Integration of Evidence for Genetic Risk of Abnormal Neurodevelopment in Preterm Infants

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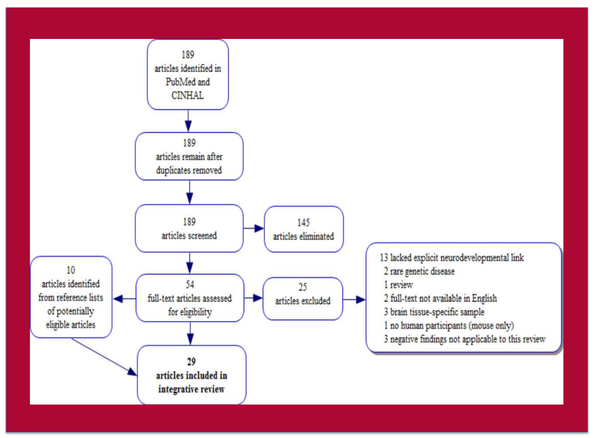
Introduction/Background

- Preterm infants are at increased risk of neurodevelopmental problems throughout the lifespan
- Genetics may play a role in susceptibility to neurodevelopmental harm following preterm birth
- Genetic risk profiles may allow early identification and intervention for those at highest risk

Search Strategy

- Terms "neurodevelopment" and "genetic."
- Search limits were: English-language, human, peer-reviewed primary research or meta-analysis reports (July 2009 to July 2014).
- Exclusions: no explicit genetic link with neurodevelopment



Results of Literature Review

- 29 articles included
- 5 categories of neurodevelopmental outcomes emerged:
  - Infant Behavior & Development
  - Childhood-Onset Disorders
  - Adolescent & Adult-Onset Disorders
  - General Measures of Cognition, Attention, & Perception
  - Brain Structure

Findings Consistently Associated with Neurodevelopmental Outcomes

Genetic Finding	Associated Outcomes	Description of Known Gene Characteristics
MET	Schizophrenia[1]	Proto-oncogene. Previously associated with the development of certain types of cancers which are noted to have lower rates among schizophrenics
	Cognition[1]	
	Facial Recognition[2]	
SLC6A4	Altered Amygdala Brain Volumes	A serotonin-transporter gene previously associated with susceptibility to mood disorders, SIDS, and aggression among Alzheimer's patients
	Delayed Disengagement from Emotional Stimuli[3]	
	Newborn infant irritability, alertness, and vigor[4]	
NRG3	Schizophrenia symptom profiles[5,6]	A neuregulin gene which may be important in brain plasticity. Previously associated with Alzheimer's disease diagnosis and age of onset.
	Low IQ in schizophrenics[7]	
	Cognitive Processing Speed in schizophrenics[8]	
	Activation of Prefrontal Cortex in controls[7]	
Large Deletion Copy Number Variants	Schizophrenia[9]	Deletions can be *de novo* (a new mutation) or inherited from one or both parents. Deletions that effect gene exons or coding regions have a more profound impact on the phenotype.
	Autism Spectrum Disorders[10,11]	
	Low IQ <85[12]	
	School Grade Repetition[12]	

Synthesis of Evidence

- SNP or haplotype variants of 43 genes and multiple copy number variants were associated with neurodevelopmental outcomes in at least one included study
- Only six genes were studied in >1 article. Of these, three were consistently associated with multiple measures of neurodevelopmental outcomes in rigorous studies
- Of these three, only SLC6A4 has been examined in preterm infants, and that only in relation to maternal use of SSRI

MET
ch7q31

SLC6A4
ch17q11.2

NRG3
Ch10q22-23

Discussion

Genetic research into processes of neurodevelopment is a relatively new field and multiple limitations exist in this body of literature.

- While some high-quality studies were available, many lacked scientific rigor.
- Specifically, some studies did not include comparison groups, use statistical controls for multiple tests, or attempt to control for confounders.
- Others failed to report even basic information such as number of participants and demographics.
- Homogenous samples (of predominantly Western-European descent) also limit generalizability.

Future research should attempt to replicate these findings in preterm infants using well-designed, controlled studies in ethnically diverse populations.

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References

1. Burdick KE, DeRosse P, Kane JM, Lencz T, Malhotra AK. Association of genetic variation in the MET proto-oncogene with schizophrenia and general cognitive ability. *Am J Psychiatry*. 2010;167(4):436-443. doi:10.1176/appi.ajp.2009.09050615.
2. Lin M-T, Huang K-H, Huang C-L, Huang Y-J, Tsai GE, Lane H-Y. MET and AKT genetic influence on facial emotion perception. *PloS One*. 2012;7(4):e36143. doi:10.1371/journal.pone.0036143.
3. Beevers CG, Wells TT, Ellis AJ, McGeary JE. Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *J Abnorm Psychol*. 2009;118(3):670-681. doi:10.1037/a0016198.
4. Brummelte S, Teuchert-Noodt G. Postnatal development of dopamine innervation in the amygdala and the entorhinal cortex of the gerbil (Meriones unguiculatus). *Brain Res*. 2006;1125(1):9-16. doi:10.1016/j.brainres.2006.10.006.
5. Kao W-T, Wang Y, Kleinman JE, et al. Common genetic variation in Neuregulin 3 (NRG3) influences risk for schizophrenia and impacts NRG3 expression in human brain. *Proc Natl Acad Sci U S A*. 2010;107(35):15619-15624. doi:10.1073/pnas.1005410107.
6. Meier S, Strohmaier J, Breuer R, et al. Neuregulin 3 is associated with attention deficits in schizophrenia and bipolar disorder. *Int J Neuropsychopharmacol*. 2013;16(03):549-556. doi:10.1017/S1461145712000697.
7. Tost H, Callicott JH, Rasetti R, et al. Effects of neuregulin 3 genotype on human prefrontal cortex physiology. *J Neurosci Off J Soc Neurosci*. 2014;34(3):1051-1056. doi:10.1523/JNEUROSCI.3496-13.2014.
8. Anjos T, Altmäe S, Emmett P, et al. Nutrition and neurodevelopment in children: focus on NUTRIMENTHE project. *Eur J Nutr*. 2013;52(8):1825-1842. doi:10.1007/s00394-013-0560-4.
9. Kirov G, Rujescu D, Collier D, O'Donovan M, Owen M. Neurexin 1 (NRXN1) deletions in schizophrenia. *Schizophr Bull*. 2009;35(5):851-854.
10. Rosenfeld JA, Ballif BC, Torchia BS, et al. Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. *Genet Med*. 2010;12(11):694-702. doi:10.1097/GIM.0b013e3181f0c5f3.
11. Sorte HS, Gjevik E, Sponheim E, Eiklid KL, Rødningen OK. Copy number variation findings among 50 children and adolescents with autism spectrum disorder. *Psychiatr Genet*. 2013;23(2):61-69. doi:10.1097/YPG.0b013e32835d718b.
12. Pietiläinen OPH, Rehnström K, Jakkula E, et al. Phenotype mining in CNV carriers from a population cohort. *Hum Mol Genet*. 2011;20(13):2686-2695. doi:10.1093/hmg/ddr162.

For more information, see: Blair, L. M., Pickler, R. H., & Anderson, C. Integrative review of genetic factors influencing neurodevelopmental outcomes in preterm infants. *Biological Research for Nursing*. [epub ahead of print]