The (Epi)genetics and (epi)genomics of learning
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A(s)&C(s) of the presentation

• Assumptions & contexts (3)
• Accomplishments & challenges (1.1-3.2)
• Applications & consequences (3)
Assumptions & contexts (3)

• Stable (structural) and dynamic (temporal) characteristics of the genome
  – Caveats: the former is not ubiquitous (somatic variation) and the latter is not necessarily transient (can become stable and alter structure/become structural)

• Know more about structural than dynamic characteristics of the genome (2:1 here)
  – Caveats: the rapid development of “new” paradigmatic and measurement approaches/techniques

• Know more about deviations from a normative developmental trajectory than the trajectory itself
  – Caveats: the dominance of A theoretical empirical discoveries
Accomplishment (1.1)

• The contribution of quantitative-genetic (biometric or behavioral-genetic) work by obtaining
  – Heritability estimates for all or near-all processes/functions/indicators related to learning ($h^2$ 50%+)
  – Caveat: most studies used the twin method, which is well known for inflation of $h^2$ (Tenesa & Haley, 2013)

• The contribution of the common (5+%) variant approach by documenting
  – Genes/alleles that seem to contribute to learning (and other “things”?) in its various forms ubiquitously
  – Selective combinations of genes/alleles that substantiated relative specificity of different facets of learning
  – Caveat: the missing heritability problem (Maher, 2008)
An illustration

• $h^2$ for reading (↑) and mathematics (↓)
  – Lingering around 50% (Tenesa & Haley, 2013)
• Translating $h^2$ into molecular mechanisms
  – Candidate genes identified in “disordered” families/behavior of variants in these genes in the general population (e.g., $KIAA0319$ in the Avon study and $ROBO1$ in an Australian sample)
  – Known players and variation in these players in representative samples (e.g., $BDNF$)
Brain-derived neurotrophic factor (BDNF)

• Highly complex (multiple isoforms)
• Highly pleiotropic (cognitive functioning, affective functioning, a variety of disorders, including depression, schizophrenia, obsessive-compulsive disorder, Alzheimer's disease, Huntington's disease, Rett syndrome, and dementia, as well as anorexia nervosa and bulimia nervosa)
• Highly “interactive” (multiple pathways—e.g., neurotrophic tyrosine kinase receptor type 2, reelin)
• When sampled univariately (rs6265)—contradictory findings (Mandelman & Grigorenko, 2011)
• When sampled multivariately (6 polymorphisms, n ~1,115, a representative sample)—$p<10^{-15}$ for reading

Boulle et al., 2012
Challenge (1.1)

- Normative developmental trajectory
  - Assumed contributions of specific genes/alleles are expected to be relatively small
    - Large samples
  - Assumed complexity of the genetic mechanisms (measuring and modeling issues)
    - Multi-trait/multi-measure approaches at both behavioral and genetic levels
- Assumed time-based machinery
  - Longitudinal trajectories of acquisition
Accomplishment (2.1)

Although typical developmental trajectories seem to be, by nature, not highly deterministic, plastic, and “protected” by the contributors’ small individual effects, these trajectories can be broken down in multiple ways, often with a single genetic/genomic structural event (a structural variant is a sequence variant of at least 50 bp in size).

As they are rather deleterious, such events are rare. At this point, many such structural events (Weischenfeldt et al., 2013) have been documented and related to a number of complex phenotypes (referred to as genomic syndromes); virtually in all of these syndromes, learning is jeopardized.
An illustration

- Rare (what is rare? <1%)
- What is large (deterministic in the family, but negligible in the population)?
- Homogeneity across heterogeneity (events at all locations)
- Rare events in *BDNF*
  - BDNF-linked complex polymorphic region, BDNF-LCPR &BD (Okada et al., 2006)

Hoffman & State, 2010
# Genomic syndromes and learning

<table>
<thead>
<tr>
<th>Disease or phenotypic trait</th>
<th>Type of structural variant</th>
<th>Region</th>
<th>Size</th>
<th>Causative genes</th>
<th>Type of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>Aneuploidy (triplication)</td>
<td>Chr21</td>
<td>&gt;10 Mb</td>
<td>Multiple</td>
<td>Increased dosage</td>
</tr>
<tr>
<td>Smith–Magenis syndrome (SMS)</td>
<td>Del</td>
<td>Chr17p11.2</td>
<td>3.7 Mb</td>
<td>Multiple, including RAI1</td>
<td>Haploinsufficiency</td>
</tr>
<tr>
<td>Potocki–Lupski syndrome (PLS)</td>
<td>Dup</td>
<td>Chr7q11.2</td>
<td>3.7 Mb</td>
<td>Multiple</td>
<td>Increased dosage</td>
</tr>
<tr>
<td>Williams–Beuren syndrome (WBS)</td>
<td>Del</td>
<td>Chr7q11.23</td>
<td>1.5–1.8 Mb</td>
<td>Multiple, including ELN and LIMK1</td>
<td>Haploinsufficiency</td>
</tr>
<tr>
<td>22q11 deletion syndrome (which includes velo-cardio-facial (VCF) syndrome and DiGeorge syndrome (DG))</td>
<td>Del</td>
<td>Chr22q11</td>
<td>1.5–3.0 Mb</td>
<td>Predominantly TBX1, but modifying loci include COMT and CRKL</td>
<td>Haploinsufficiency</td>
</tr>
<tr>
<td>Thrombocytopenia-absent radius (TAR) syndrome</td>
<td>CNV</td>
<td>Chr1q21.1</td>
<td>~2 Mb</td>
<td>RBM8A</td>
<td>Mutation or gene dosage</td>
</tr>
<tr>
<td>Distal 1q21.1 deletion/duplication syndromes</td>
<td>Maternal del</td>
<td>Chr15q11–13</td>
<td>Variable, ~3 Mb</td>
<td>UBE3A</td>
<td>Loss of function (imprinted)</td>
</tr>
<tr>
<td>Prader–Willi syndrome (PWS)</td>
<td>Paternal del</td>
<td>Chr15q11–13</td>
<td>~3 Mb</td>
<td>Multiple, including SNRPN and NDN</td>
<td>Loss of function (imprinted)</td>
</tr>
</tbody>
</table>

*A more comprehensive version of Table 1, including references and descriptions of the disease phenotypes, can be found as Supplementary information S1 (Table). APP, amyloid beta (A4) precursor protein; CNV, copy-number variant; COMT, catechol-O-methyltransferase; CRKL, v-crk sarcoma virus CT10 oncogene homologue (avian)-like; Del, deletion; Dup, duplication; ELN, elastin; HYDIN, HYDIN axonemal central pair apparatus protein; LIMK1, LIM-domain-containing protein kinase 1; NDN, nectin; RAI1, retinoic-acid-induced 1; RBM8A, RNA-binding motif protein 8A; SNRPN, small nuclear ribonucleoprotein N; TBX1, T-box 1; UBE3A, ubiquitin protein ligase E3A.*

Weischenfeldt et al., 2013
Potocki–Lupski Syndrome

Case Report

Searching for Potocki–Lupski syndrome phenotype: A patient with language impairment and no autism

A. Gulhan Ercan-Sencicek a,b,c, Nicole R. Davis Wright a,b,c, Stephen J. Frost e, Robert K. Fulbright e,f,g, Susan Felsenfeld e,h, Lesley Hart b, Nicole Landi b,e, W. Eimar Menci e, Stephan J. Sanders a,b,c,d, Kenneth R. Pugh i,j,k,l, Matthew W. State a,b,c,d,r, Elena L. Grigorenko b,d,m,o,p.
Mechanistic heterogeneity
Challenge (2.2)

• Understanding and cataloguing genomic deleterious events is a laborious and complex task. Although detectable in single individuals, they are rare on the population scale. In addition, there appears to be much heterogeneity both at the levels of the genome and phenome.

• Only in a context of a very careful and detailed characterization of both the genomic lesion and its phenotypic manifestations can the impact of such rare events be understood and their generalizability for models of learning appraised.
Accomplishment (3.1)

- Even though present in the literature for over 50 years, epigenetic mechanisms and their role in learning are just becoming evident to the field. These mechanisms appear to be a material foundation of the gene/genome functioning and its dynamic changes in environments (e.g., gene-by-environment phenomena—interaction, correlation, co-action...however named). There is a rapid accumulation of relevant literature (primarily animal model literature) that marks the (epi)genetic/(epi)genomic mechanisms as the key to cellular learning.
An illustration

Molecular Psychiatry

Boulle et al., 2012
Back to *BDNF*

- Pilot data with a small sample (n=18)
- BDNF methylation profile (2 sites only)
- An interesting (and diverse) pattern of correlations
Challenge (3.2)

- As (epi)genetic/genomic markers are tissue-/gene (or gene region)-specific, most studies today either rely on cell types that are commonly available (i.e., saliva or blood), sample postmortem tissue (i.e., are able to reflect only on the past, not ongoing epi-regulation), or are researchable only in animal models. Although exciting, this field of research is saturated with limitations of understanding and generalizability, and has to be navigated with great caution.
Applications & consequences (3)

• Being proactive in talking to the public about epi(genetics) & epi(genomics) & learning
  – Educated public learning right along with the researchers

• “Healthy” competition with commercial services
  – Commercial services are out there (e.g., 23&Me), but what are “we” up to?

• What should educators be ready for (i.e., educating educators & considering impacts for IDEIA in its upcoming editions; Grigorenko, 2010)
  – Supreme Court & DNA
Always with gratitude

- Sam Mandelman
- Johanna Bick, Dan Campbell, Maria Lee, Carolyn Yrigollen, Julia West, Joe Chang
- Gulhan Ercan-Sencicek, Nicole Davis Wright, Stephen Frost, Rob Fulbright, Susan Felsenfeld, Lesley Hart, Nicole Landi, Einar Mencl, Stephan Sanders, Ken Pugh, Matt State
- Oksana Naumova, Johanna Bick, Maria Lee, Baptiste Barbot, Suniya Luthar

- NIH
  - Fogarty
  - NICHD
  - NINDS
  - NIDA