Investigation of the Overlapping Phenotypes of Rett Syndrome (RTT)

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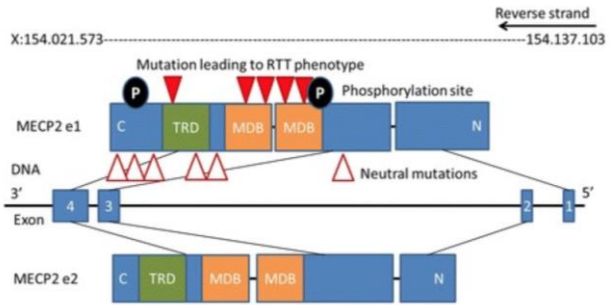
Rett Syndrome

- Rare genetic disorder
  - 1:10.000 female life births
- Decreased brain development and brain function
- Motoric, developmental and cognitive problems
- Developmental stages characterized by phenotypes
  - Developmental arrest, hand stereotypies, autistic like behavior, seizures, microcephaly

Dunn, H.G. (2001) Brain Dev
Ehrhart, F., et al. (2016) Orphanet J Rare Dis
Ip, J. P. K., et al. (2018) Nat Rev Neurosci

Causes

- De novo mutations in *MECP2* (X chromosome)
  - Transcriptional repression and activation
  - Alternative splicing
  - Regulation of microRNAs and long non-coding RNAs
- FO
- CD
- Wh



→ additional 70 genes

Ehrhart, F., et al. (2016) Orphanet J Rare Dis
Ehrhart, F., et al. (2018) Current opinion in psychiatry
Ip, J. P. K., et al. (2018) Nat Rev Neurosci

Diagnosis

- Diagnosis based on phenotypes
  - Regression followed by a stabilization phase
  - Main criteria
  - Supportive criteria
- Genetic testing

- Diagnosis of genetic disorders based on phen
- Disorders have similar phenotypes

➢ Misdiagnosis

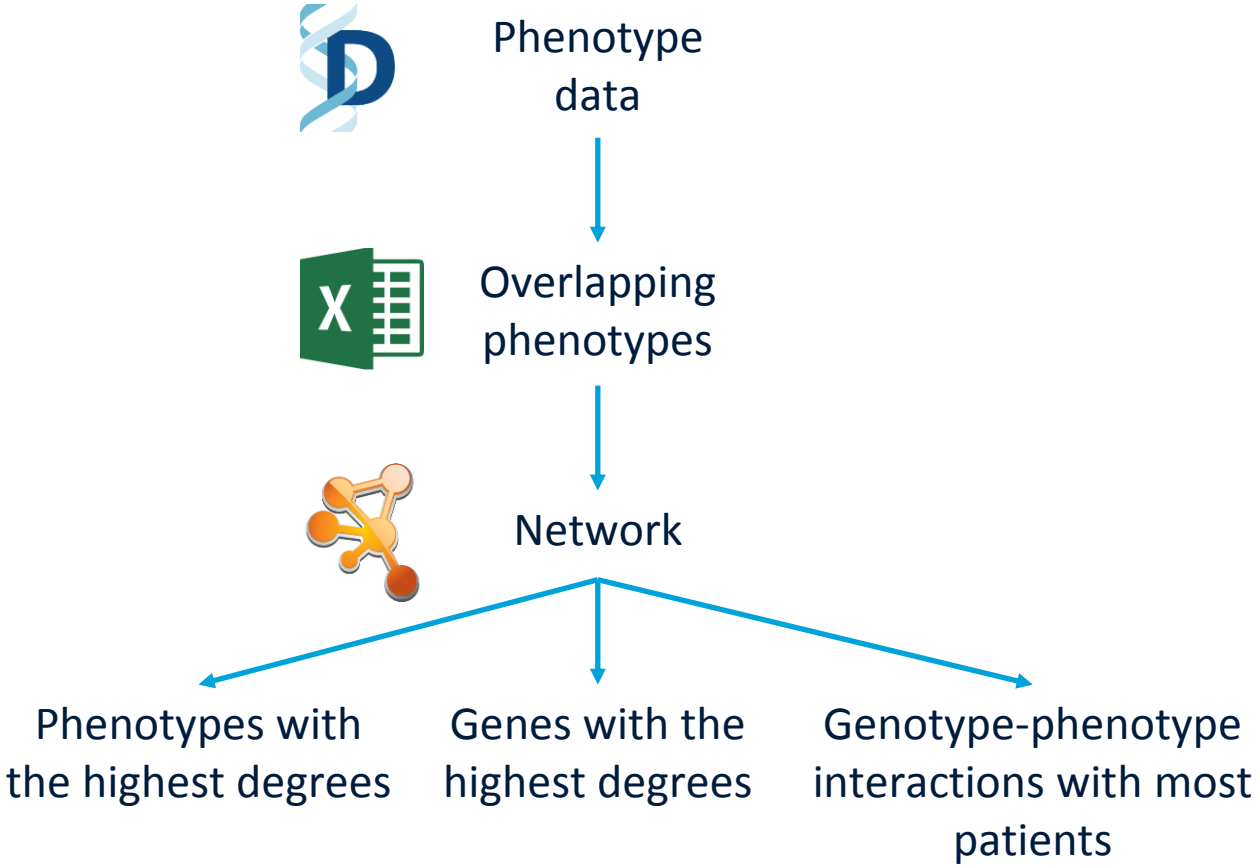
- ➢ Hand stereotypies
- ➢ Loss of speech
- ➢ Gait abnormalities
- ➢ Loss of purposeful hand skills
- ➢ disturbances
- ➢ Scoliosis
- ➢ Growth retardation
- ➢ Small cold feet/hands
- ➢ Inappropriate laughing
- ➢ Diminished pain response
- ➢ Intense eye communication

Ehrhart, F., et al. (2018) Current opinion in psychiatry

Research question

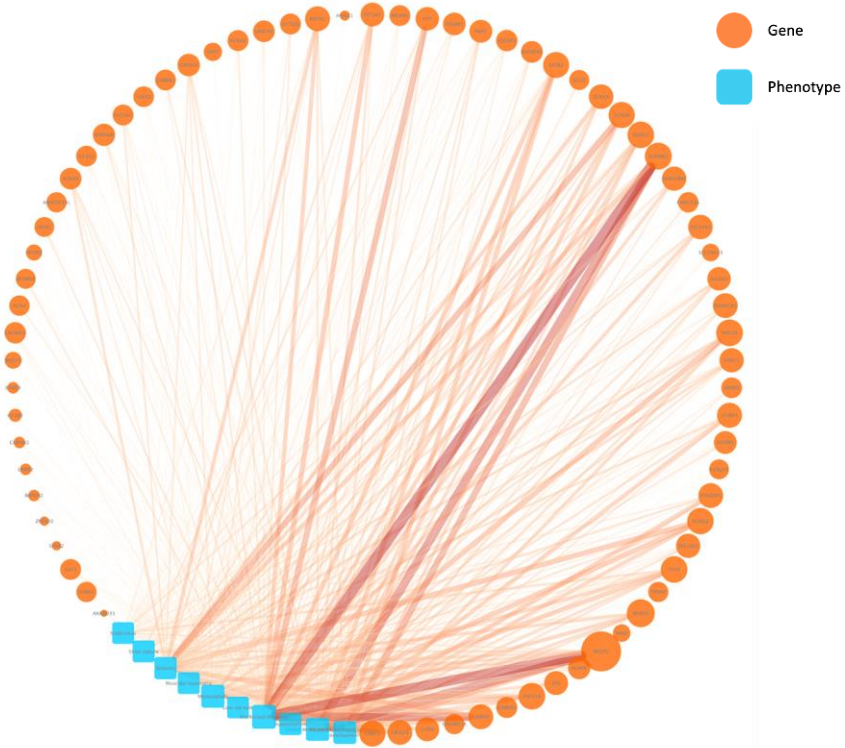
To which extend do the phenotypes of genes responsible for a RTT-like phenotype overlap with the phenotypes associated with a mutation in *MECP2*?

Method



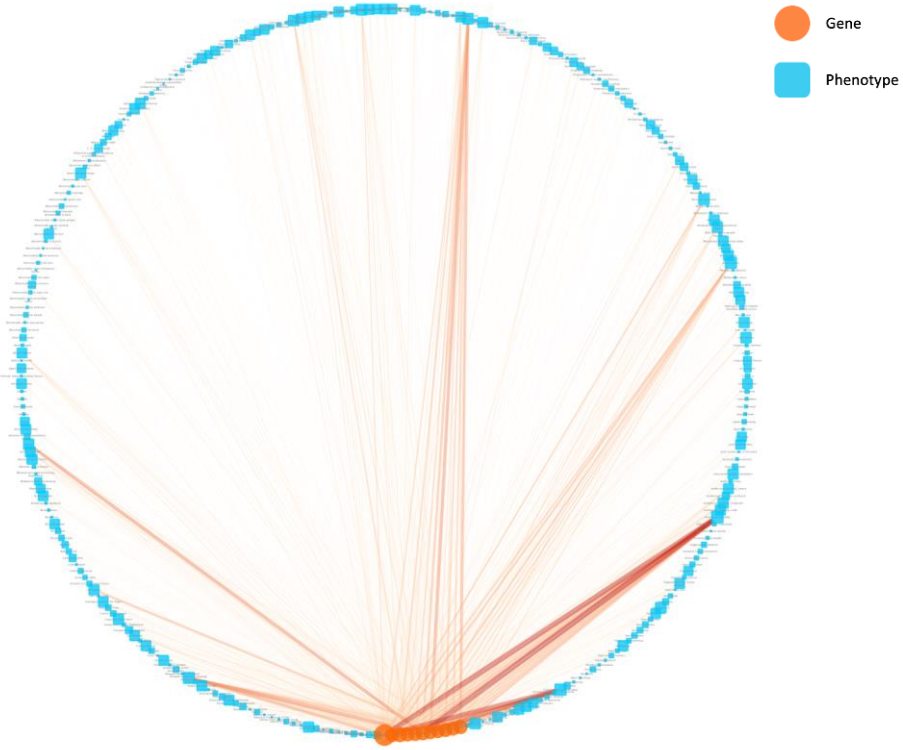
Firth, H.V., et al. (2009) Am J Hum Genet
Shannon, P., et al. (2003) Genome Res

Phenotypes



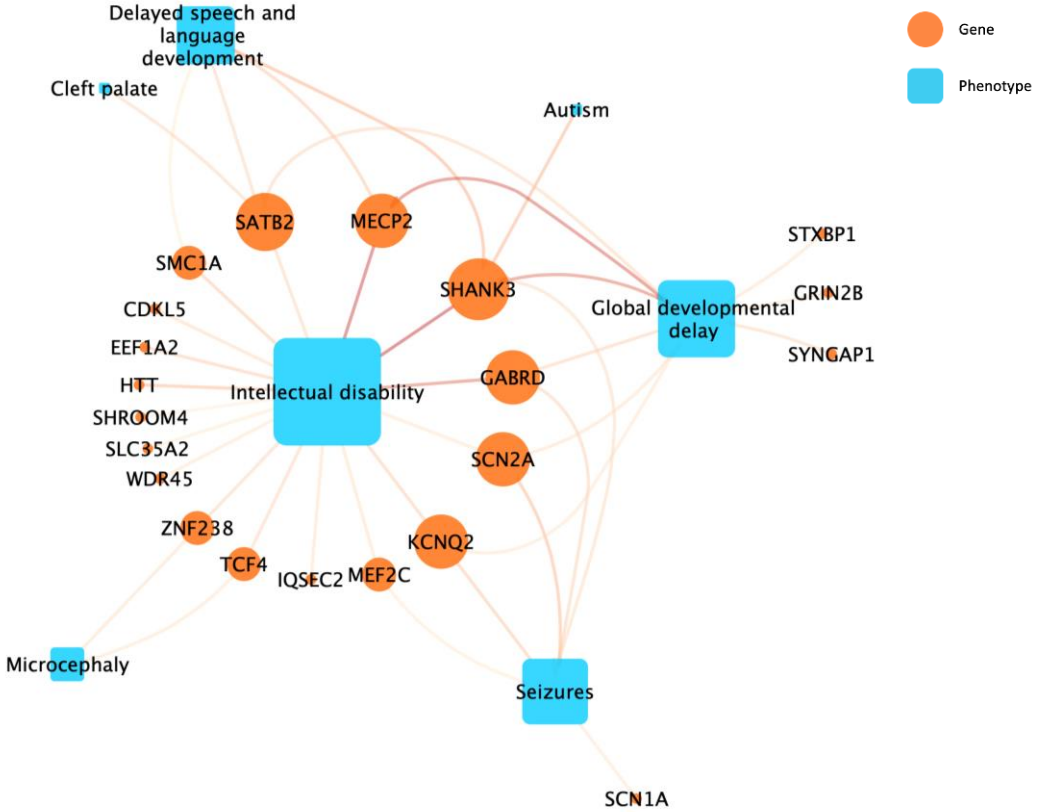
Phenotype	Degree
Intellectual disability	71
Global developmental delay	63
Microcephaly	61
Delayed speech and language development	60
Seizures	50
Hypertelorism	49
Short stature	49
Muscular hypotonia	48
Low-set ears	45
Strabismus	45

Genes



Gene	Degree
WDR45	127
SHANK3	114
SMC1A	112
ZNF238	111
IQSEC2	109
TCF4	109
KCNQ2	107
SCN2A	104
CDKL5	103
SATB2	102

Genotype-phenotype interactions



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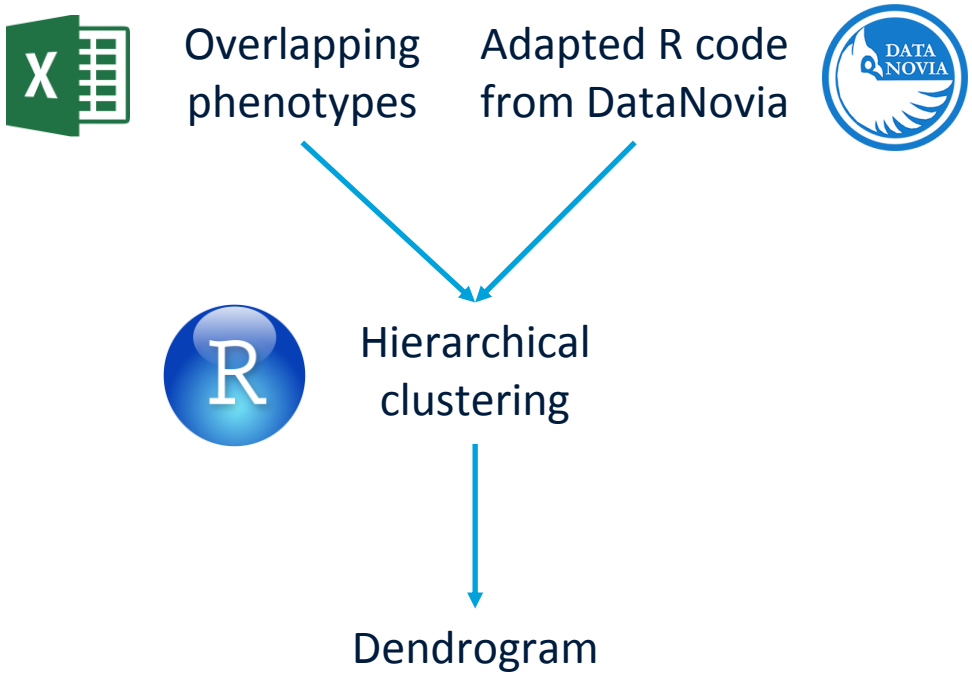
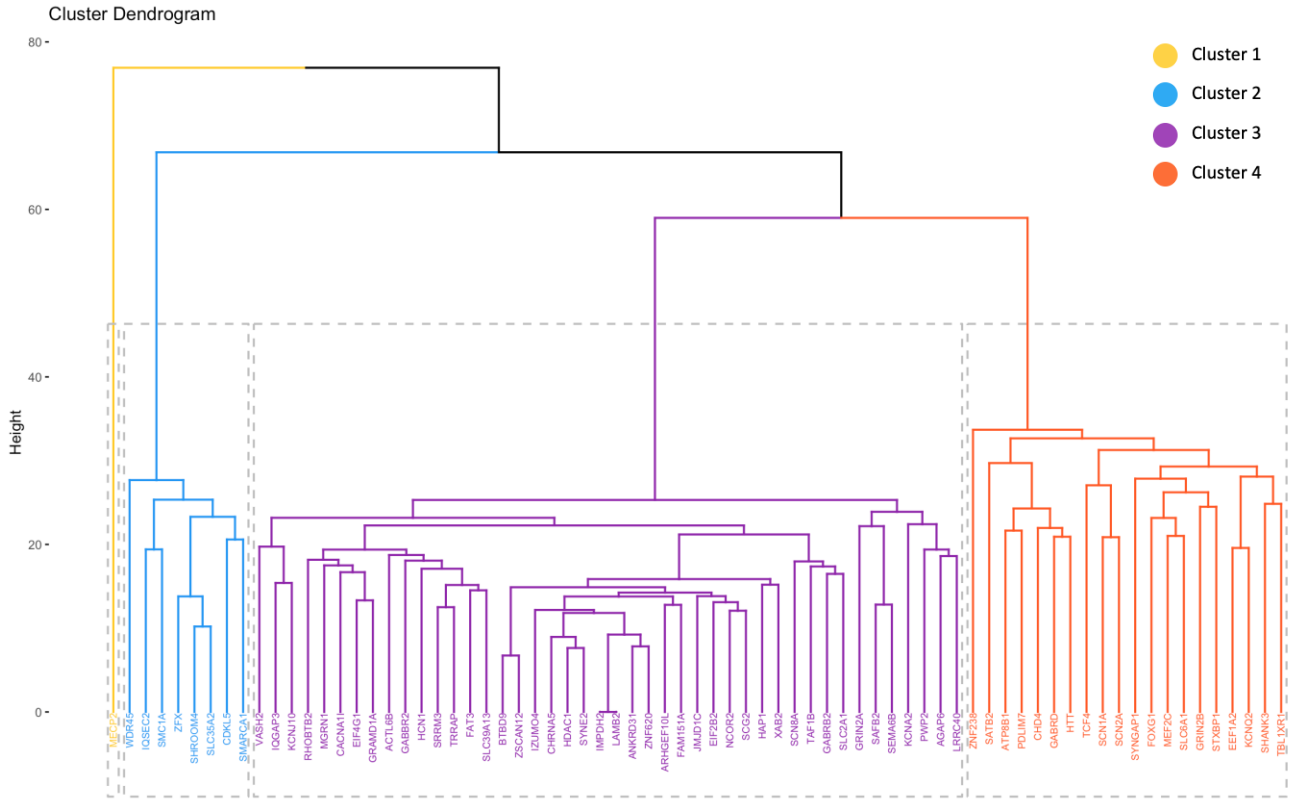
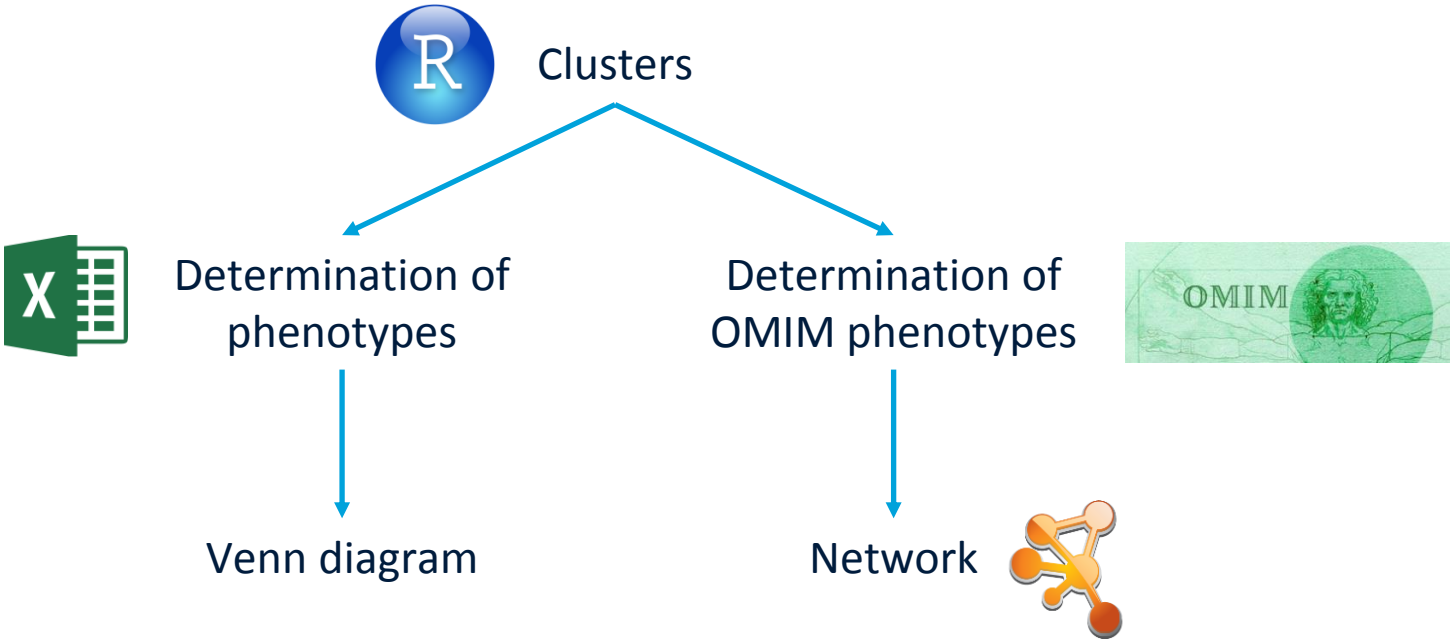


Datanovia. Types of Clustering Methods: Overview and Quick Start R Code
Rstudio Team (2015) *http://www.rstudio.com*

Hierarchical clustering

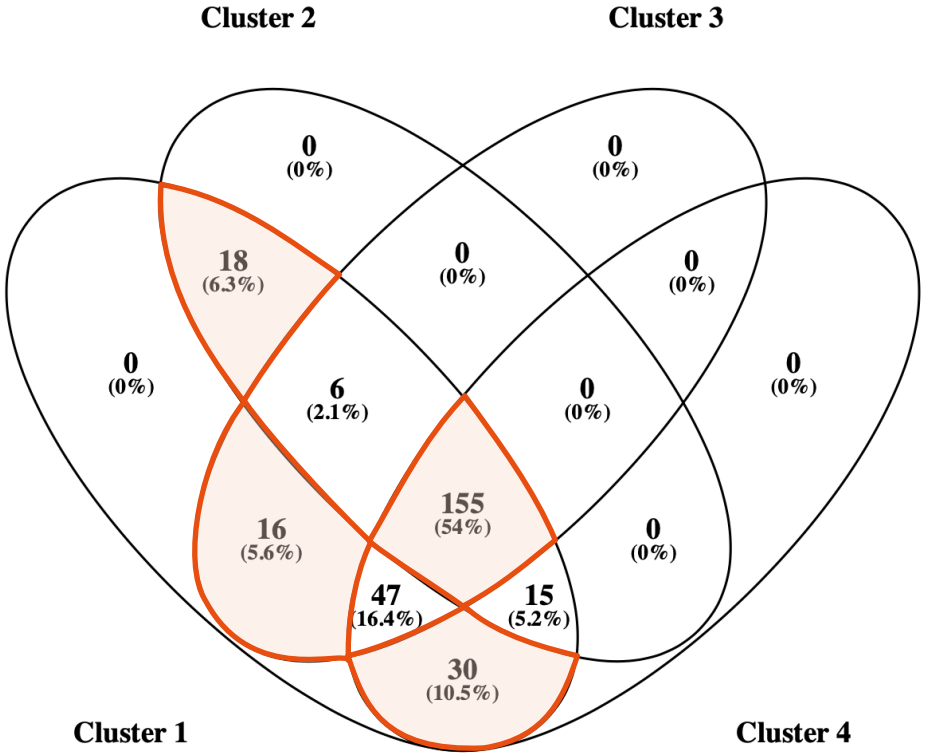


Method

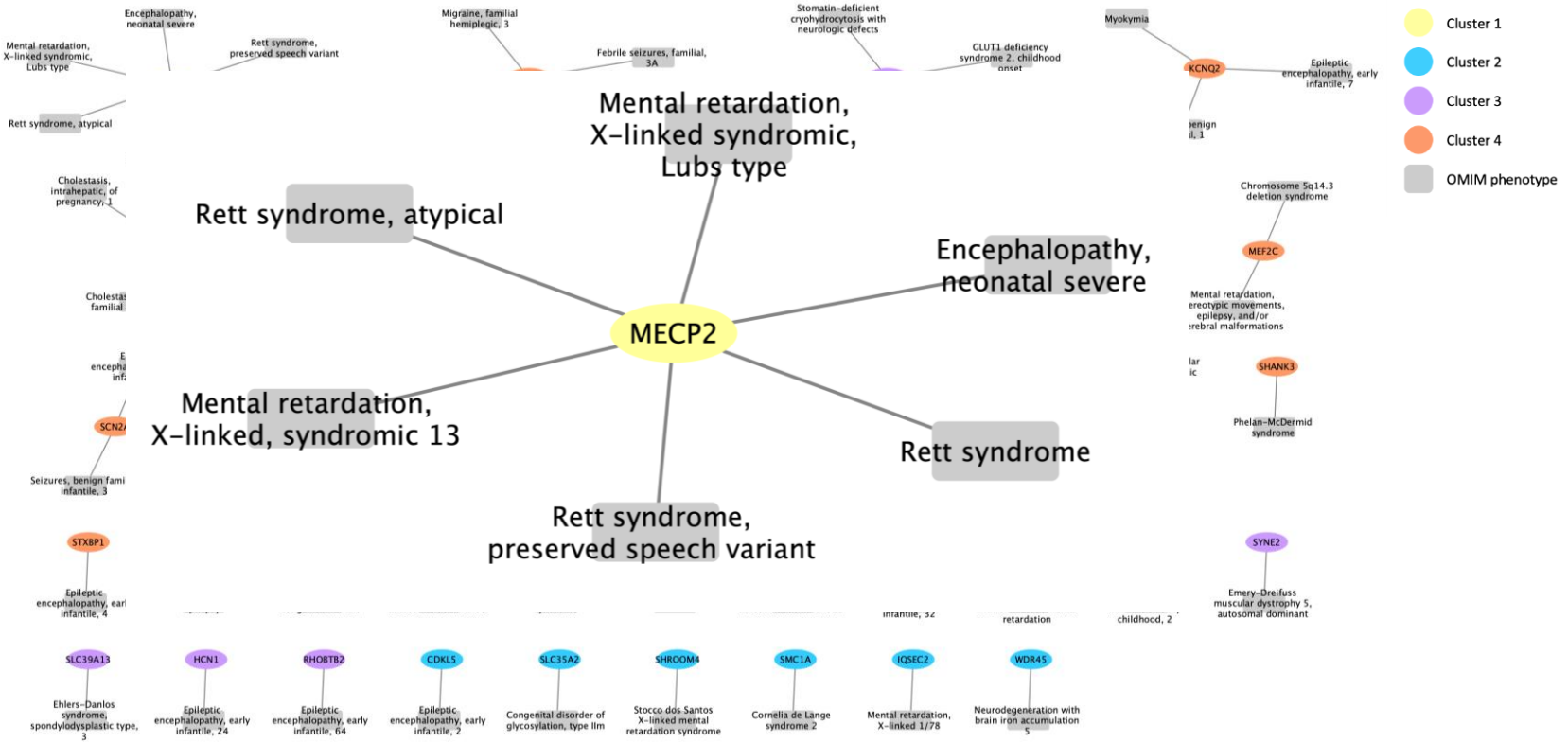


Rstudio Team (2015) *http://www.rstudio.com*
Online Mendelian Inheritance in Man, OMIM. *http://omim.org*
Shannon, P., et al. (2003) Genome Res

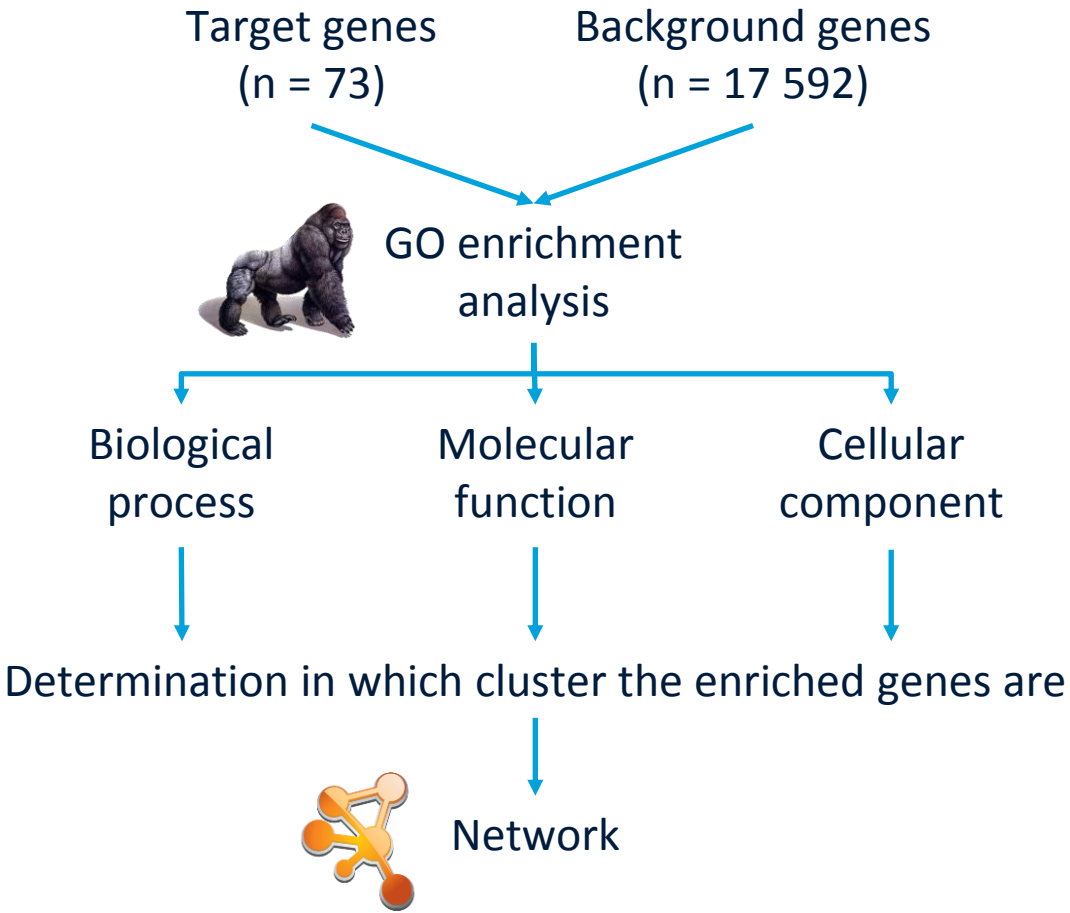
Phenotypes


Cluster 2
Cluster 3
0
(0%)
0
(0%)
18
(6.3%)
0
(0%)
0
(0%)
0
(0%)
6
(2.1%)
0
(0%)
0
(0%)
16
(5.6%)
155
(54%)
0
(0%)
47
(16.4%)
15
(5.2%)
30
(10.5%)
Cluster 1
Cluster 4

OMIM

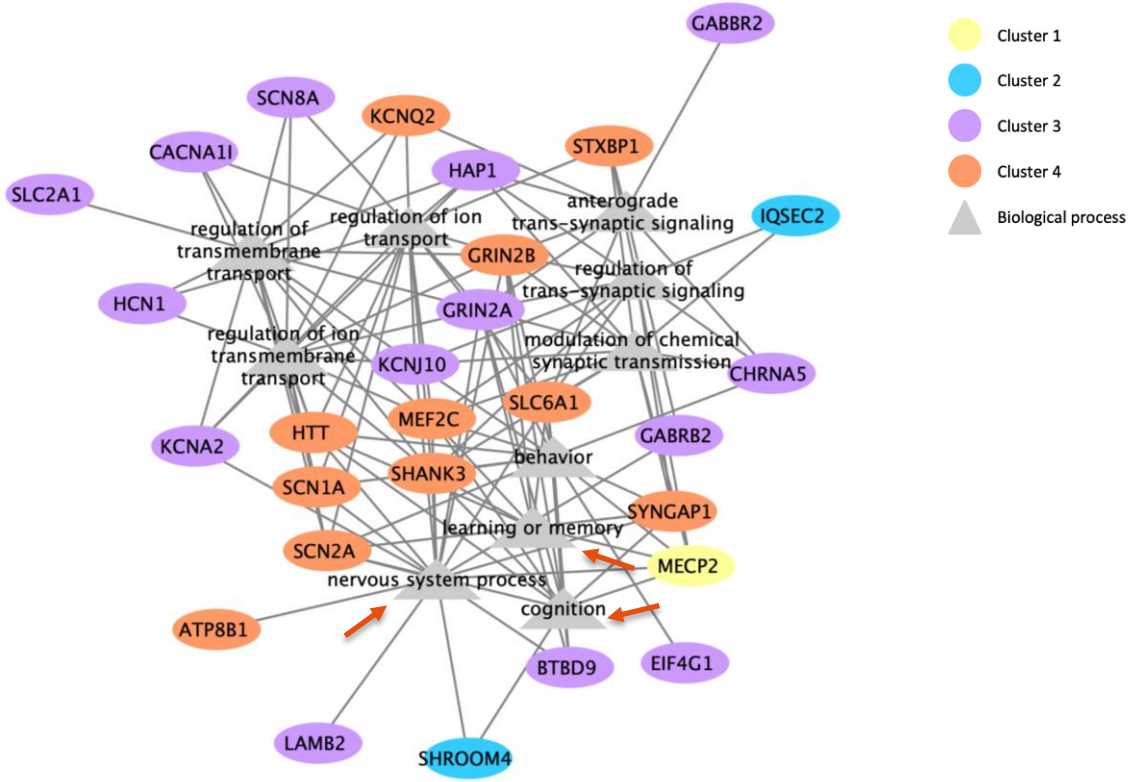

Cluster 1
Cluster 2
Cluster 3
Cluster 4
OMIM phenotype
MECP2
Mental retardation, X-linked syndromic, Lubs type
Rett syndrome, atypical
Encephalopathy, neonatal severe
Mental retardation, X-linked, syndromic 13
Rett syndrome
Rett syndrome, preserved speech variant
Encephalopathy, neonatal severe
Mental retardation, X-linked syndromic, Lubs type
Rett syndrome, preserved speech variant
Rett syndrome, atypical
Migraine, familial hemiplegic, 3
Febrile seizures, familial, 3A
Stomatin-deficient cryohydrocytosis with neurologic defects
GLUT1 deficiency syndrome 2, childhood onset
Myokymia
KCNQ2
Epileptic encephalopathy, early infantile, 7
Cholestasis, intrahepatic, of pregnancy, 1
Chromosome 5q14.3 deletion syndrome
MEF2C
SHANK3
Phelan-McDermid syndrome
SCN2A
Seizures, benign familial infantile, 3
STXBP1
Epileptic encephalopathy, early infantile, 4
SYNE2
Emery-Dreifuss muscular dystrophy 5, autosomal dominant
SLC39A13
Ehlers-Danlos syndrome, spondylodysplastic type, 3
HCN1
Epileptic encephalopathy, early infantile, 24
RHOBTB2
Epileptic encephalopathy, early infantile, 64
CDKL5
Epileptic encephalopathy, early infantile, 2
SLC35A2
Congenital disorder of glycosylation, type IIm
SHROOM4
Stocco dos Santos X-linked mental retardation syndrome
SMC1A
Cornelia de Lange syndrome 2
IQSEC2
Mental retardation, X-linked 1/78
WDR45
Neurodegeneration with brain iron accumulation 5

Method

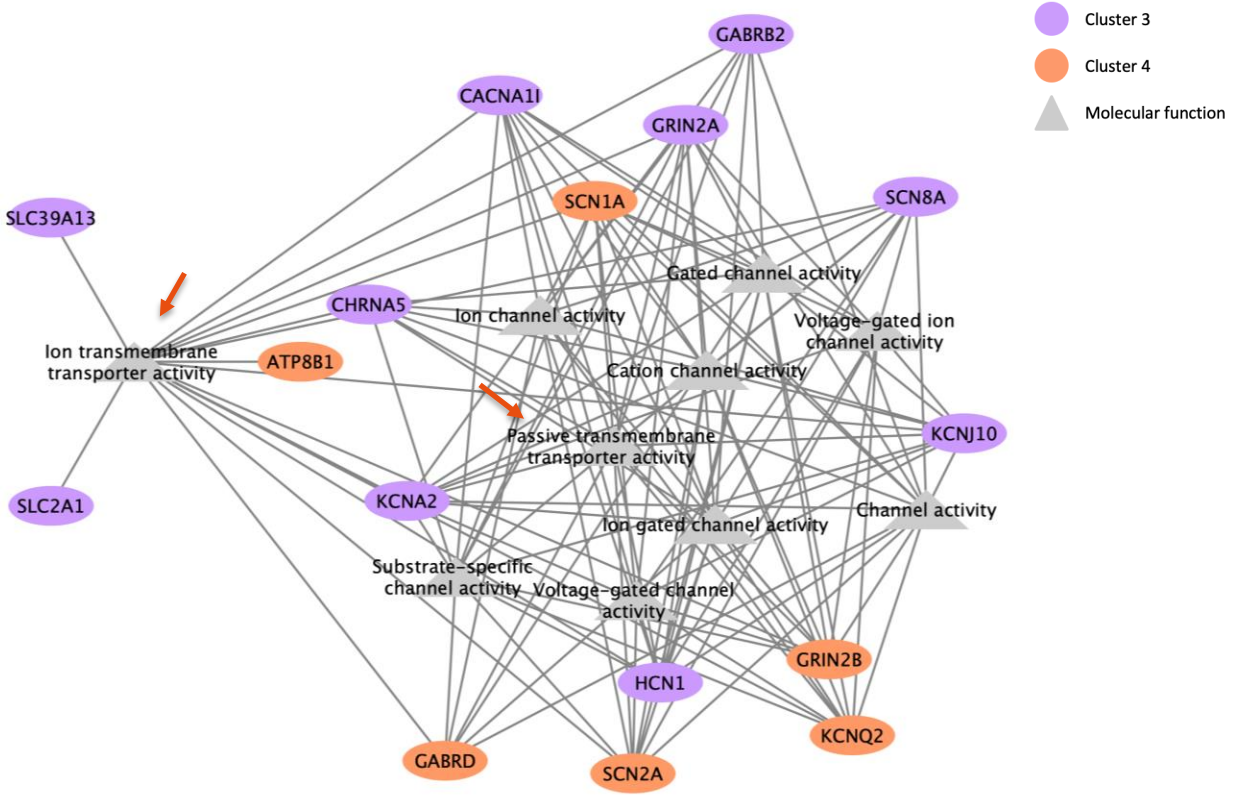


Eden, E., et al. (2009) BMC Bioinformatics
Shannon, P., et al. (2003) Genome Res

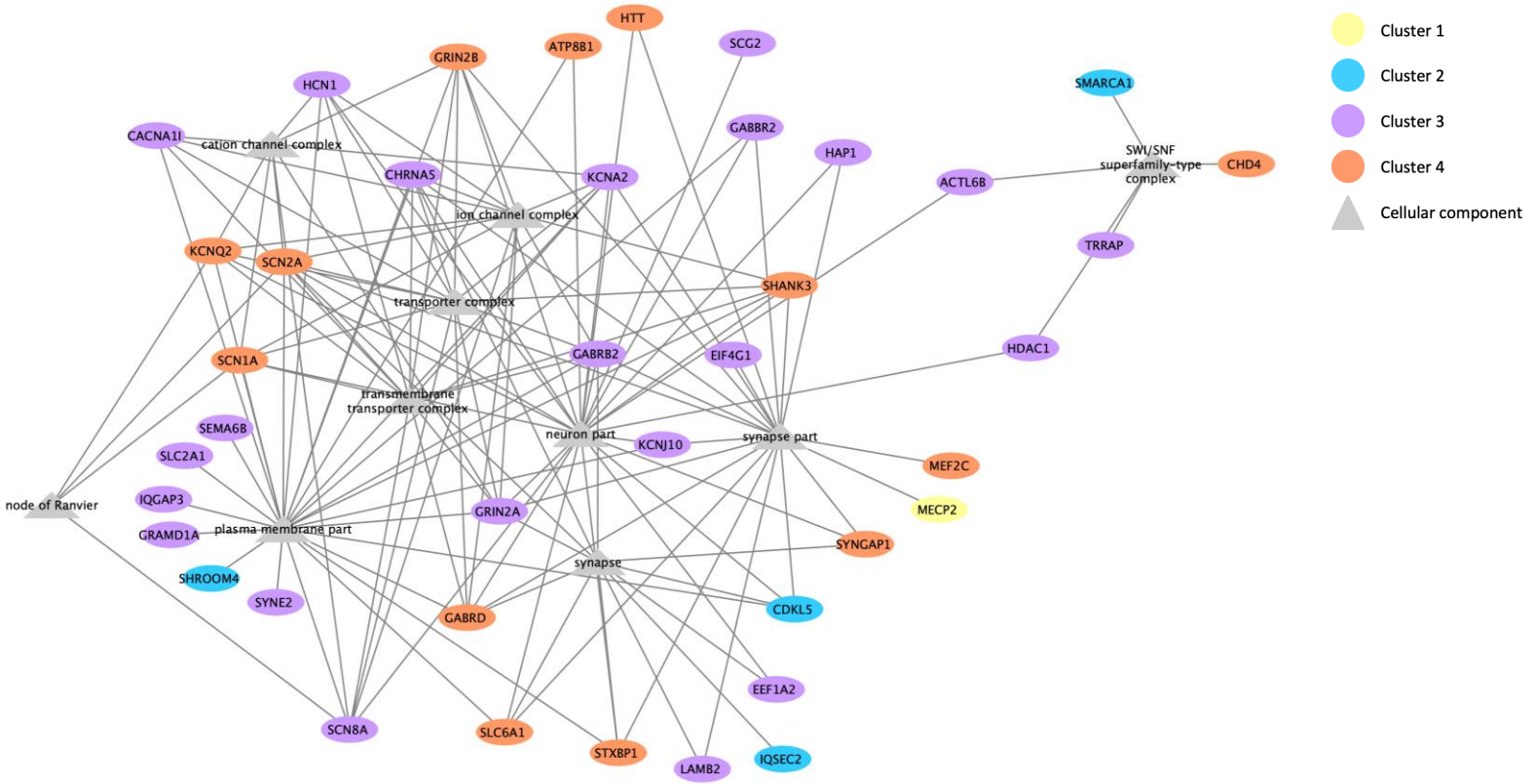
GO – Biological process



GO – Molecular function



GO – Cellular component



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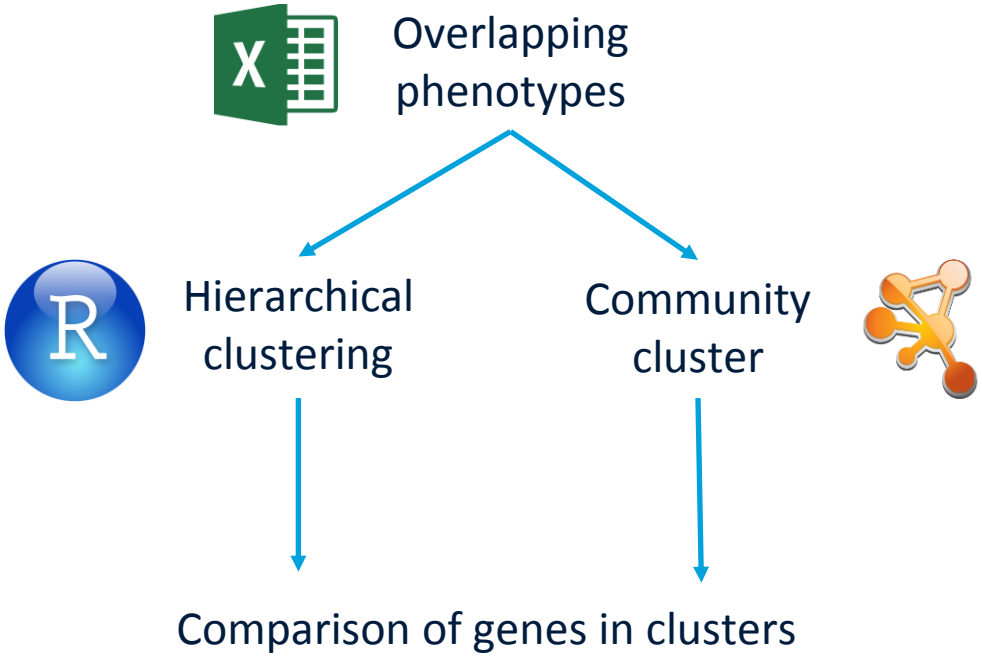

Rstudio Team (2015) *http://www.rstudio.com*
Shannon, P., et al. (2003) Genome Res

Community Cluster

Cluster	Genes
1	ACTL6B, AGAP6, ANKRD31, ARHGEF10L, CACNA1I, CHD4, CHRNA5, EEF1A2, EIF2B2, EIF4G1, FAM151A, FAT3, GABBR2, GABRB2, GABRD, GRAMD1A, GRIN2A, HAP1, HDAC1, HTT, IMPDH2, IZUMO4, JMJD1C, KCNA2, LAMB2, LRRC40, MGRN1, NCOR2, PDLIM7, PWP2, RHOBTB2, SAFB2, SCG2, SCN1A, SEMA6B, SLC39A13, SRRM3, SYNE2, TAF1B, TRRAP, XAB2, ZNF238, ZSCAN12
2	ATP8B1, BTBD9, FOXG1, GRIN2B, KCNQ2, MEF2C, SATB2, SCN2A, SCN8A, SHANK3, SLC2A1, SLC6A1, STXBP1, SYNGAP1, TBL1XR1, TCF4, ZNF620
3	CDKL5, HCN1, IQGAP3, IQSEC2, KCNJ10, MECP2, SHROOM4, SLC35A2, SMARCA1, SMC1A, VASH2, WDR45, ZFX

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Discussion

- Genes with the highest degrees more similar to *MECP2*
  - Associated with other disorders
- ➢ Similar manifestation to RTT

- Several phenotypes differed between clusters
  - No correlation between phenotypes
- ➢ Inconclusive results

Discussion

- Hierarchical and community clusters similar
- GO enrichment analysis showed tendencies
- ➢ Clustering and GO enrichment analysis could improve understanding of overlapping phenotypes

- OMIM phenotypes not specific for clusters
  - Mental retardation and Encephalopathy most common
- ➢ Indirect involvement in pathogenesis of RTT?

Discussion

- Spectrum disorder instead of monogenic disorder

- Misdiagnosis of patients
- ➢ Broadened genetic screening

- Overlapping phenotypes due to overlap in pathways
  - *NCOR2* and *HDAC1* in co-repressor complexes
  - Mutations in *MEF2C* decrease *MECP2* expression

Ehrhart, F., et al. (2018) Current opinion in psychiatry
Nan, X., et al. (1998) Nature
Vidal, S., et al. (2019) Eur J Paediatr Neurol
Zweier, M., et al. (2010) Hum Mutat

Limitations

- Inconsistent amounts of phenotype data
  - Genes with highest degrees → most phenotype data
- ➢ Results were influenced
- A different clustering method would have resulted in a different dendrogram

Gene name	Number of phenotypes Total (overlap)	Number of patients with phenotype data
MECP2	331 (287)	150
SHANK3	248 (214)	134
GABRD	200 (86)	86
SMC1A	189 (112)	81
IQSEC2	179 (109)	80
KCNQ2	194 (107)	75
WDR45	209 (127)	73
SCN2A	194 (104)	73
SATB2	210 (102)	70
CDKL5	162 (103)	70
TCF4	213 (109)	66
ZNF238	213 (111)	61

Conclusion

- There was phenotypic overlap to a certain extend
  - However, overlap influenced by the available amount of phenotype data
- Patient phenotype data beneficial to understand the overlap
- ➢ Better understanding of Rett syndrome
  - Misdiagnosis or spectrum disorder

Outlook

- Repeat when more data is available
- Normalization of the data
- Include data from other databases
  - DisGeNET, Human Phenotype Ontology
- More research on the mechanisms behind overlap

Acknowledgement

I would like to thank my supervisor Friederike Ehrhart for guiding and advising me during my internship

Questions?