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 Down syndrome (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

- 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)
- Relative expansion during hominin evolution (Barton & Venditti, 2014)

FUN FACTS

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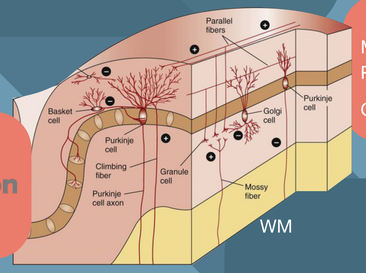
- Enrichment analysis with ToppGene, Enrichr, String, NetworkAnalyst
- Transcription factor prediction with iRegulon
- Tissue expression profile with Human Protein Atlas
- Candidate gene priorisation with ToppGene
- Literature review

What's different?

Why is that?



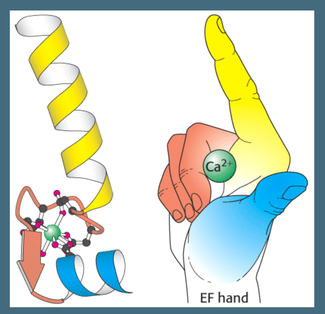
What does that mean?

A functional interpretation

Calcium homeostastis dysregulation

- Differential activation of downstream pathways (e.g. cAMP, MAPK, PI3K) (Berridge et al., 2012)
- Influence on synaptic excitability and spiking behaviour (Gall et al., 2005)
- Possible link between calcium homeostasis and increased number of inhibitory synapses in DS?

Shared disregulation of Ca^{2+} and Wnt related processes?



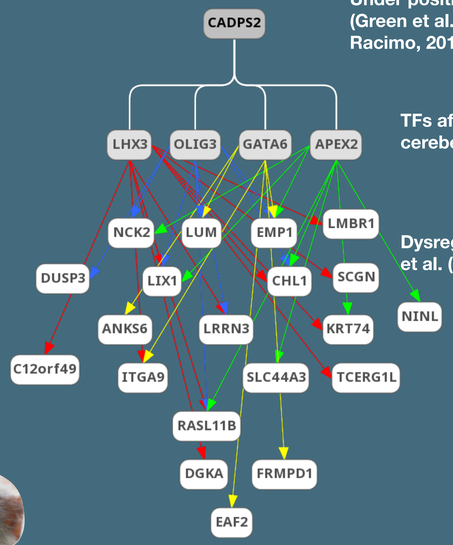
Shared DEX genes: EF hand motif enrichment (DGKA, SCGN, EFCAB12, NINL)
Macaque/humans: 21 EF hand motif genes
Trisomic/euploid: 15 EF hand motif genes

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 Ca^{2+} 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)

Exploring connections to modern human specific SNPs...



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)

Other TFs of interest
- KLF4: 10 targets, high number of high frequency SNPs specific to modern humans (Kuhlwilm & Boeckx, 2019)
- RREB1: 13 targets, high number of regulatory differences in modern and 0 in archaic (Kuhlwilm & Boeckx, 2019)

→ 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)

A role for p53 in human evolution?

- Pro-apoptotic phenotype in DS linked to p53 (e.g. Tramutola et al., 2016)
- Cross-talk between p53 and Shh during cerebellar development (Barthelery et al., 2012)
- Positive selection on apoptosis-related genes (da Fonseca et al., 2010)
- Differential regulation of p53 during development in human evolution?

Spotlight on BRCA1

- Evolved rapidly in humans and other primates, positive selection (Lou et al., 2014)
- KO leads to increased apoptosis and reduced cerebellar (and neocortex) volume via p53 (Pao et al., 2014)
- Reduced breast cancer risk in DS (Dey et al., 2017)

Conclusions

- Processes that have changed in recent human evolution regulating cerebellar development are in part shared with those that are differentially regulated in DS
- Calcium-binding proteins are differentially expressed during postnatal cerebellar development
- Aberrant calcium homeostastis in DS could be a model for studying role of calcium in human evolution
- Candidates for further study: CADPS2 and its downstream network; Wnt signalling pathway; calcium buffers and sensors
- BRCA1 as a candidate for increasing apoptosis and reducing cerebellar volume