Cerebellar development in Down syndrome and human evolution

Cognitive Biology of Language Group

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What motivated this project?

- Which changes in the genome caused the brain changes that underlie complex human cognitive function?
- What is the role of the cerebellum in complex human cognitive functions?
- How in the evolutionary development of primates did the cerebellum get bigger?
- Can DS help us to answer these questions?

→ Exploratory analysis of differential regulation comparing trisomic and euploid humans, contrasted with human species-specific regulation!

Developmental cerebellum

FUN FACTS

- Increase from 5.7% to 10% of total brain weight between birth and 9 months and prolonged postnatal development in primates (Marzban et al., 2014)
- Probably a large amount of programmed cell death during development (Cocito et al., 2016)
- Granule cells rely on the correct levels of Wnt signaling to balance their proliferation and differentiation (Lorenz et al., 2011)

Combining two data sets:
- Differential expression of RNA-seq
- Postnatal cerebellum
- Trisomic vs. euploid humans (Olmos-Serrano et al., 2017)
- Human vs. rhesus macaque (Zhu et al., 2018)
- p = 0.003

Methods

- Intersection of two RNA-seq DEX data sets
- Exploratory bioinformatic analysis of the intersection (47 genes)
- Interpretation of possible functional connections between the genes

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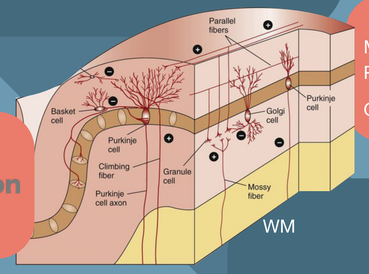
- Enrichment analysis with ToppGene, Enrichr, String, NetworkAnalyst
- Transcription factor prediction with iRegulon
- Tissue expression profile with Human Protein Atlas
- Candidate gene priorisation with ToppGene
- Literature review

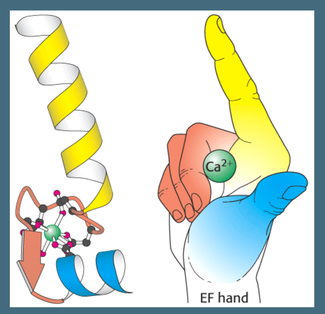
What's different?

Why is that?

What does that mean?



Shared disregulation of Ca2+ and Wnt related processes?

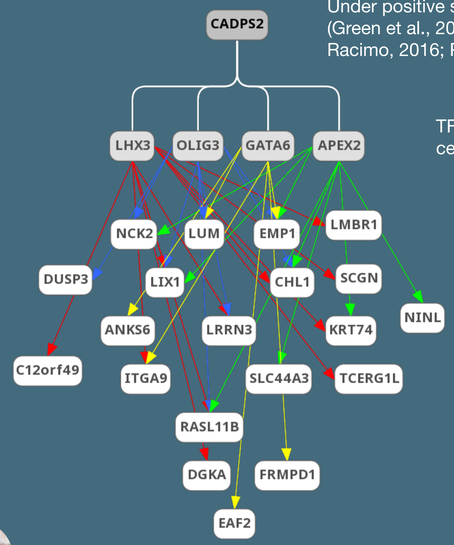


EF hand motif enrichment, calcium bindig: DGKA, SCGN, EFCAB12, NINL

Literature review shows: At least 11 genes in our set can be linked to **Ca^{2+} signalling**, 15 or more can be linkted to **Wnt pathway**!

Top genes linked to Ca2+ KEGG

BRCA1	loss of BRCA1 induces apoptosis via p53 (Pao et al., 2014) interacts with MAPK pathway (Gilmore et al., 2004)
NCK1	target of Wnt pathway (Ziegler et al., 2005) depletion leads to apoptosis (Errington & Macara, 2013) (via p53)
ITGA9	related to Wnt/β-Catenin (Pérez-Palma et al., 2016)
LUM	suppresses cell proliferation (Vij et al., 2004, Williams et al., 2011) involved in folding of neocortex (Long et al., 2018)
CHL1	CHL1 as a synapse-targeting cue for Hsc70, which is involved in protein folding and sorting, signal transduction, and apoptosis (Leshchyns'ka et al., 2006)



Under positive selection in modern humans (Green et al., 2010; Prüfer et al., 2014; Racimo, 2016; Peyrégne et al., 2017)

TFs affected by CADPS2 knockout in cerebellum (Sadakata et al., 2017)

Dysregulated in Olmos-Serrano et al. (2017) and Zhu et al. (2018)

- → CADPS2 as a candidate for further study?
- → GATA6 under selection as well (Racimo, 2016); link to DYRK1A
- → Targets of HAND1 linked to Ca^{2+} and Wnt signalling
- → MECP2 important in Rett syndrome (Shah & Bird, 2017)