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# Exploring genetic and phenotypic variation in intellectual disability

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## Every two hours, an Australian child will be diagnosed with intellectual disability\*

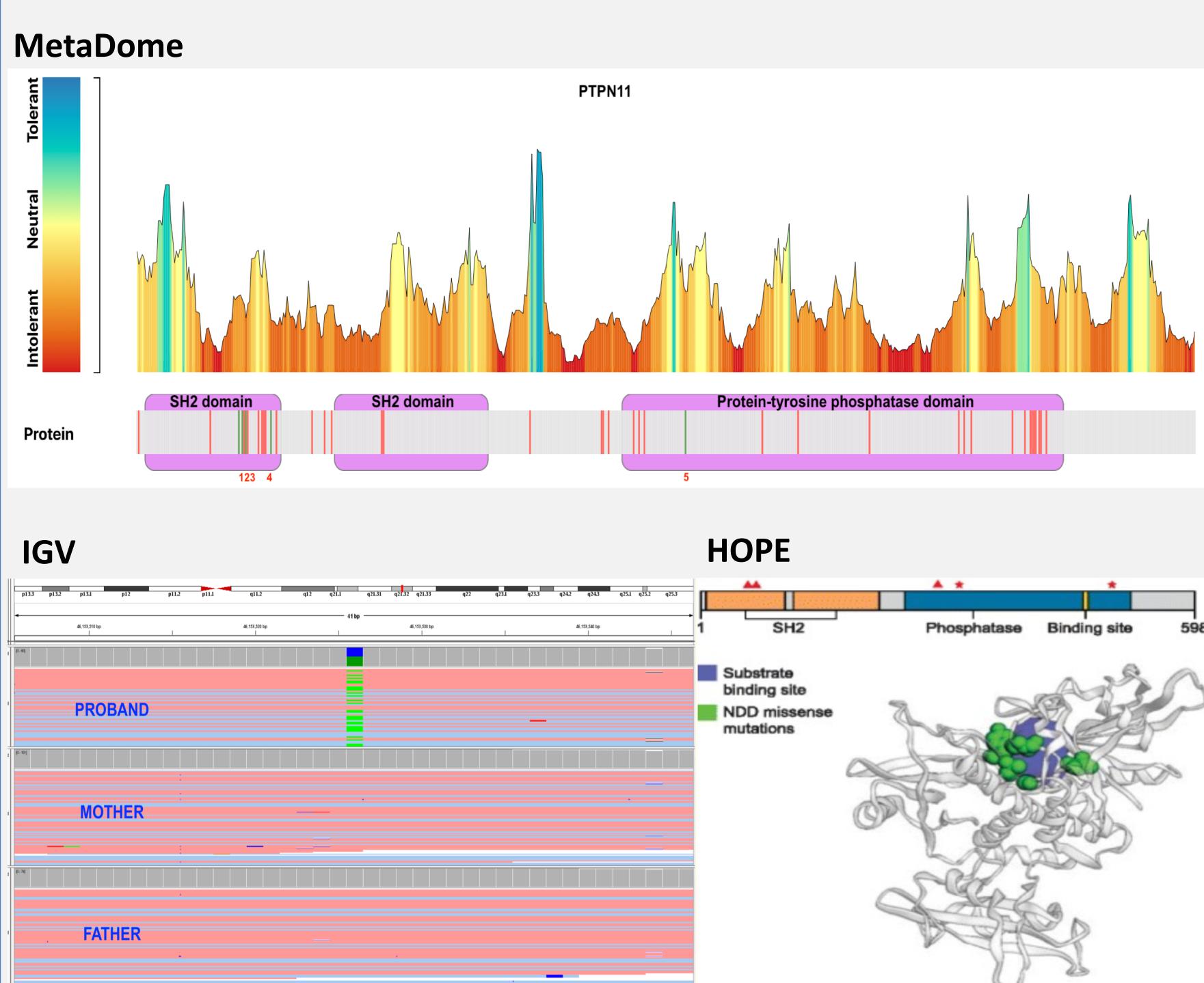
The cause, presence and severity of intellectual disability (ID) is extremely variable. By examining families with divergent ID genotypes and phenotypes, my research aims to explain the enigmatic biological mechanisms that drive this variability, by:

1. Exploring coding and non-coding regions of the genome to identify pathogenic and novel ID genes
2. Developing a database of all known pathogenic ID genes to enable comprehensive annotation for novel ID genes
3. Creating brain organoids from CRISPR/Cas9-edited induced pluripotent stem cells and using epigenetics and transcriptomics to functionally validate novel ID genes

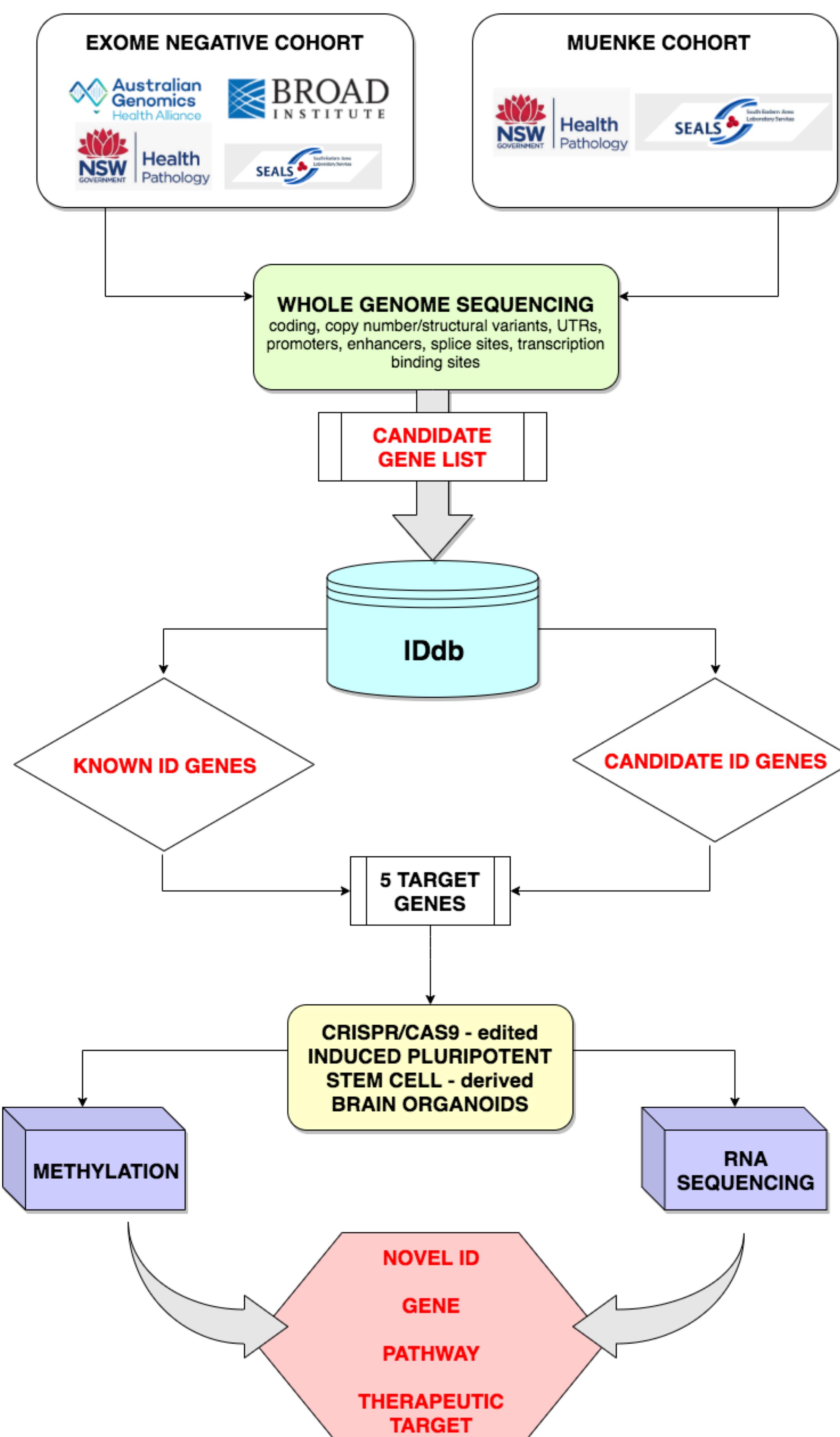
### 1. GENOMICS

A **novel gene/variant** is found and its pathogenicity<sup>1,2</sup> is based on its:

- tolerance to variation
- type and location
- inheritance mode
- frequency in population
- clinical relevance
- previous reports

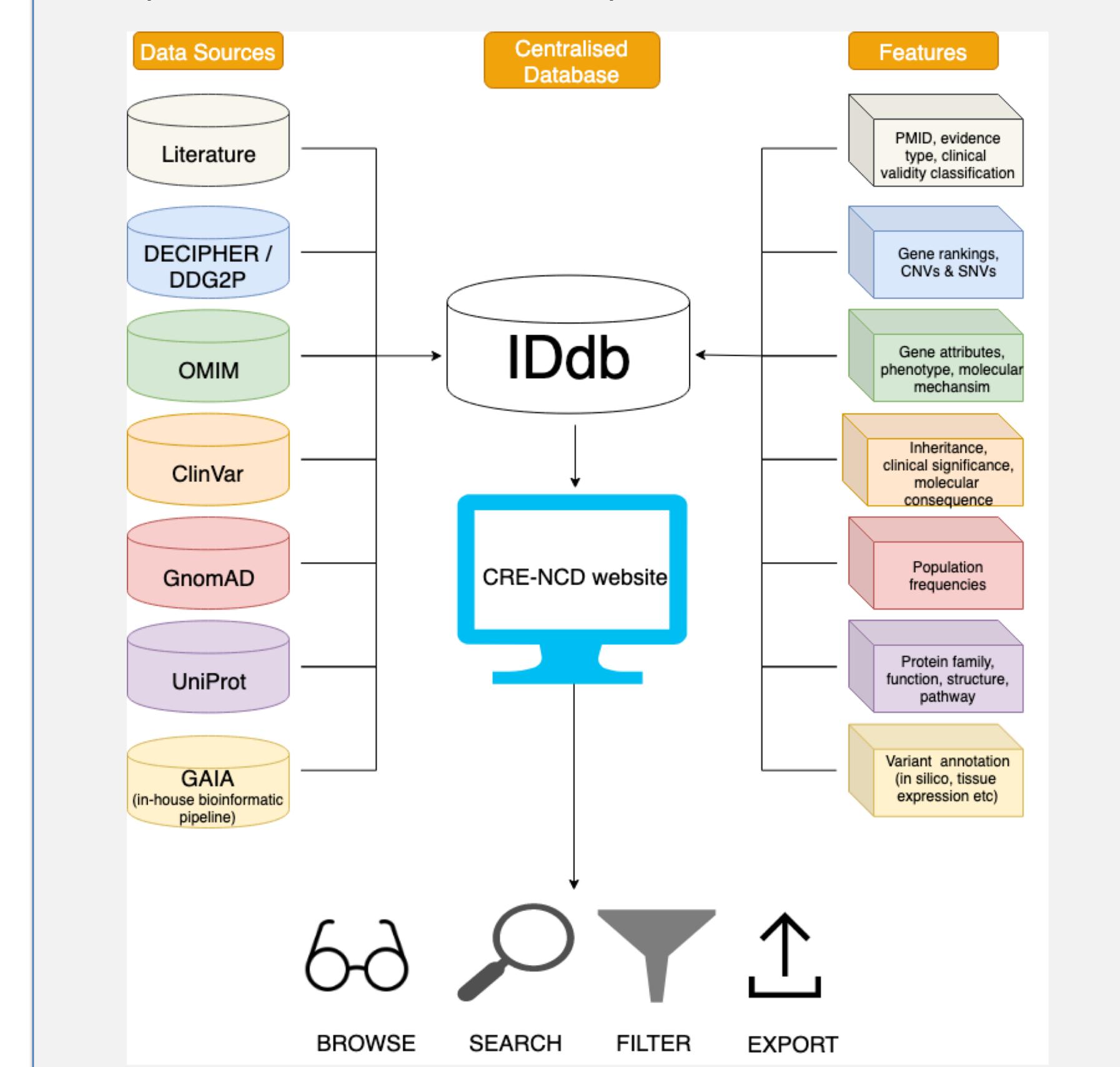


### STUDY DESIGN

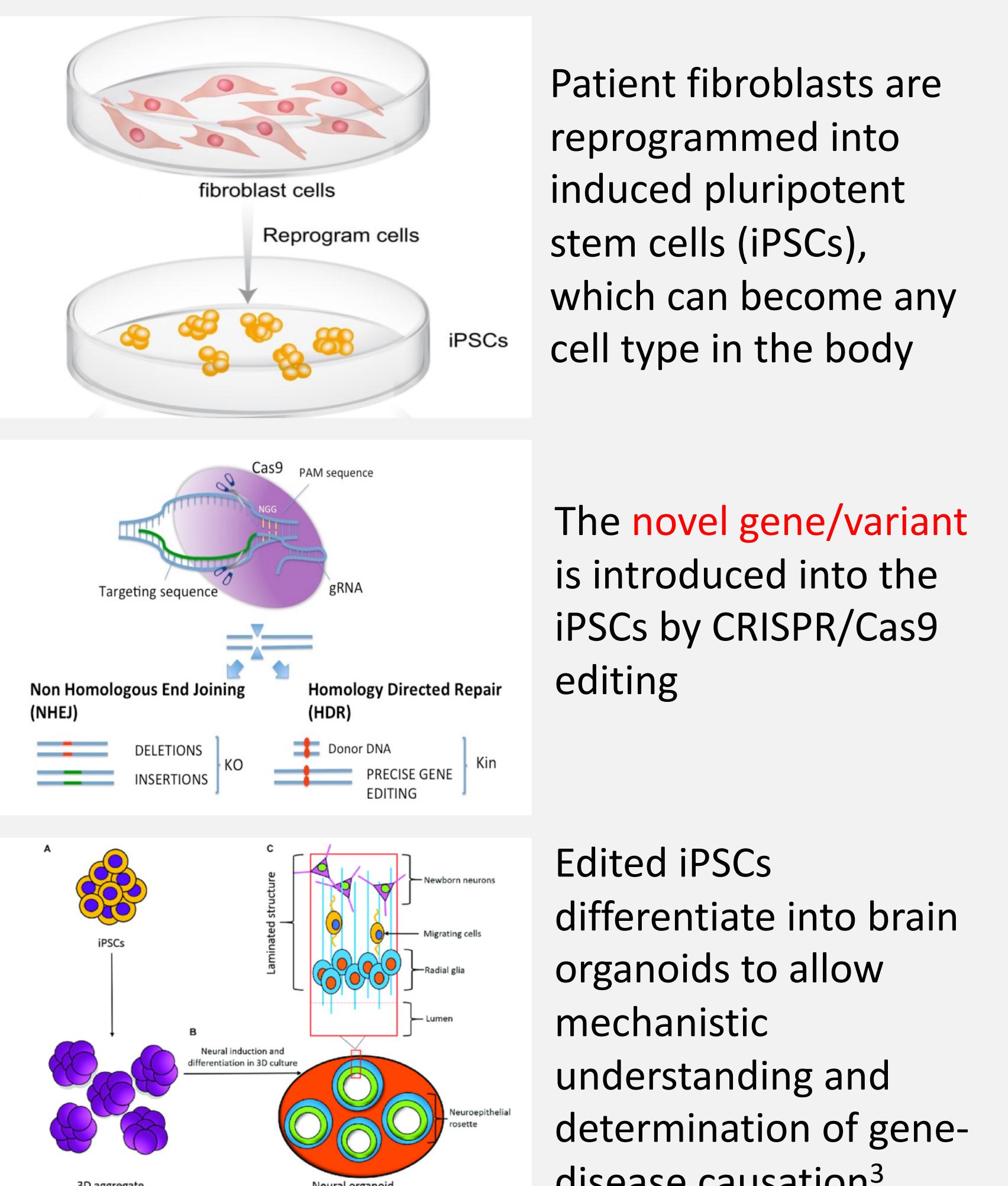


### 2. BIOINFORMATICS

The **novel gene/variant** is queried in IDdb, a database of annotated ID genes, which consolidates data from multiple sources, to enable rapid variant curation



### 3. DISEASE MODELLING

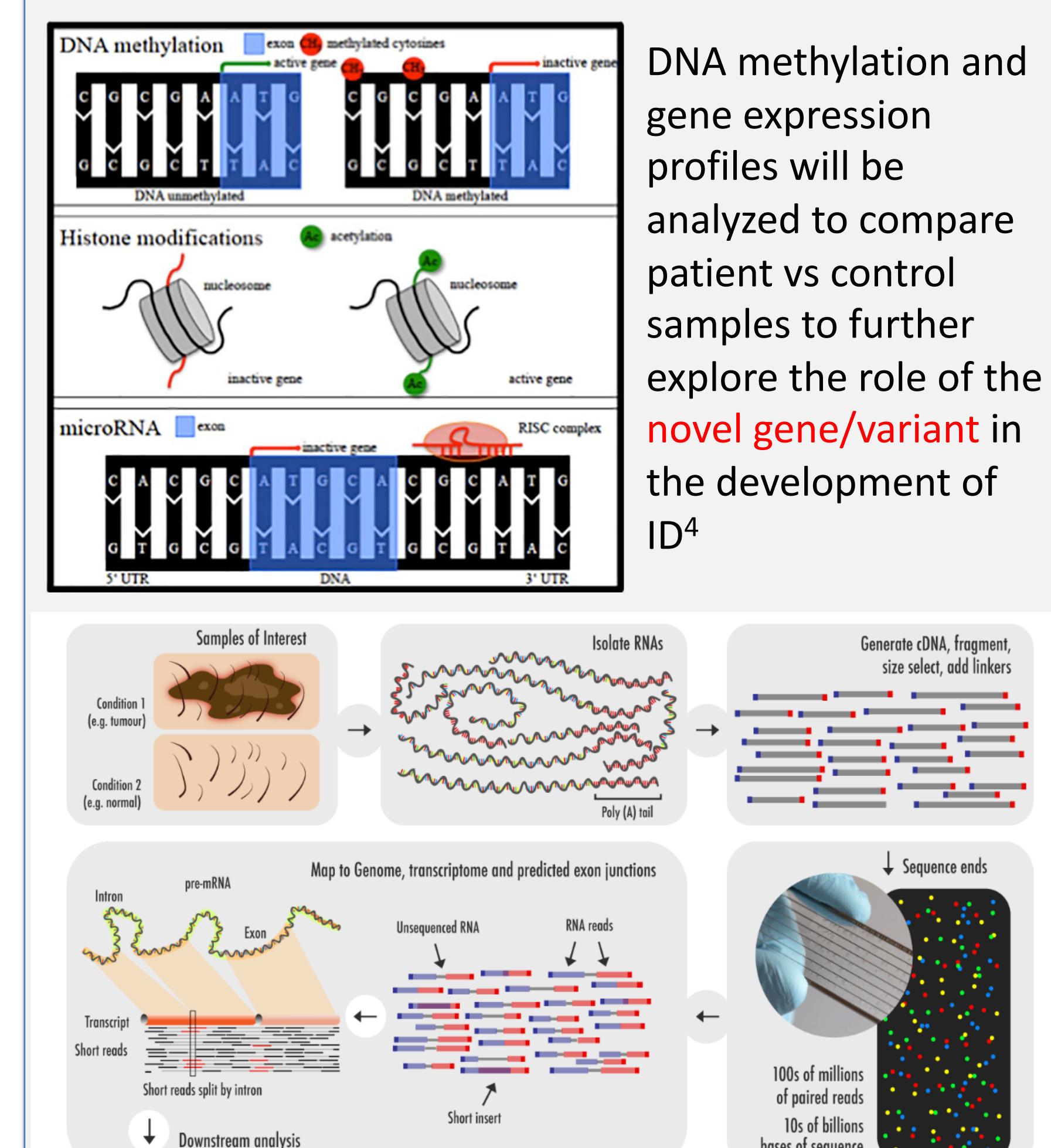


Patient fibroblasts are reprogrammed into induced pluripotent stem cells (iPSCs), which can become any cell type in the body

The **novel gene/variant** is introduced into the iPSCs by CRISPR/Cas9 editing

Edited iPSCs differentiate into brain organoids to allow mechanistic understanding and determination of gene-disease causation<sup>3</sup>

### 4. EPIGENETICS & TRANSCRIPTOMICS



DNA methylation and gene expression profiles will be analyzed to compare patient vs control samples to further explore the role of the **novel gene/variant** in the development of ID<sup>4</sup>

The outcomes of this research could enable earlier genomic diagnosis, improvements in clinical phenotyping and enhance fundamental knowledge of ID biology

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### REFERENCES

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