Centre for Human Molecular Genetics

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From genotype to phenotype: *in silico* modelling of serotonergic system

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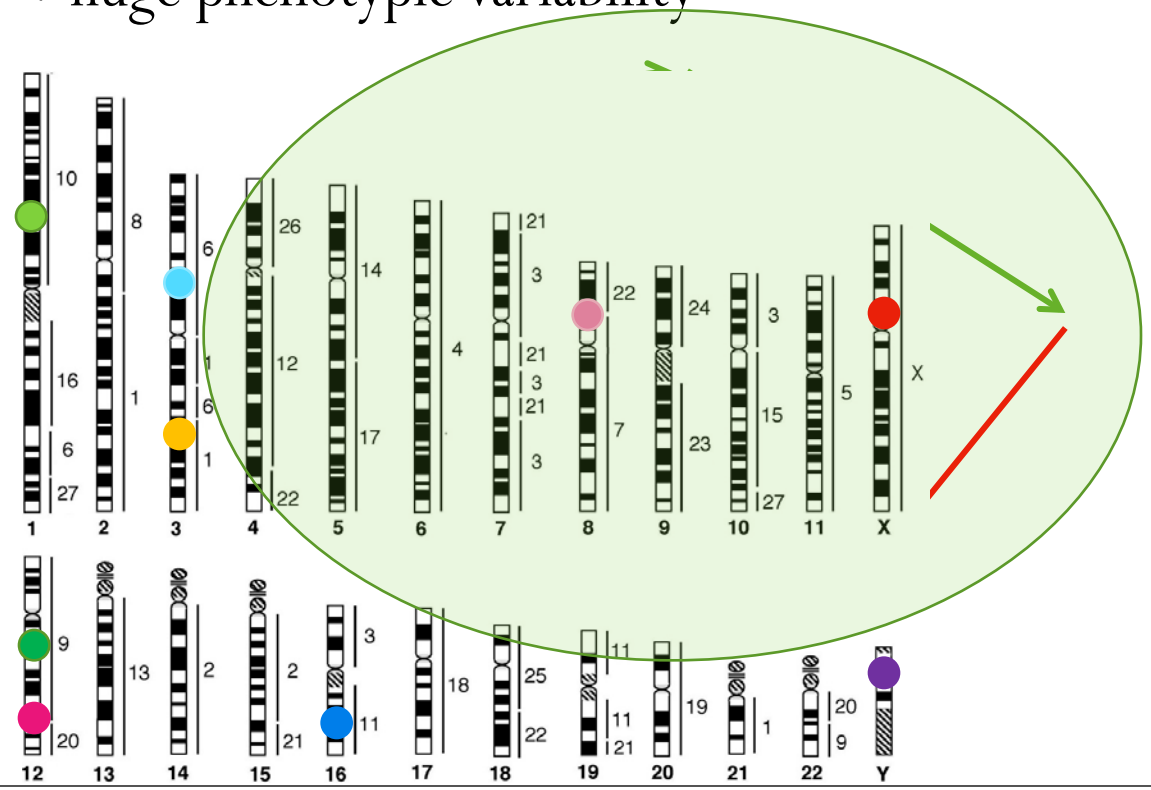
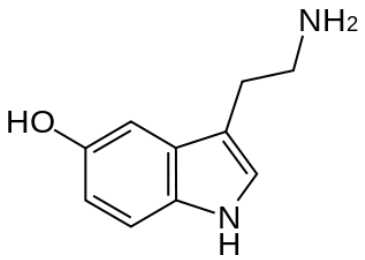
Systems biology approach to serotonergic signaling

- Systems biology approach in unraveling polygenic disorders
  - gene × gene interactions (*epistasis*)
  - gene × environment interactions
  - → huge phenotypic variability



Systems biology approach to serotonergic signaling

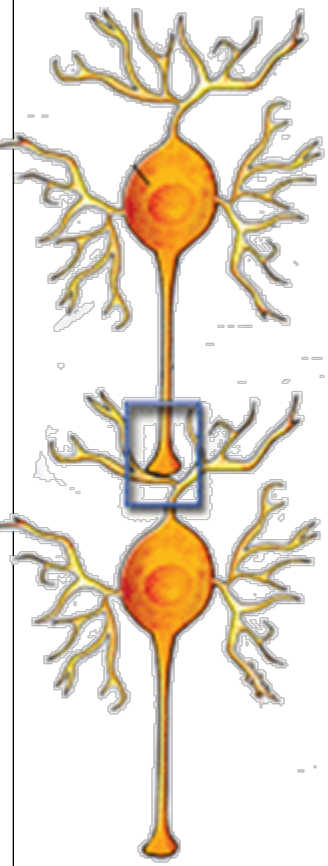
- Major depressive disorder (MDD)
  - Melancholic and atypical type
  - Antidepressant therapy response
- Monoamine hypothesis of depression: dysregulation of serotonergic transmission
- Major neurotransmitter system in central nervous system involved in regulation of food intake, mood and aggression

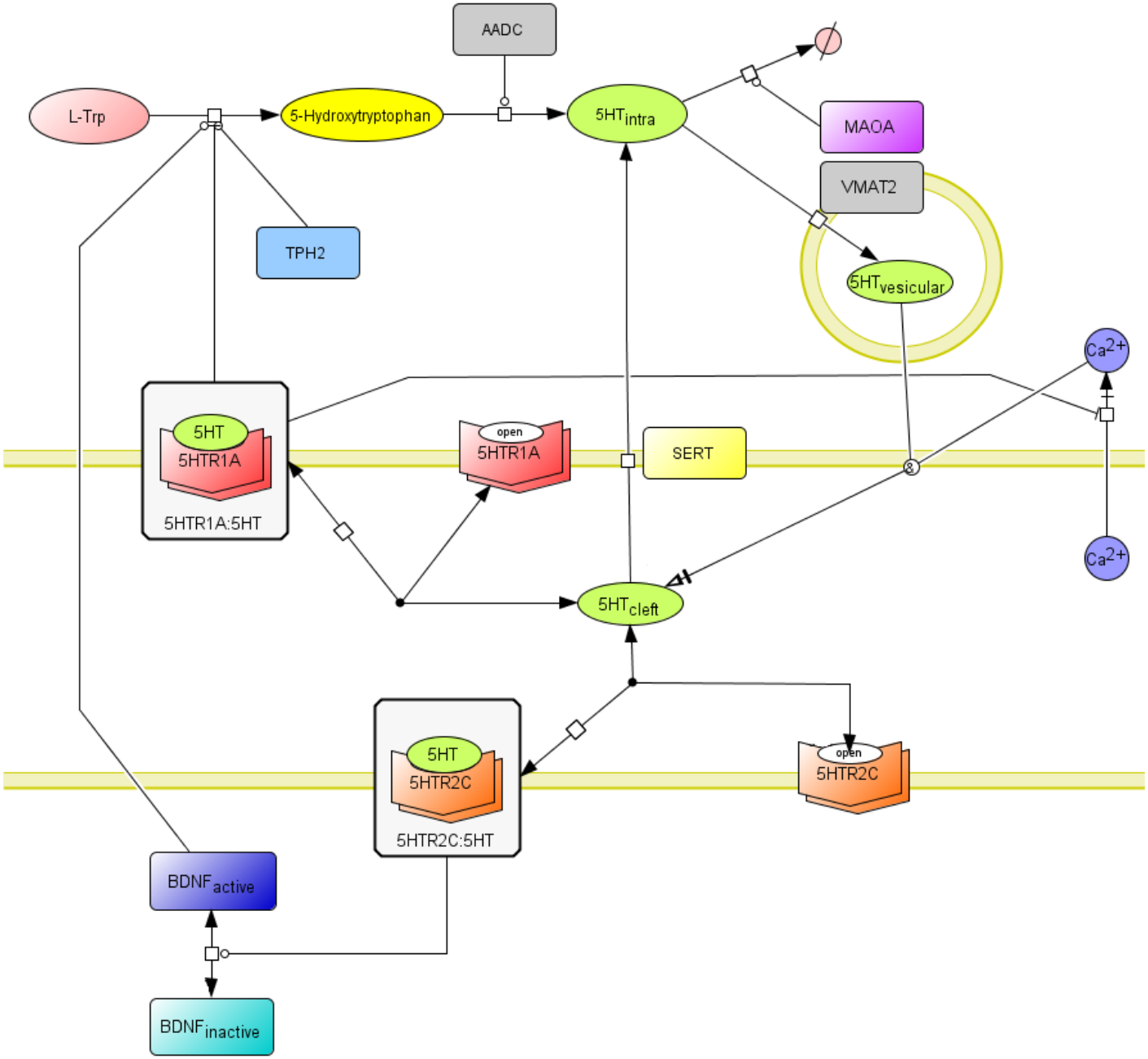


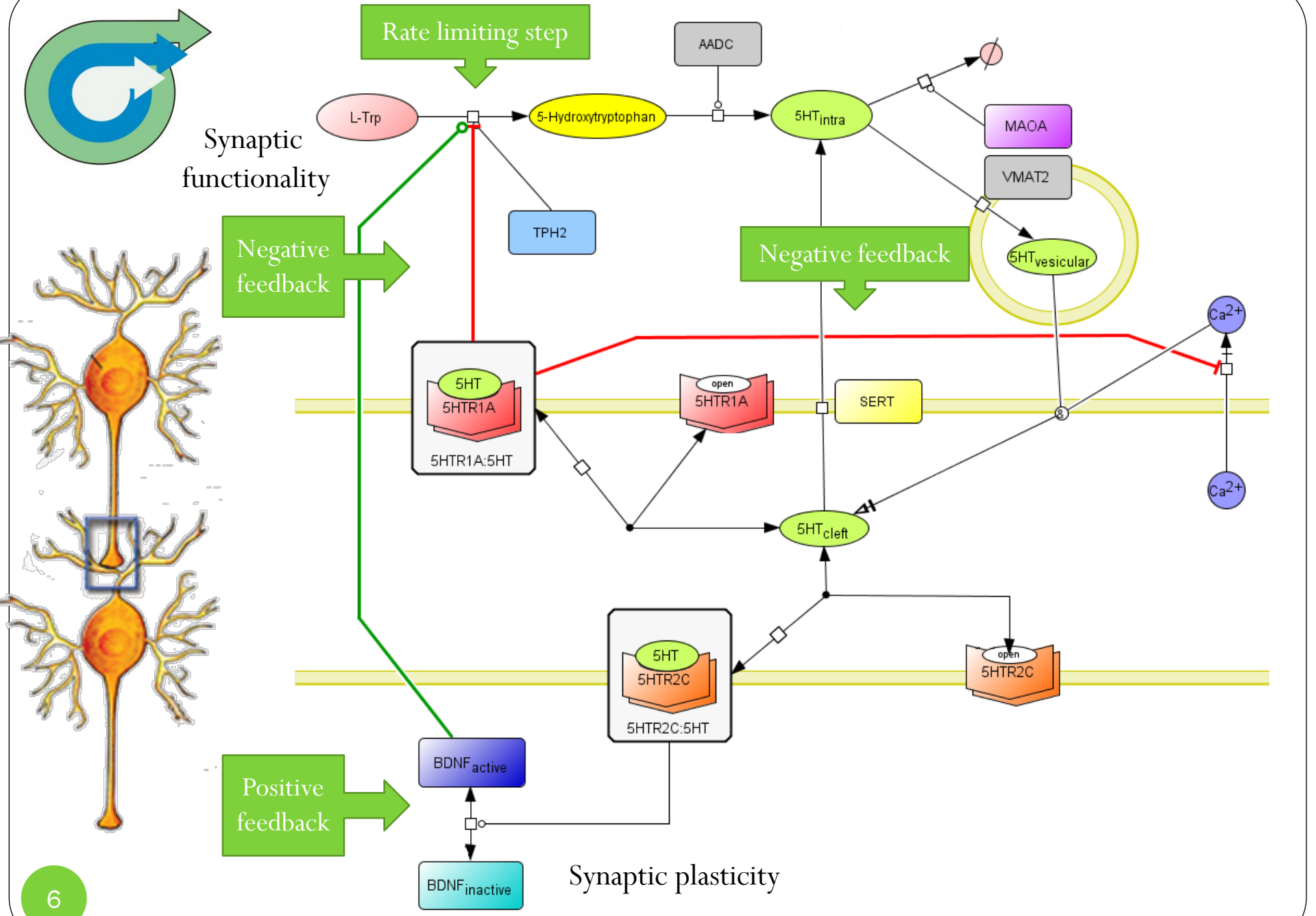
Serotonin
(5-hydroxytryptamine)

Modelling

- Computational modeling using Cell Designer v4.2 and Systems Biology Workbench
- Microarray data from wholebrain tissue sample from BioGPS
- Enzyme kinetics from BRENDA database
  - K_M
  - $V_{max} = E \times k_{cat}$
- Empirically estimated parameters

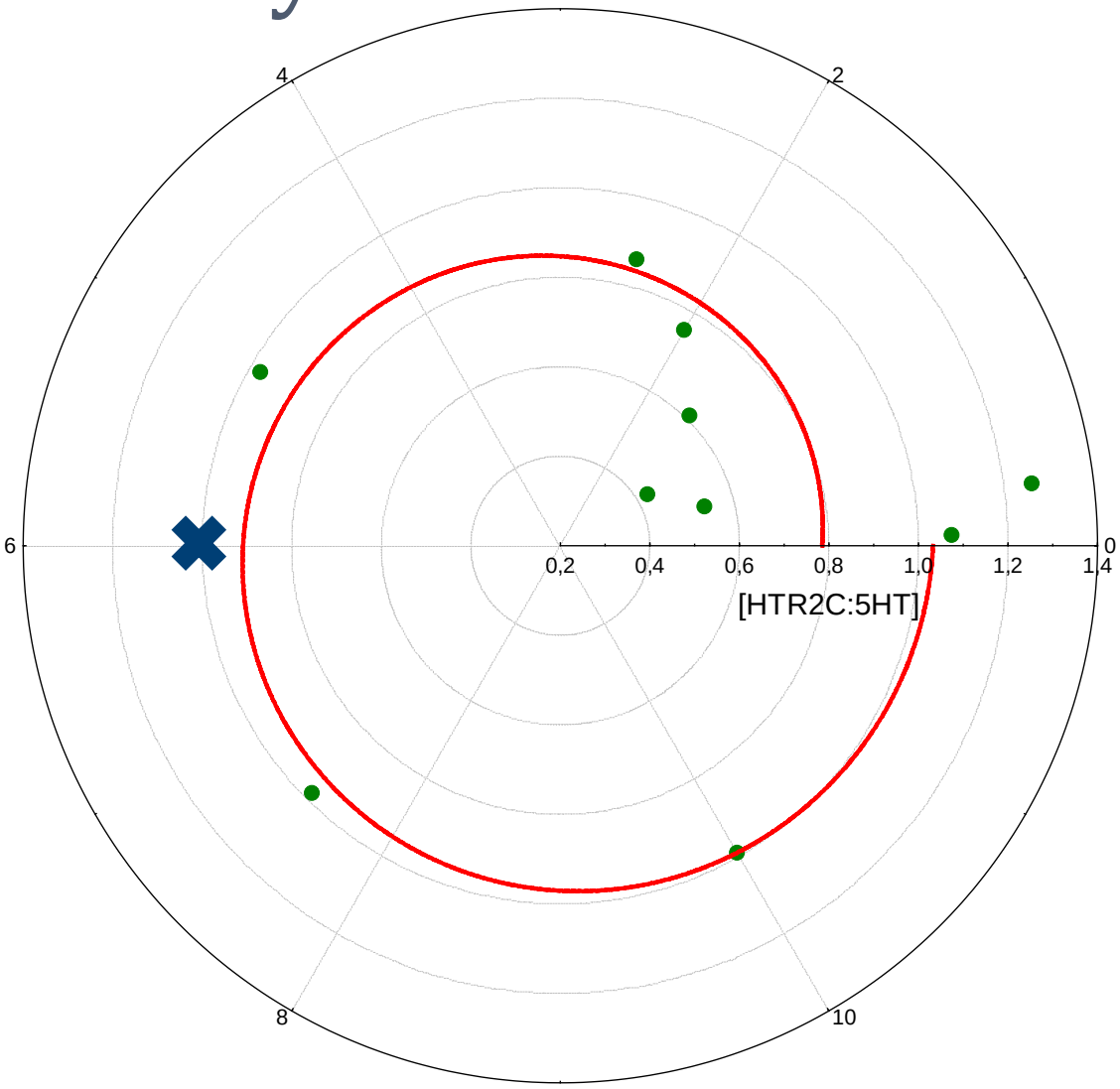



AADC
L-Trp
5-Hydroxytryptophan
5HTintra
MAOA
VMAT2
TPH2
5HTvesicular
Ca2+
5HT
5HTR1A
5HTR1A:5HT
open
5HTR1A
SERT
Ca2+
5HTcleft
5HT
5HTR2C
5HTR2C:5HT
open
5HTR2C
BDNFactive
BDNFinactive


Rate limiting step
AADC
L-Trp
5-Hydroxytryptophan
5HTintra
MAOA
VMAT2
Synaptic functionality
Negative feedback
TPH2
Negative feedback
5HTvesicular
Ca2+
5HT
5HTR1A
5HTR1A:5HT
open
5HTR1A
SERT
Ca2+
5HTcleft
5HT
5HTR2C
5HTR2C:5HT
open
5HTR2C
Positive feedback
BDNFactive
BDNFinactive
Synaptic plasticity

System stability

- Nyquist plot
- K=open/closed
- 0.3-30 Hz
- System is robust and stable!

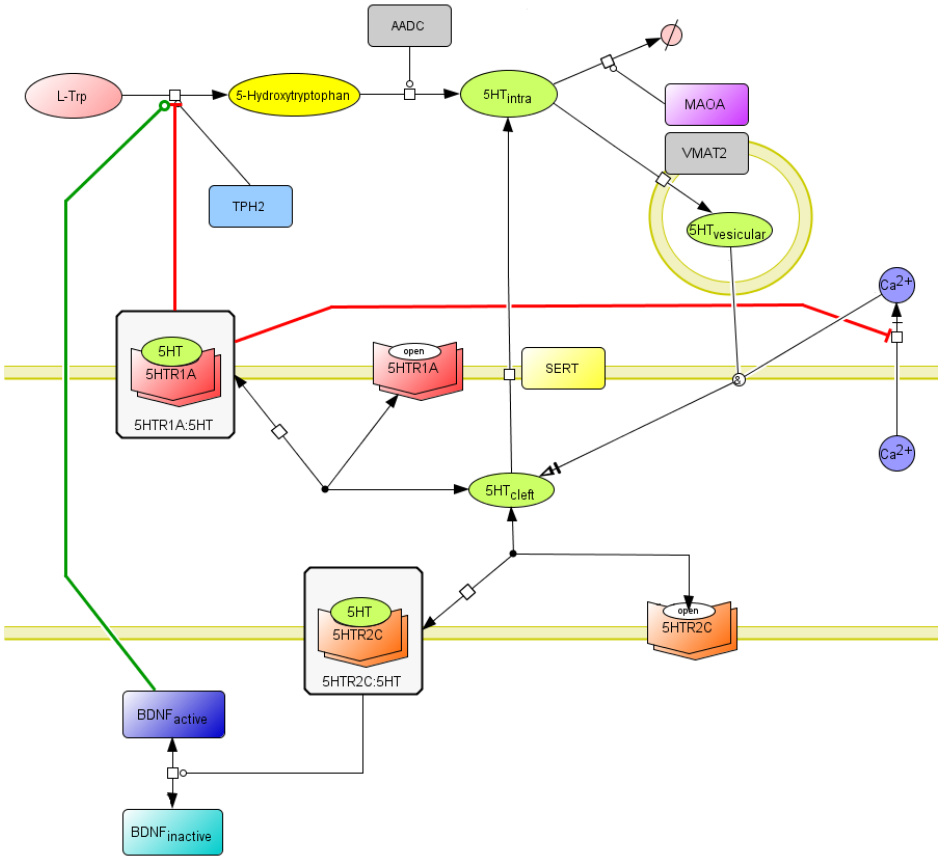


Analyzing complex phenotypes (1)

- 59 MDD patients and 81 healthy control
- Genotyping 9 loci in 6 genes

$$[E] = \frac{\sum_{i=1}^{i} k_i}{i} \times [E]_0$$

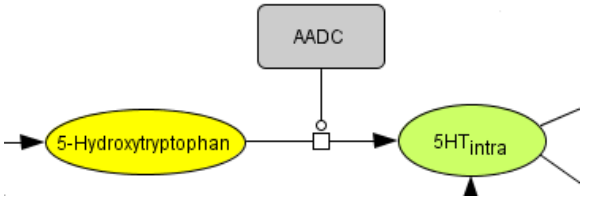
Gene	Variant	k_i	
TPH2	rs11178997	T = 1	A = 0.78
	rs4290270	A = 1	T = 0.5
	rs7305115	A = 1.74	G = 1
MAOA	uVNTR	2R = 1.2 4R = 0.125	3R = 1 5R = 1.18
5HTR1A	rs6295	G = 1	C = 1.2
5HTR2C	rs6318	G = 1	C = 2.3
SERT	5HTTin2	9 = 2.4 10 = 1.2	10 = 1.2 12 =1
	5HTTLPR	s = 0.8	l = 1
BDNF	rs6265	C = 1	T =0.33



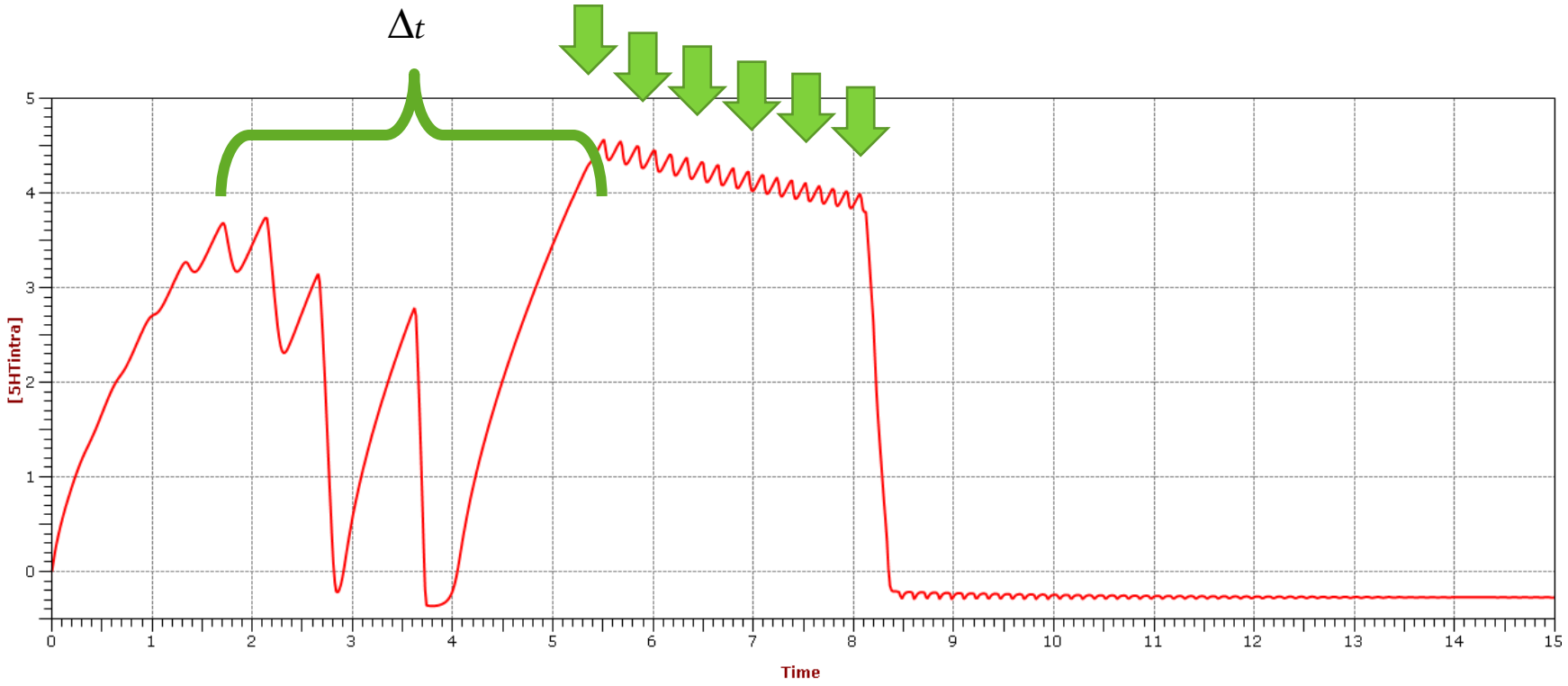
Analyzing complex phenotypes (2)

- We analyzed 51 kinetic parameters describing:
  - Serotonin synthesis
  - Serotonin degradation
  - Release into synaptic cleft
  - Receptor binding kinetics
- 5 parameters were statistically significantly lower in control subjects than in MDD patients

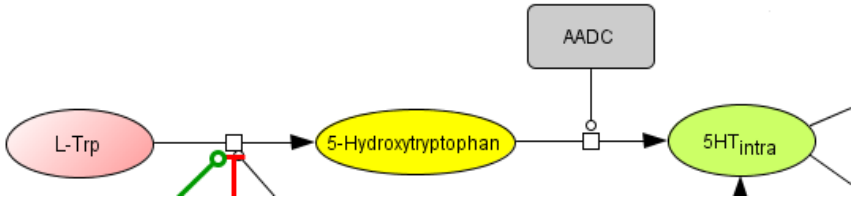
Results (1)



- Control subjects synthesize serotonin faster than MDD
- Time delay is greater in MDD subjects
- Controls have lower number of peaks

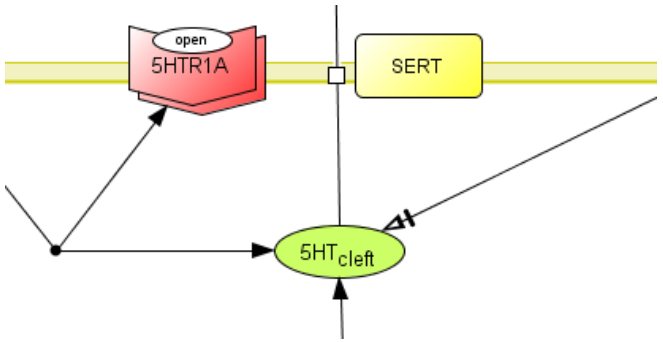


Results (2)

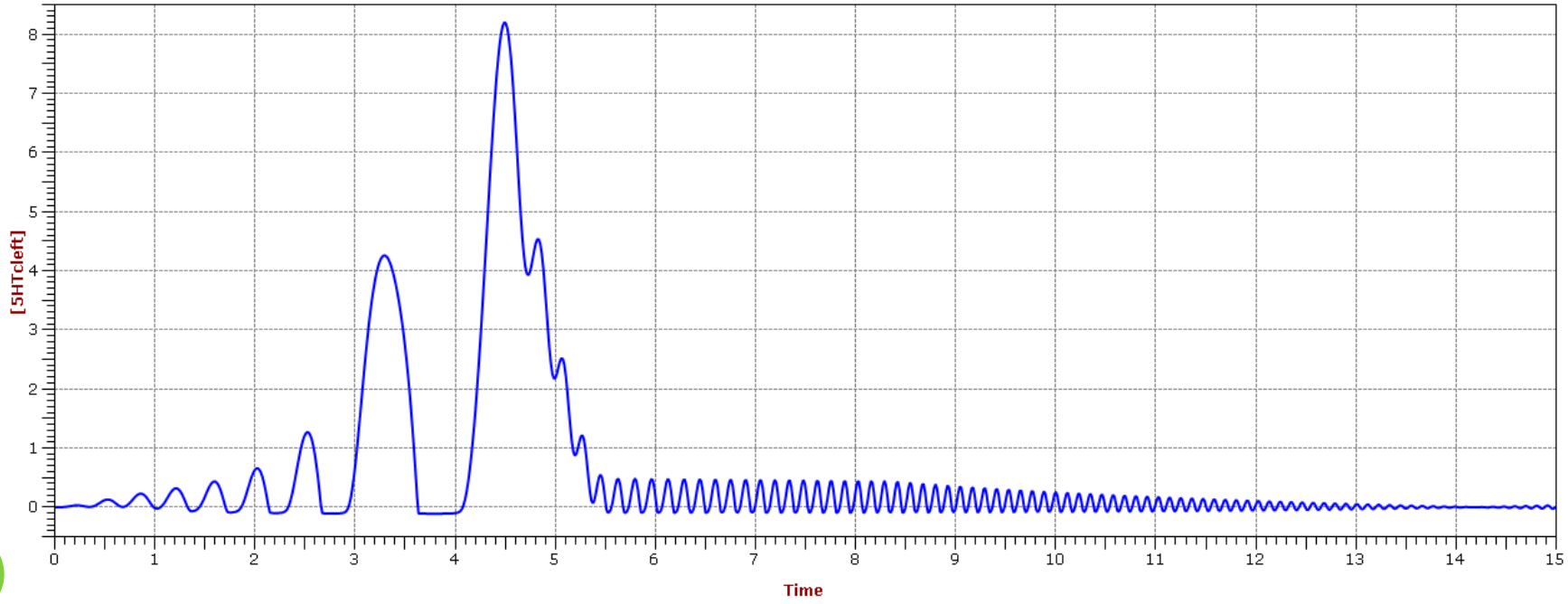


- 5-hydroxytryptophan is depleted faster in controls
- 5-hydroxytryptophane in control subjects reaches minimum in less time than in MDD
- Peak is lower in control subjects than in MDD

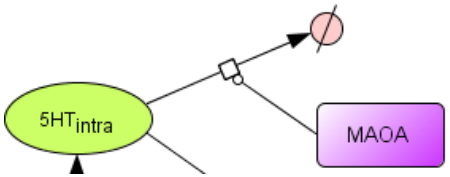
Results (3)



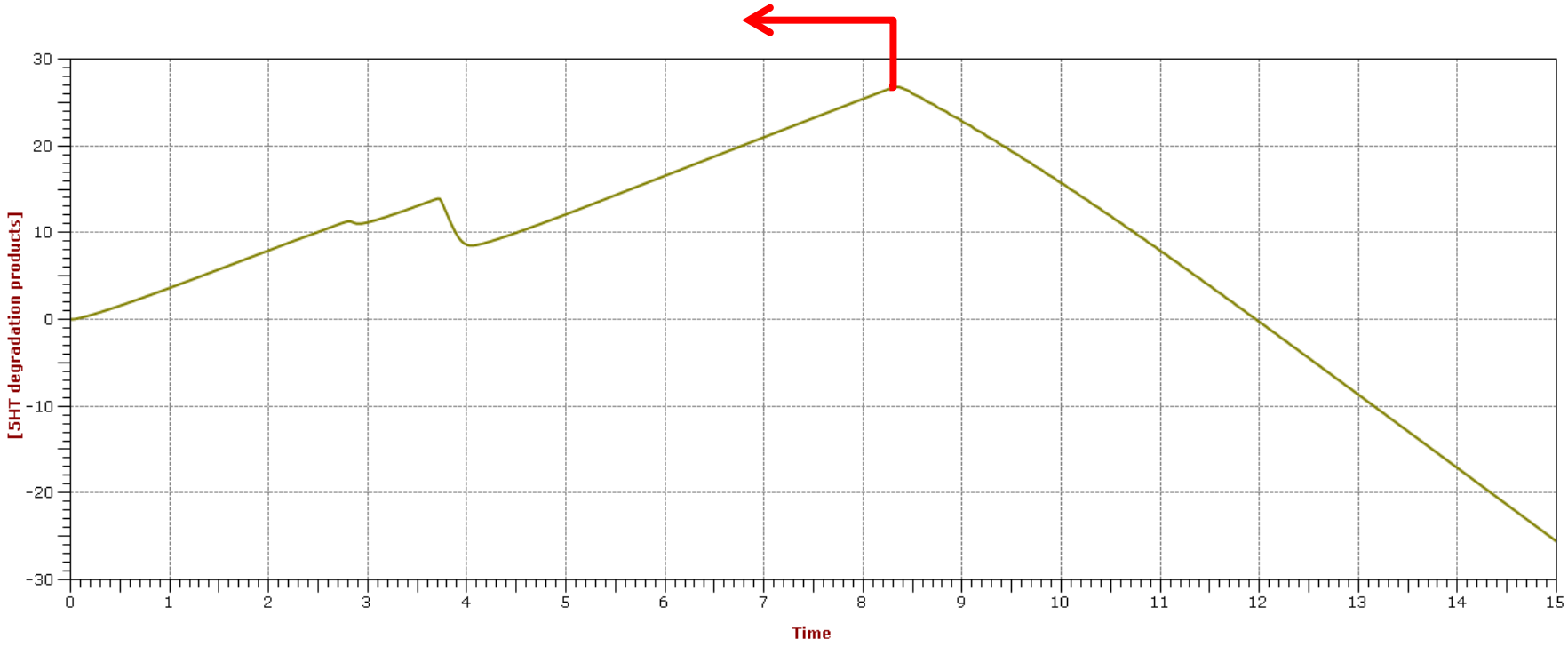
- Serotonin is released faster into synaptic cleft
- Controls have lower number of peaks



Results (4)

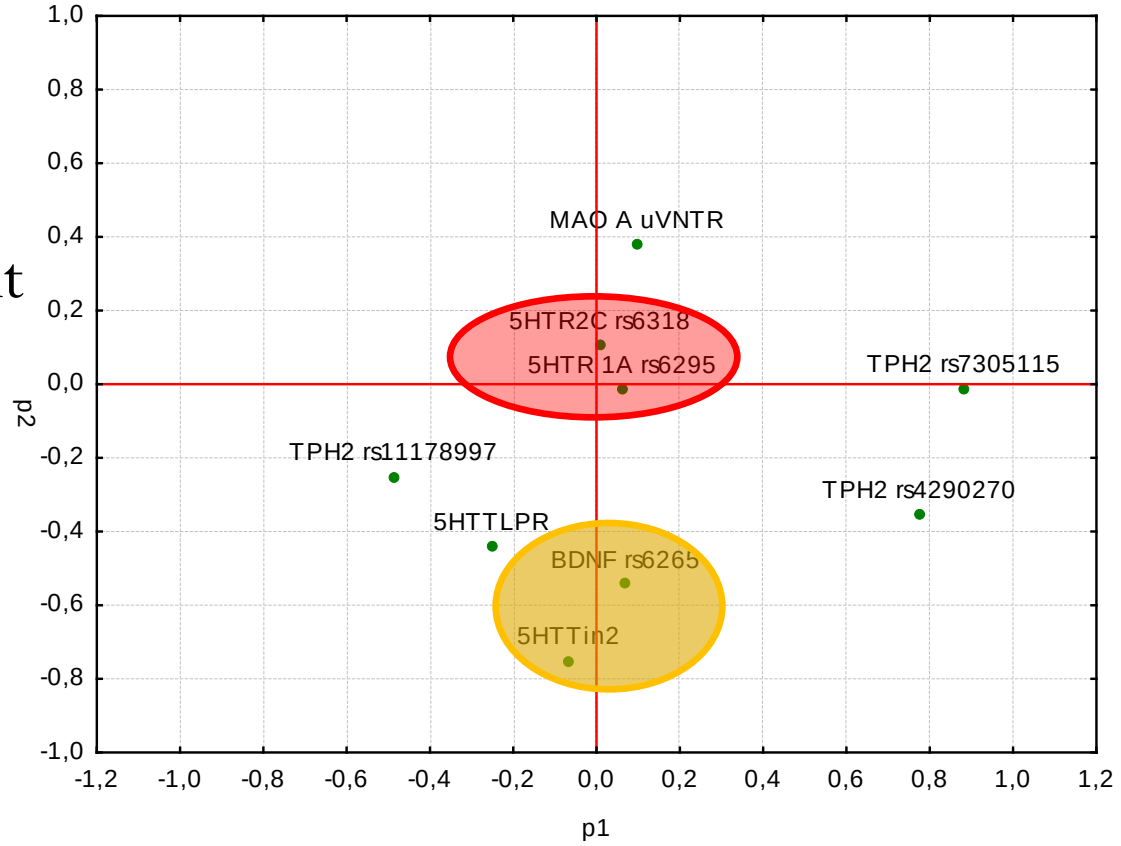


- MAOA deactivates faster in control subjects



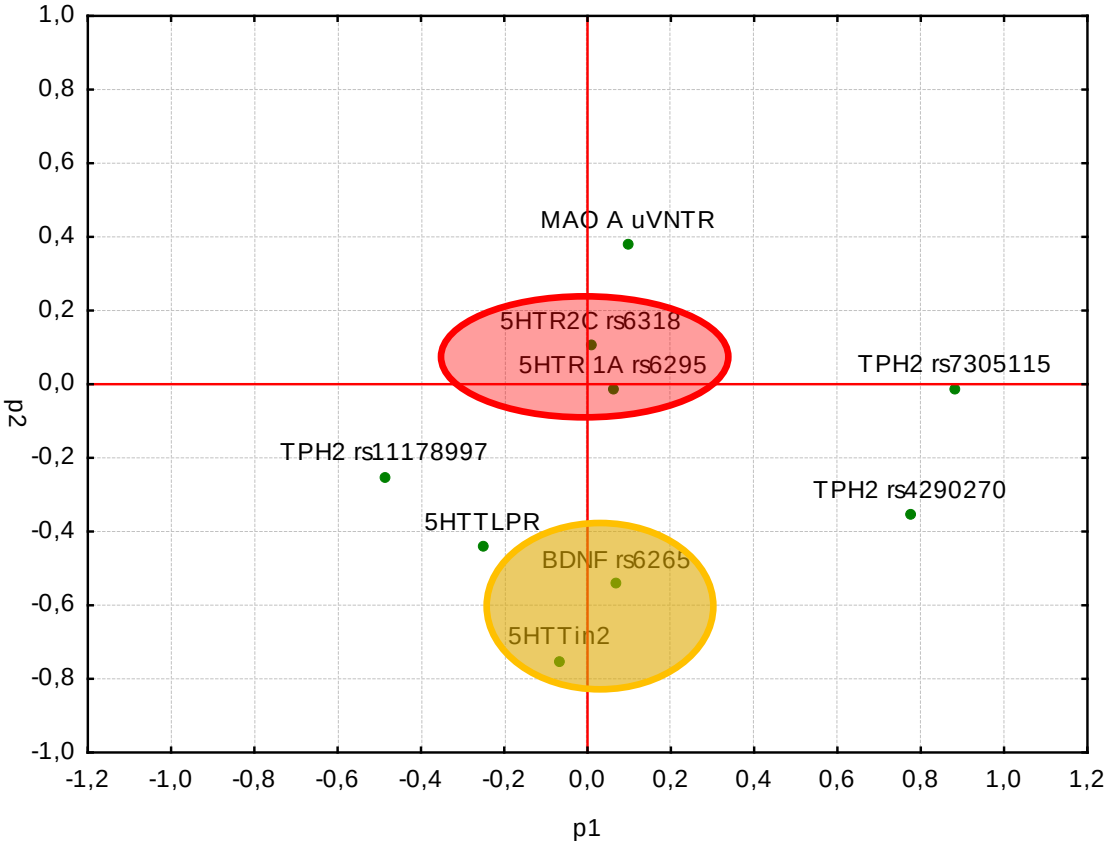
PCA

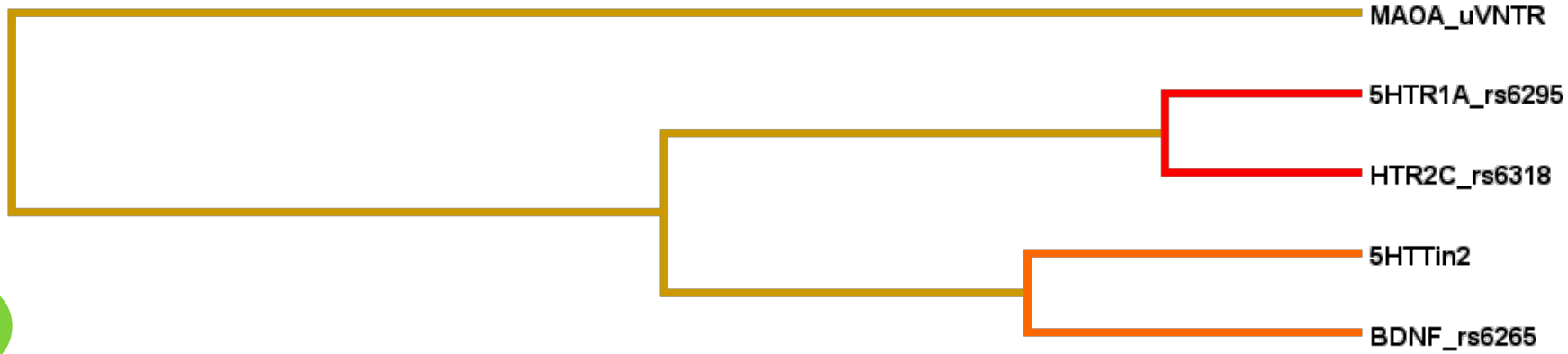
- Principal Component Analysis
- SNPs in TPH2 show the greatest importance
- 5HTTin2



PCA

- Epistasis
- Multifactor dimensionality reduction
- Synergistic epistatic interaction





PCA

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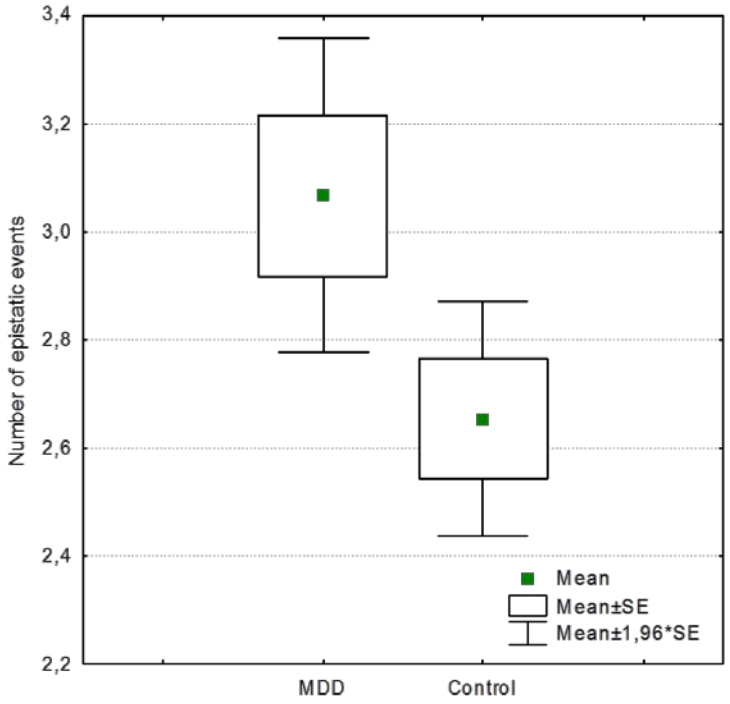
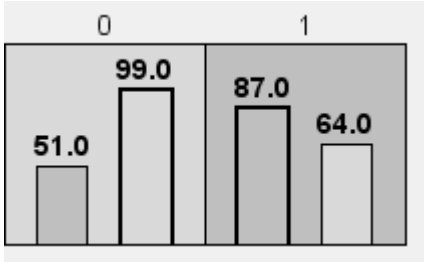
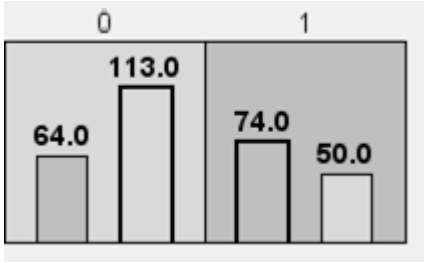
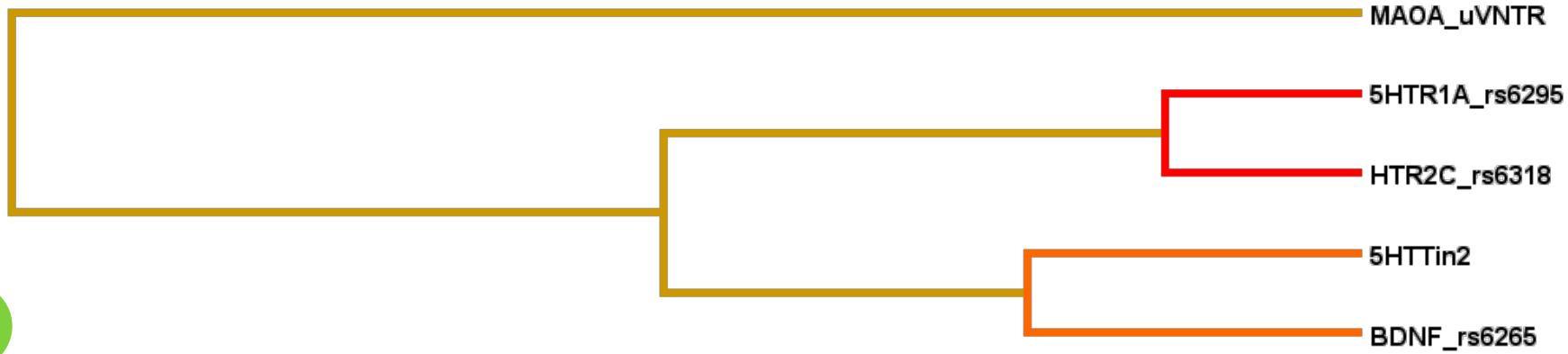


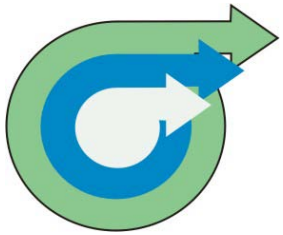
5HTR1A × 5HT2C



5HTTin2 × BDNF





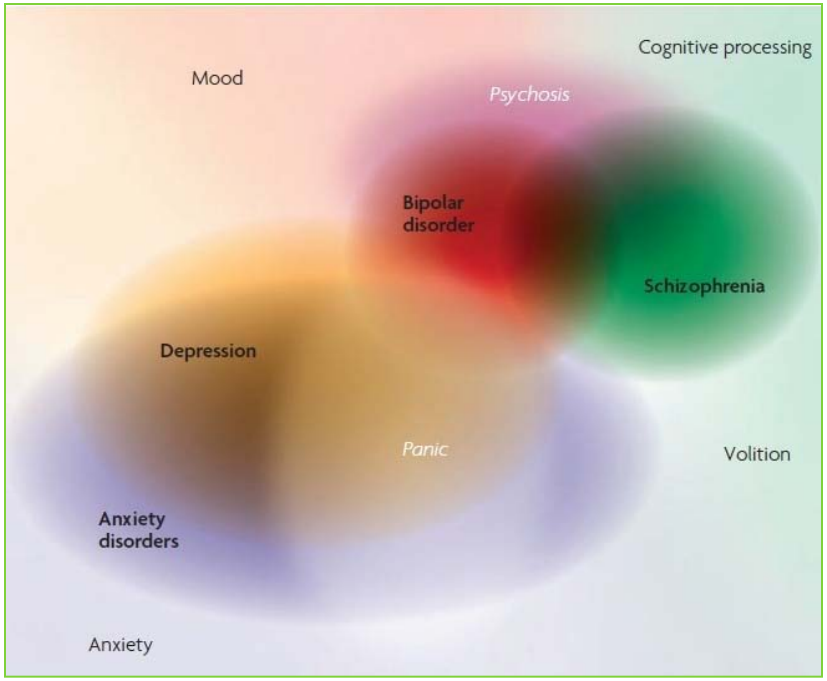


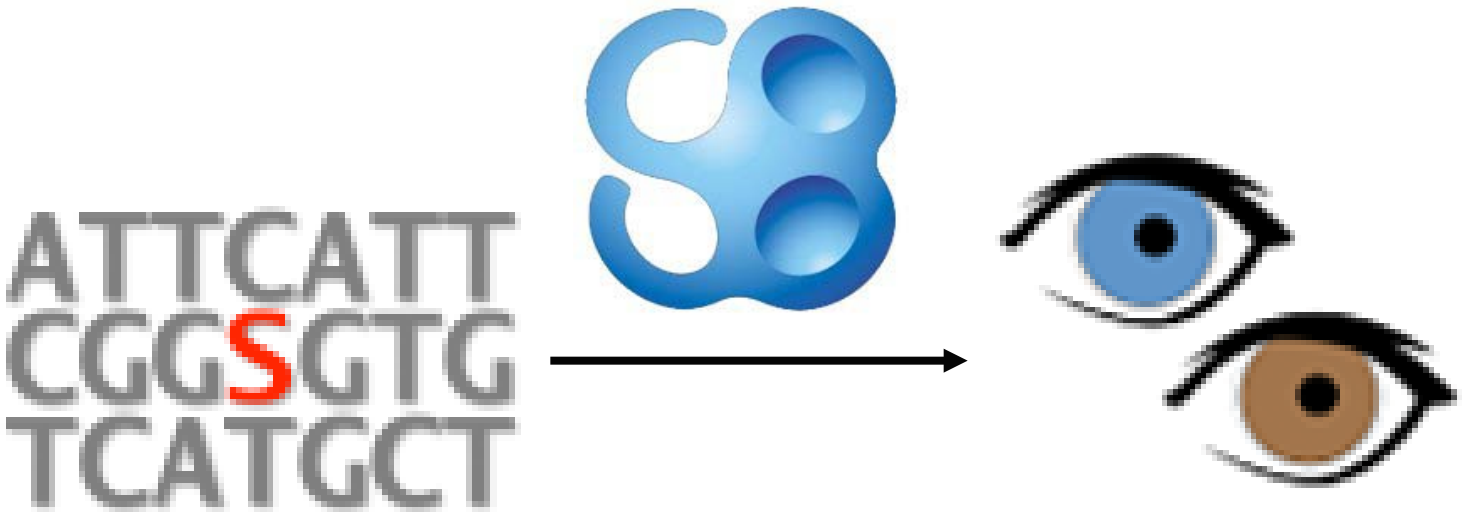
Outlook

- Generalized Linear Models
- Mathematical prediction of :
  - risk to MDD based on kinetic parameters – accuracy 82%
  - MDD type – accuracy 65%
  - Response to antidepressant therapy – accuracy: 89%
  - Suicide attempt – accuracy 100%

Outlook

- Additional genes
- Environmental effects
- Brain-region specific modeling
  - Three-, four-, n-cell system
- Disorder continuum

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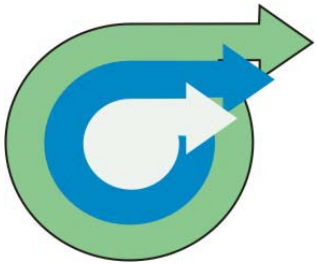
TCATGCT

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