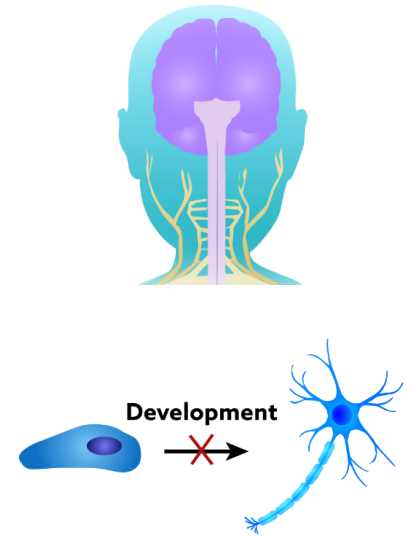
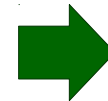
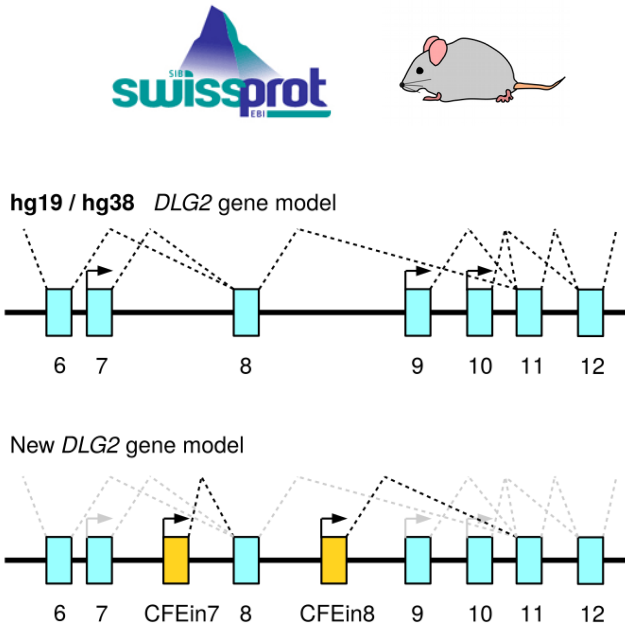
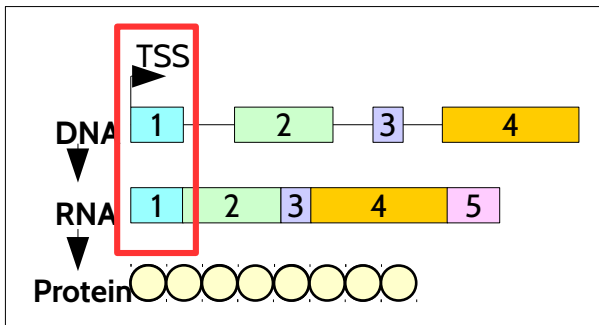
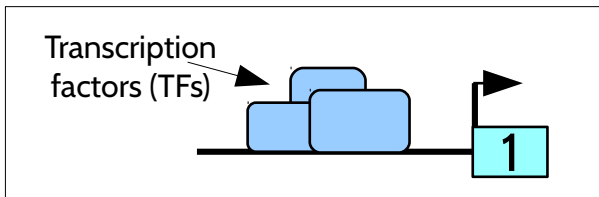
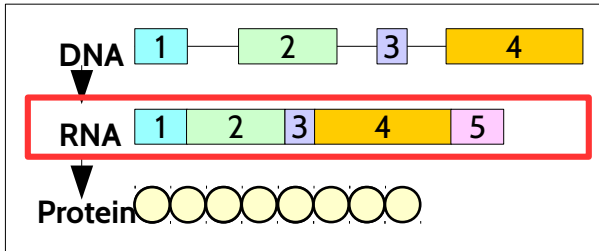
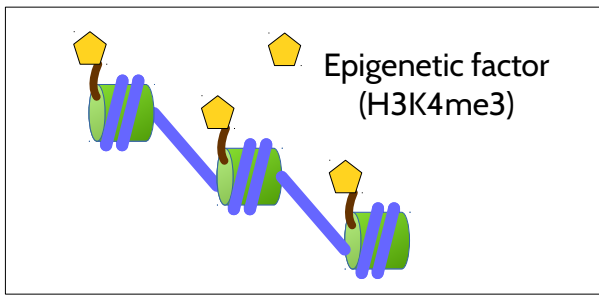
hg19 / hg38 *DLG2* gene model

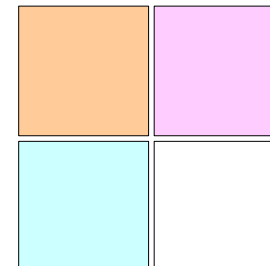
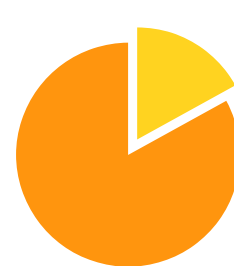
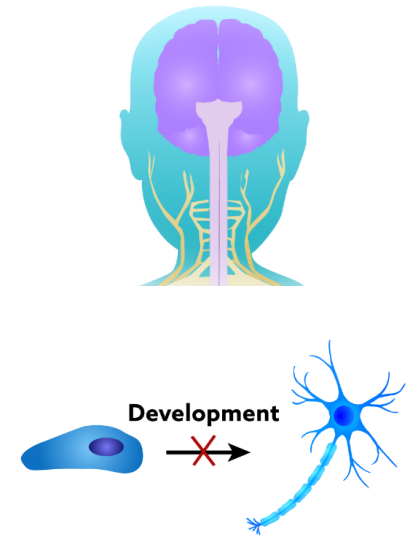
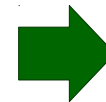
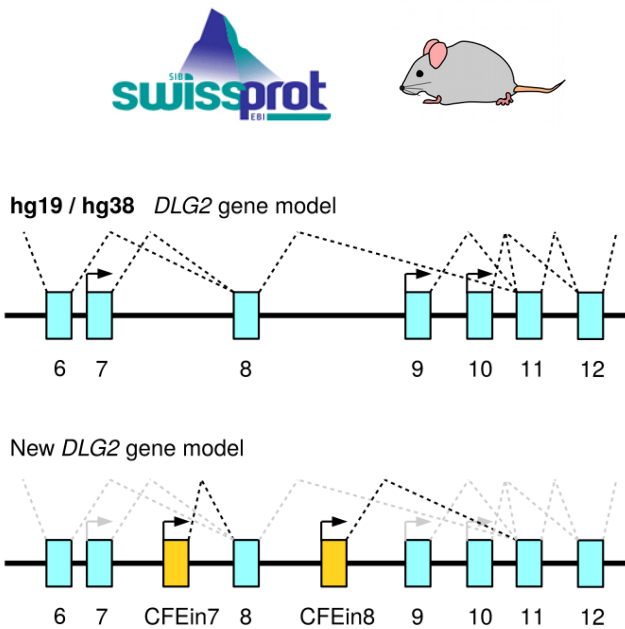
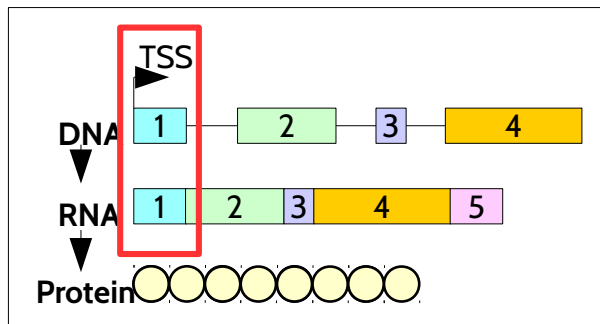
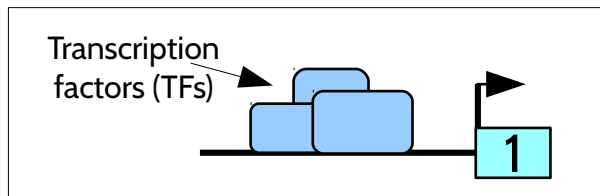
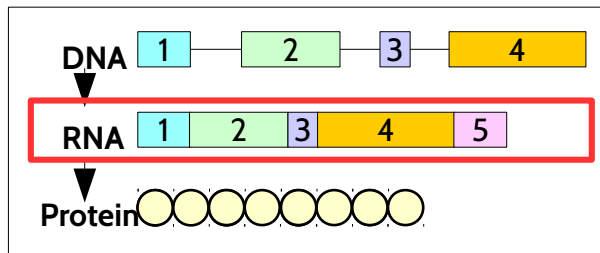
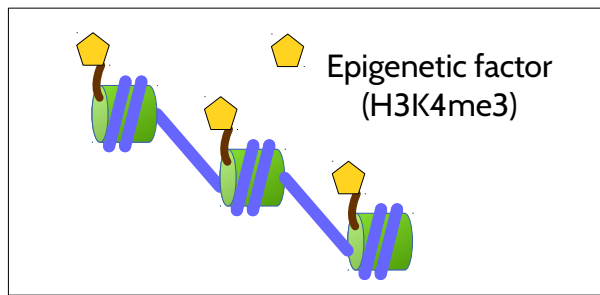


New *DLG2* gene model









*DLG2* HP/CFE deletion as NDD risk factor

# Acknowledgements

