Polygenic Risk Score (PRS) of Hypothalamic-Pituitary-Adrenal (HPA) axis reactivity to stress and neurodevelopmental outcomes of Extremely Low Birth Weight (ELBW, <1000 grams) infants

G Worley, MD1, G Page, PhD2, Y. Nikolova, PhD3, RF Goldstein, MD4, A. Hariri, PhD5, CM Cotten, MD, MHS1.

1Department of Pediatrics, Duke University, Durham, North Carolina 27710; RTI International, Atlanta, GA, 2Department of Psychology, Duke University 27710

In preterm infants, Neonatal Intensive Care Unit (NICU) stress has been associated with abnormalities on neurobehavioral examination and diminished frontal and parietal brain growth (GC Smith et al, Ann Neurol 2011). Polygenic risk scores (PRS) can be used to assess the cumulative influence of alleles of different genes that act in the same direction toward a common phenotype. Five Single Nucleotide Polymorphisms (SNPs) with established effects on HPA axis reactivity to stress and cortisol level were identified:

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs#</th>
<th>Risk allele or genotype</th>
<th>Protective allele/genotype</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>FKBP5</td>
<td>rs1360780</td>
<td>T</td>
<td>C</td>
<td>Appel et al., 2011</td>
</tr>
<tr>
<td>CRHR1</td>
<td>rs110402</td>
<td>G</td>
<td>A</td>
<td>Bradley et al., 2008</td>
</tr>
<tr>
<td>NR3C2</td>
<td>rs4635799</td>
<td>CA</td>
<td>TA</td>
<td>Bogdan et al., 2012</td>
</tr>
<tr>
<td>NR3C2</td>
<td>rs5522</td>
<td>TG</td>
<td>TA</td>
<td>Bogdan et al., 2012</td>
</tr>
<tr>
<td>CRHBP</td>
<td>rs10473984</td>
<td>T</td>
<td>C</td>
<td>Binder et al., 2010</td>
</tr>
</tbody>
</table>

These were summed into a single PRS, with high scores corresponding to greater HPA axis reactivity and cortisol levels in response to stress. One point was assigned for each SNP (maximum=2 per gene) and the individual SNP scores were summed for a PRS (range=0-10 per subject).

The NICHD Neonatal Research Network is a research collaboration of 16 NICUs.

Objectives

We wished to examine if genetic predisposition to greater HPA reactivity as assessed by PRS, is related to smaller head circumference (HC) at 18 and 30 months and worse cognitive and motor development.

Methods

Anonymized blood spots collected from 773 ELBW infants participating in a study as part of the NICHD Neonatal Research Network had a genome-wide scan using the Illumina HumanOmni-Quad 1_a, with 1.2 million SNPS.

Infants were assessed at 18 and 30 months of age corrected for prematurity by the Bayley Scales of Infant Development II, and by a standard neurologic exam to diagnose cerebral palsy, a classification of the severity of cerebral palsy (Gross Motor Function Classification System Level) and an assessment of vision and hearing. HC was also measured.

Results

Linear regression was conducted on the neurodevelopmental outcomes using the PRS and covariates including gestational age and sex. The HPA stress response PRS was related to smaller head circumference at 18 months (p=0.0375). No other association with any of the above neurodevelopmental outcomes was found.

Conclusions

The PRS for HPA reactivity to stress is associated with transient decrease in head circumference growth velocity at 18 months corrected age, but not to other neurodevelopmental outcomes. The adverse events frequent in ELBW infants in the NICU may override in importance in some infants genetic contributions to adverse neurodevelopmental outcomes.

Discussion

Advantages of the PRS approach to testing genetic associations with phenotype are: The PRS aligns genetic analysis with theoretical models of the genetic architecture of complex phenotypes—which are thought to be polygenic, i.e. influenced by many genes.

The PRS combines information from multiple variants each of which may have small effects and skewed distributions. The resulting PRS score measures a larger total effect and is normally distributed, increasing statistical power. As an example, Nikolova et al (2011) were able to demonstrate that a PRS for dopamine signaling predicted reward-related ventral striatum reactivity with a sample of only 69 subjects. The PRS reduces the number of hypothesis tests to one: the relationship of the PRS Score to an outcome or function. So, correction for multiple “looks” at the data need not be made.

Using the PRS method to predict an outcome is hypothesis-based genetic research. As new information about how individual variants in a PRS relate to the trait or phenotype of interest becomes known, this information can be built into a subsequent PRS. For example, although the weight of the individual contributions of alleles toward predicting an outcome need not be known in order to combine them into a PRS, using beta coefficients that quantify relationships between each variant and the phenotype to modify the weight of each allele in the PRS can increase the power of the model to predict an outcome.

The contributions of alleles of different genes together toward predicting one physiological function or outcome can be greater than the summed contributions of the individual gene alleles (Pearson-Fuhrhop et al 2013). Therefore, there can be a gain in power for predicting a function or outcome by combining alleles together in a PRS, not present by analyzing their contributions toward the prediction individually and summing them.

Using a PRS to predict an outcome is a relatively new idea. Recent examples of the use of this method include prediction of developmental progression to heavy, persistent smoking and nicotine dependence (Belsky et al., 2013), prediction of the development of obesity (Belsky et al. 2012) and prediction of “food addiction” (Davis et al., 2013). Therefore, there can be a gain in power for predicting a function or outcome by combining alleles together in a PRS, not present by analyzing their contributions toward the prediction individually and summing them.

Using a PRS to predict an outcome is a relatively new idea. Recent examples of the use of this method include prediction of developmental progression to heavy, persistent smoking and nicotine dependence (Belsky et al., 2013), prediction of the development of obesity (Belsky et al. 2012) and prediction of “food addiction” (Davis et al., 2013). Therefore, there can be a gain in power for predicting a function or outcome by combining alleles together in a PRS, not present by analyzing their contributions toward the prediction individually and summing them.

Next steps include:

1. Adding 9 additional SNPs to the PRS for HPA axis reactivity and cortisol level in response to stress that have been identified since our PRS was created in 2013
2. Testing associations with neurodevelopmental outcomes of the new PRS in a population subset with better neurodevelopmental outcomes, hypothesizing that in these patients, genetic effects on outcomes may be more important.

References

Appel K. et al. Neuropsychopharmacology, 36, 1882-91
Belsky, D.W. et al. (2013) JAMA psychiatry, 70, 369-377