Bioinformatic approaches to regulatory genomics and epigenomics

376-1347-00L - 2022 | week 13

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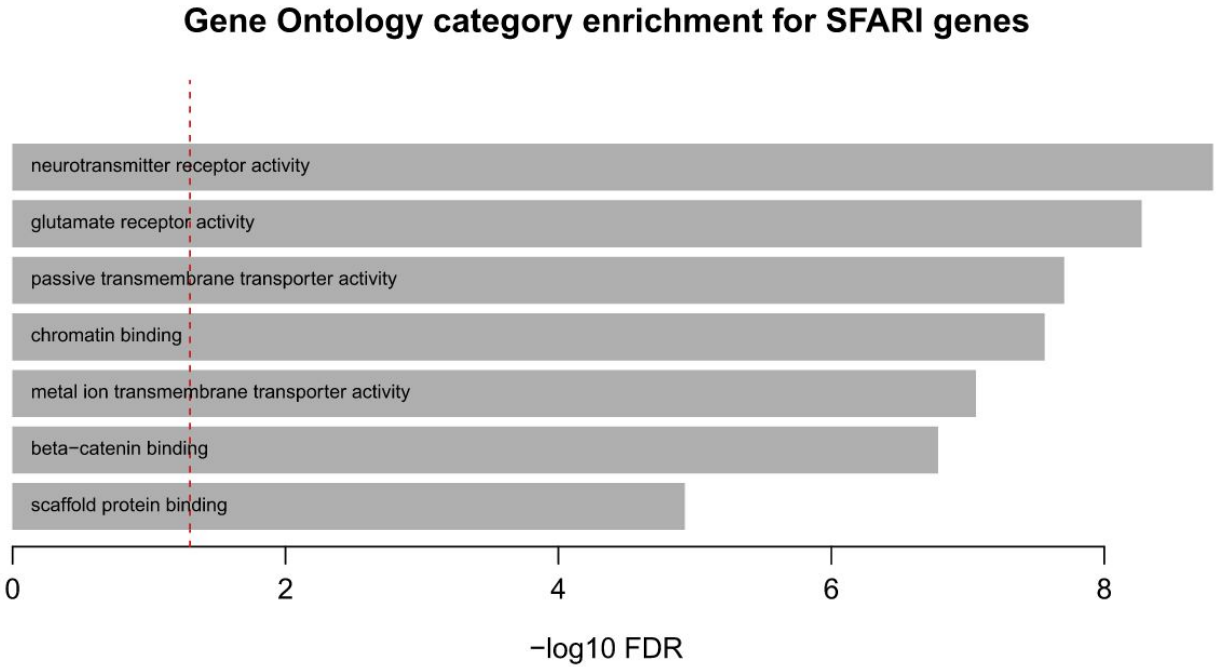
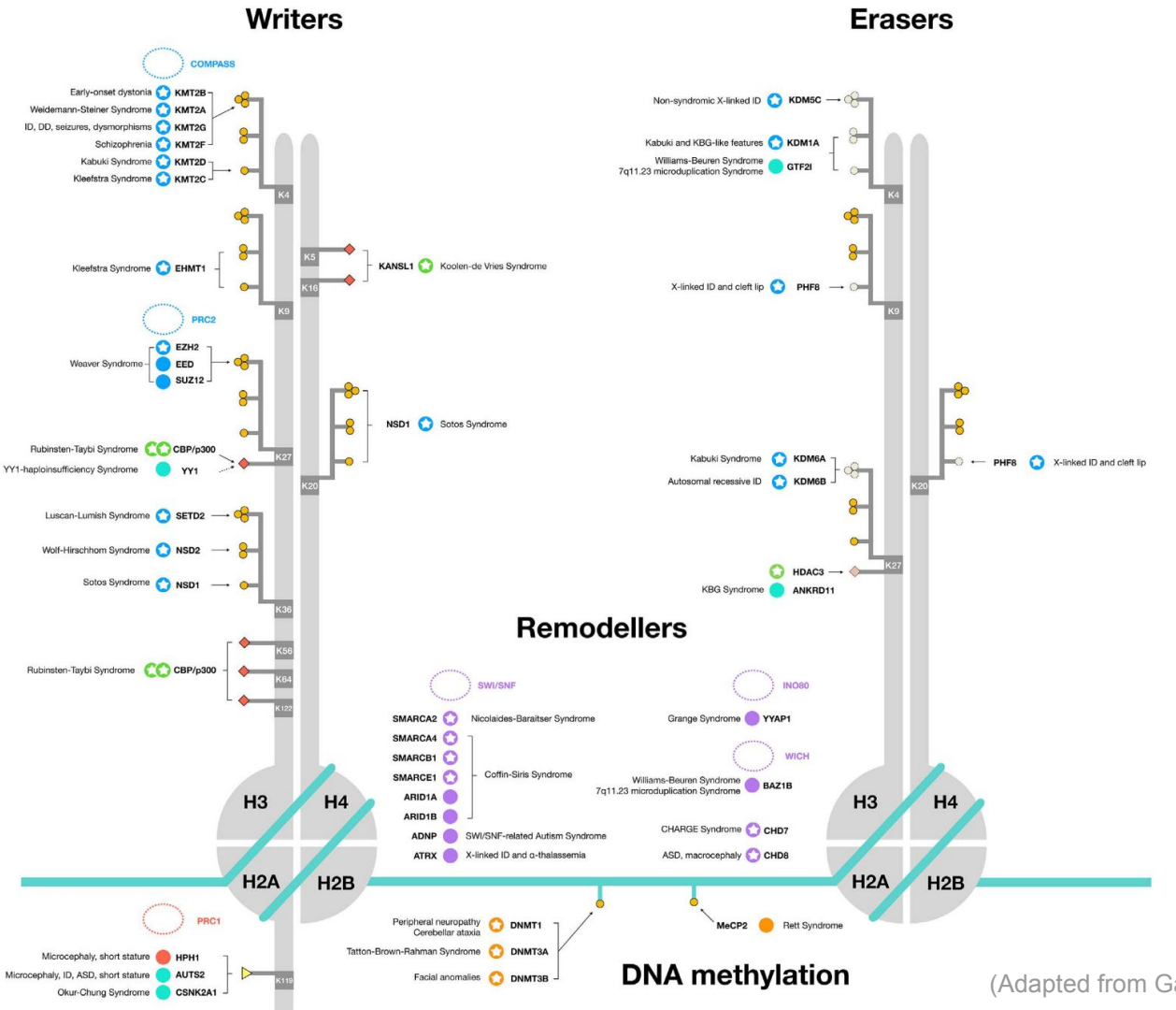
Plan

- Students’ presentations
- Chromatin and disease
- Some of our research avenues

Autism-associated genes are enriched for chromatin-binding





Nearly all epigenetic modifier genes are associated with neurodevelopmental syndromes

"The prolonged unfolding of neurogenic potential, along with the highly vascularized nature of the developing SVZ and SGZ, have both been invoked as reasons for the vulnerability of the developing human brain (Baburamani et al., 2012)"

(Adapted from Gabriele et al. 2018 10.1016/j.pnpbp.2017.12.013)

Chromatin and cancer

- Mutations within chromatin remodelling complexes are estimated to affect 10-20% of all cancers, typically leading to more “open” chromatin; in most of other cancers, the machinery is indirectly affected
- “A well-known characteristic of almost all tumours is global hypomethylation and concurrent abnormal hypermethylation at localized sites such as Cpg islands”

(Zhao et al., Nat Rev Cancer 2021)

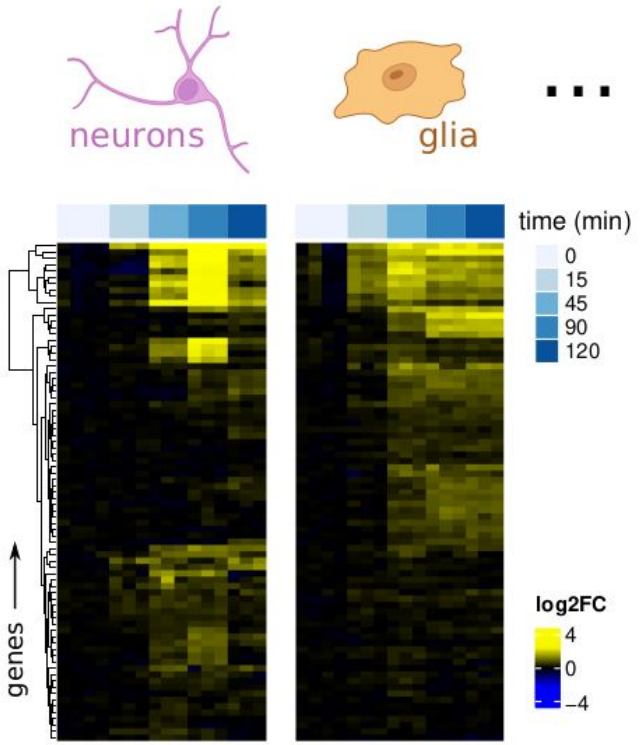
- Some cancers (e.g. infant ependymoma) don’t show relevant DNA changes, but large epigenetic alterations
- Cancerous phenotype can be induced by (mutations in) the surrounding tissue in models, in the absence of mutation of the cells themselves (see Maffini et al, J Cell Sci 2004)
- Histone acetylases (and histone deacetylase inhibitors) are having surprising success as anti-cancer drugs (they however also affect important non-chromatin pathways, such as p53 and Nfkb)

Our lines of research

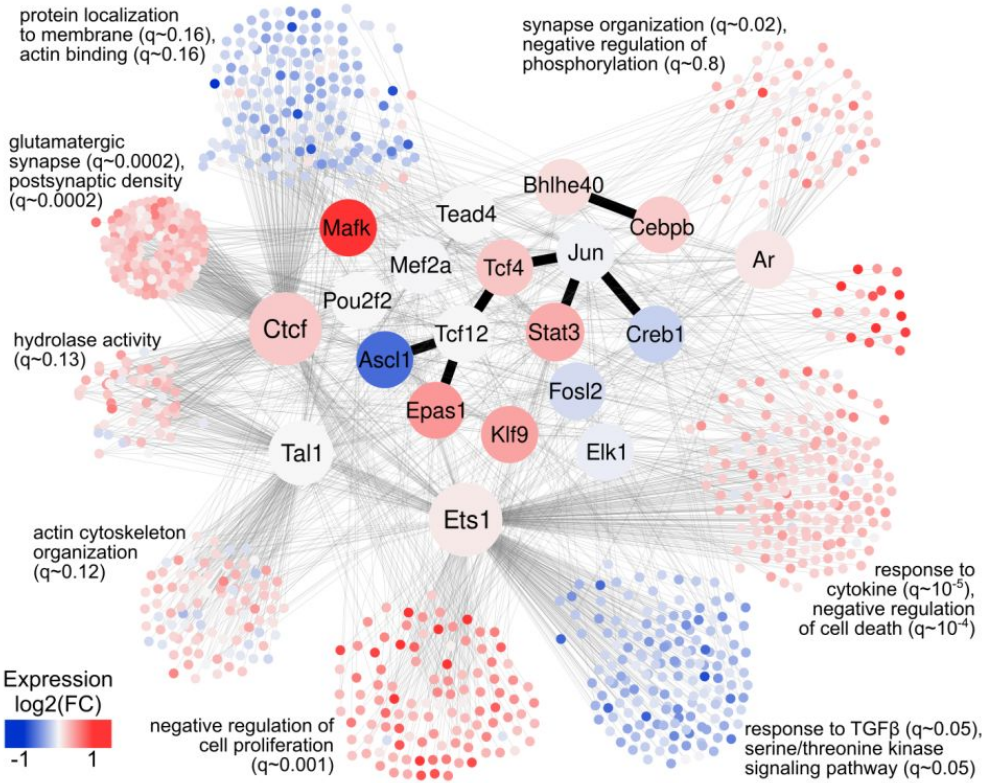
Understanding the brain’s gene expression response to stress

- How is the (gene expression) response to stress in the brain distinguish from that to normal brain activity?
- Can we decompose this response into the contributions of different inter-cellular pathways (e.g. synaptic, hormonal)?
- How much of this response is attributable to cells simply maintaining homeostasis (e.g. metabolism, oxidative stress, etc.) in the face of intense activity?

The response of different cell types to similar stimuli is partially overlapping



Can we explain these similarities and differences in terms of combinations of TF bindings?



(von Ziegler, et al., 2022)

Underlying computational challenges

- How can we best analyze that kind of data?
- How can we get a good idea of where TF bind in different cell types, in the absence of the data for most TF/celltype combinations?
- How can we best make sense of distal regulatory elements and what they regulate?
- Given a gene expression signature (e.g. of a condition/disease) and transcriptional networks, how can we best infer which TFs have a differential activity?