

## Transcriptional Modulation of the Hippo Signalling Pathway by Drugs Used to Treat Bipolar Disorder and Schizophrenia

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### INTRODUCTION

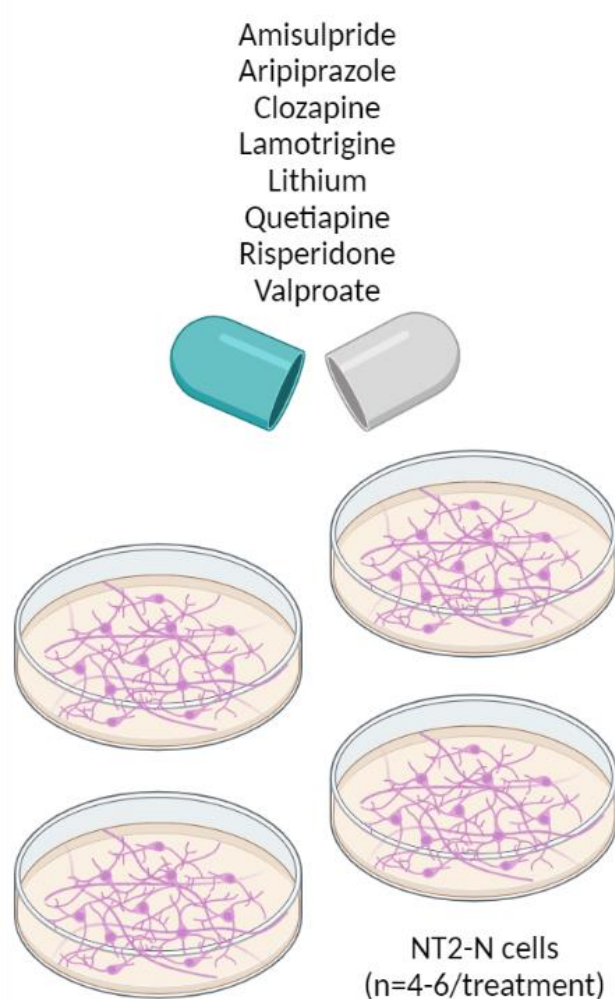
The hippo signalling pathway has an essential role in the modulation of cell survival, proliferation, differentiation, migration and apoptosis. It crosstalks with other major signalling pathways (Wnt, Notch, Hedgehog and TGF- $\beta$ ) to control tissue remodelling. The complete signalling network and its interactions are quite complex and multidimensional. The genes involved in the hippo pathway and its crosstalk have recently been associated with various psychiatric conditions<sup>1-4</sup>.

### OBJECTIVES

To evaluate the effects of commonly prescribed psychoactive drugs used in treating affective disorders on the expression of genes in the Hippo pathway.

### METHODS

#### Cell culture and treatment



#### RNA extraction

#### Library preparation

#### RNA library bridge amplification

#### RNA library sequencing

#### Alignment and data analysis

#### Gene Set Enrichment Analysis (GSEA)

#### Assembly

#### Sequencing cycles

#### Data collection

#### Reads cluster 1

#### Reads cluster 2

#### Reads cluster 3

#### Assembled sequence

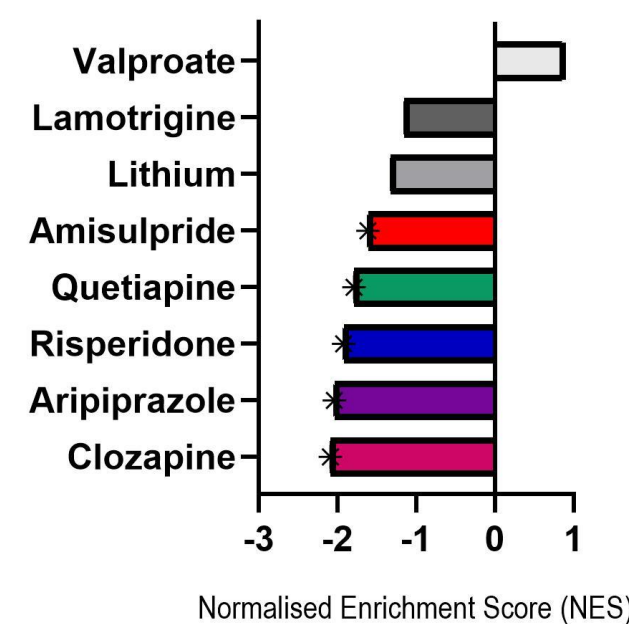
#### Gene Set Enrichment Analysis (GSEA)

#### R Studio

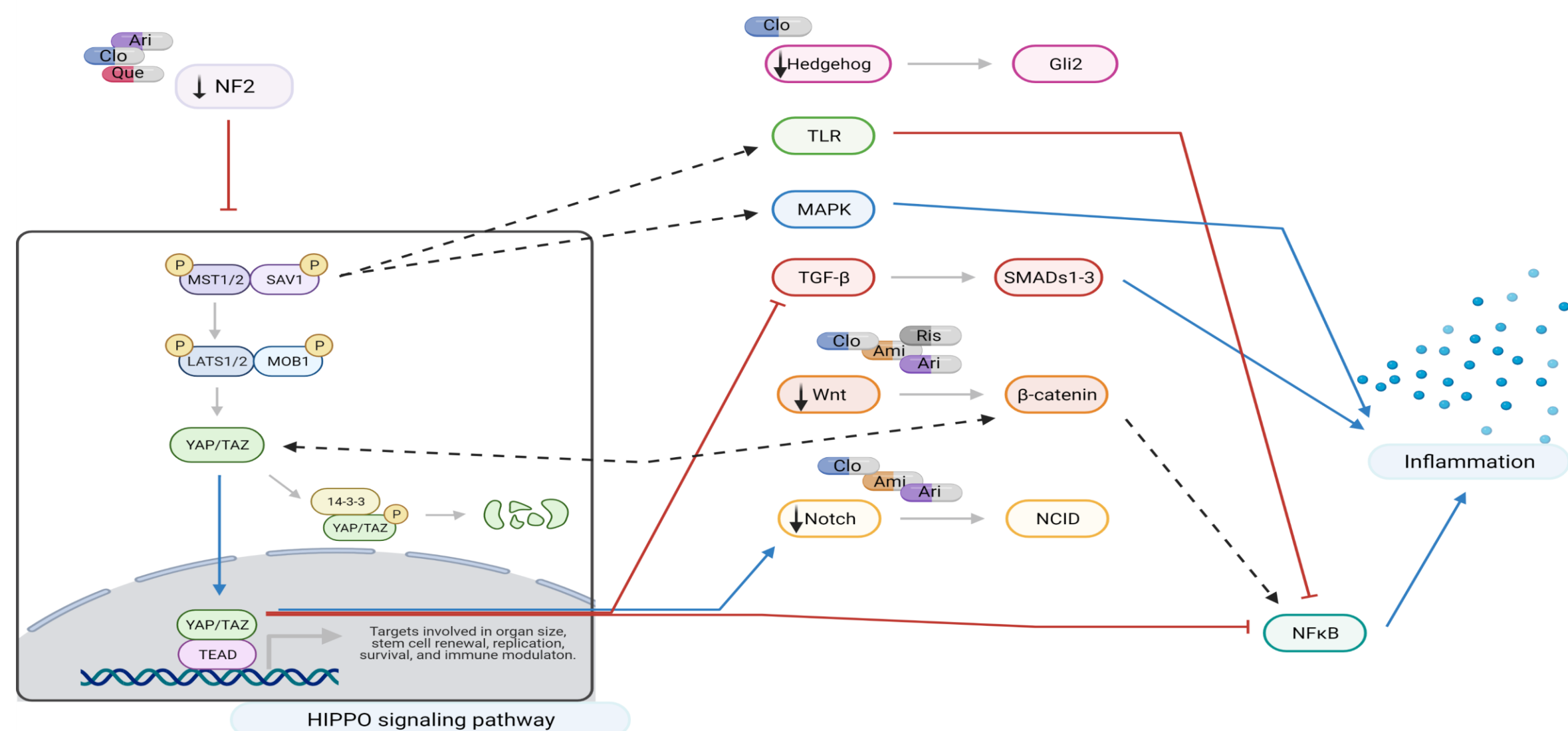
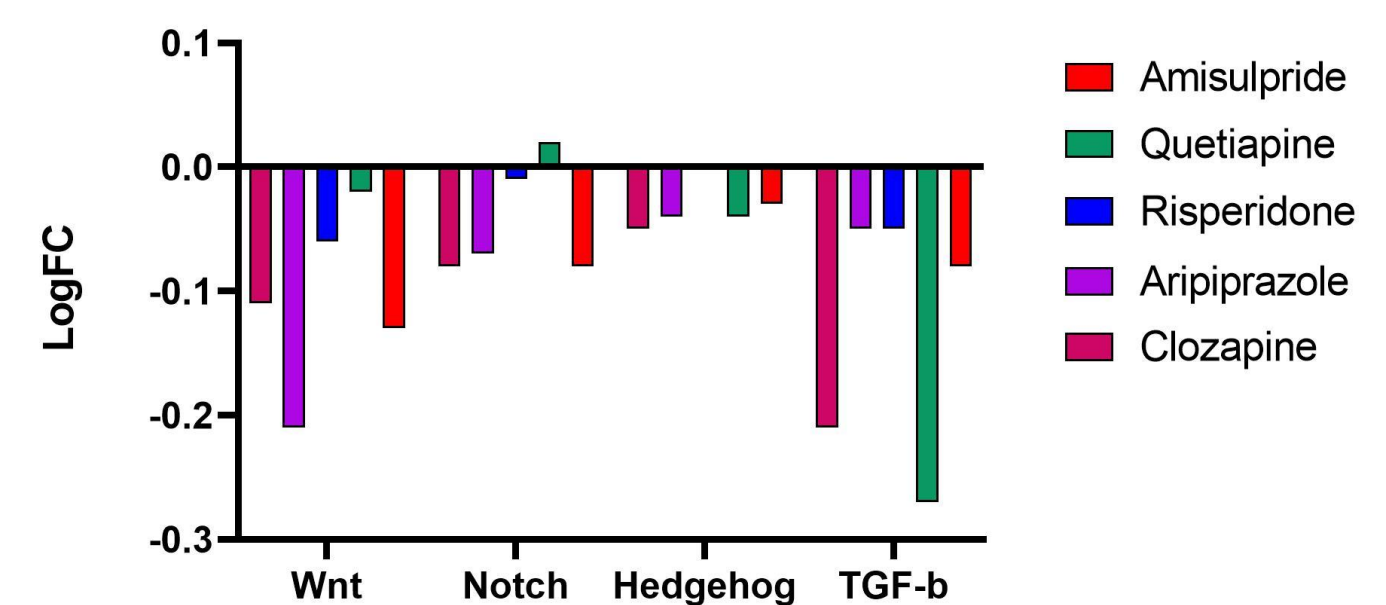
#### KEGG

### RESULTS cont.

#### Treatment effect on Hippo pathway gene expression



#### Treatment effect on interacting pathways



Hippo signaling at a glance: effects of amisulpride, aripiprazole, clozapine, quetiapine, and risperidone. Legend: Ami = amisulpride; Ari = aripiprazole; Clo = clozapine; Que = quetiapine; Ris = risperidone. In neuronal-like NT2 cells, inhibition of Hippo pathway reduces the production of pro-inflammatory cytokines through the crosstalk with TLR, MAPK, TGF- $\beta$ , Wnt, and Notch signaling pathways. Aripiprazole, clozapine, and quetiapine downregulate NF2, leading to activation and nuclear translocation of YAP/TAZ which results in a reduction in NF $\kappa$ B and TGF- $\beta$  signaling. NF2 also closely interacts with Hedgehog, TGF- $\beta$ , Wnt, and Notch pathways. Modulation of MST1/2 expression also results in reduced pro-inflammatory signaling through Toll-like receptor (TLR) and MAPK signaling. Amisulpride, aripiprazole, clozapine, and risperidone downregulate Wnt signaling interfering with NF $\kappa$ B and pro-inflammatory cytokine production. Created with BioRender.com.

### DISCUSSION

When considered as a whole, the net effects of these changes would reduce proinflammatory signalling mediated by MAPK and NF $\kappa$ B. This is of interest as aripiprazole, quetiapine, and clozapine are known to inhibit NF $\kappa$ B. The data produced in this study suggests that such inhibition may be achieved, at least in part, by downregulating Hippo, Wnt, and TGF signalling.

### CONCLUSION

The identification of new pathways associated with psychiatric conditions that can be targeted by known pharmacological treatments, such as the Hippo signalling pathway, can highlight an opportunity for the development of new treatment options for these debilitating conditions. This represents an opportunity to offset the lack of mechanistic understanding in BD and SZ, as well as other psychiatric conditions, and the curtailment in research and development by major pharmaceutical companies.

### RESULTS

	Clozapine	Aripiprazole	Risperidone	Quetiapine	Amisulpride
HIPPO*	↓↓ 0.0012	↓↓ 0.0044	↓↓ 0.0049	↓↓ 0.0052	↓ 0.016
Wnt**	↓↓ 0.0013	↓↓↓ 4.80x10 <sup>-6</sup>	↓ 0.02	0.64	↓↓ 0.0018
Notch**	↓ 0.0033	↓ 0.043	0.72	0.63	↓ 0.0032
Hedgehog**	↓ 0.025	0.07	0.67	0.26	0.18
TGF-b**	0.07	0.66	0.06	0.15	0.19

\* Adjusted p-value and \*\* p-value for the drug effects on genes involved in the Hippo and interacting pathways

### REFERENCES & ACKNOWLEDGEMENTS

#### Access full paper for detailed results

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