Impact of rs2268490 polymorphism on Brain Development in Preterm Infants

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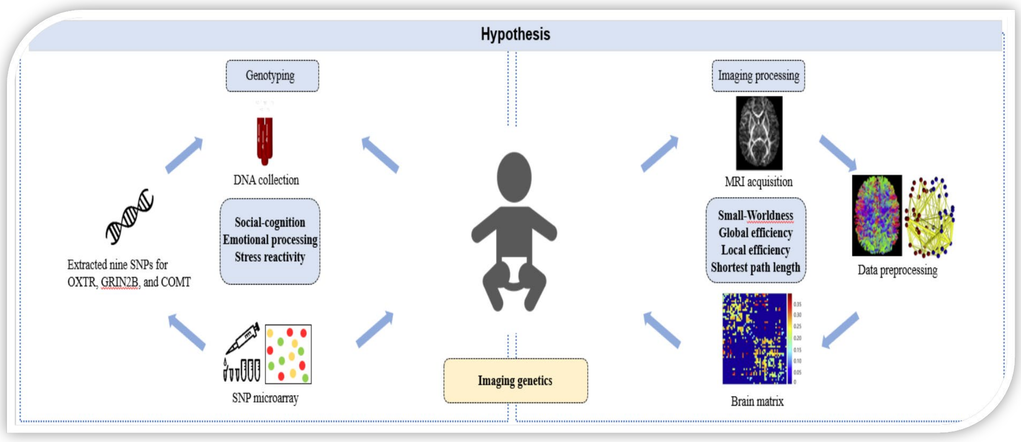
Abstracts

Back Ground: Preterm infants are at risk for developmental delays, including cognitive function, due to incomplete brain development and heightened sensitivity to stress and environmental stimuli. The OXTR rs2268490, GRIN2B, and COMT rs4818 polymorphisms could influence this sensitivity, indirectly impacting brain and social-emotional development. Our previous study reported that single-nucleotide polymorphisms in OXTR and COMT genes are associated with altered cortical development at term-equivalent age. We investigated whether OXTR, GRIN2B, and COMT polymorphisms are associated with brain development and neurodevelopmental outcomes at 18 months of corrected age.
Methods: Ninety-one preterm newborns born before 35 weeks of gestational age admitted to the NICU at Hanyang University Seoul Hospital and 28 full-term infants at outpatient clinics from Jan 2020 to Dec 2022 were recruited. Brain MRI scans at term-equivalent age and DNA samples were collected and analyzed for SNPs associated with brain volume and network. Neurodevelopmental assessments using the Korean Developmental Screening Test and Bayley Scales were conducted at 18 months of corrected age, and statistical analyses explored SNP associations with outcomes.
Results: Carrying the minor alleles for the rs2268490 variant of OXTR (p=0.027) and rs4818 variants of COMT (p=0.017) was associated with significant decreases in neurodevelopmental outcomes, including lower language and social-emotional scores, adjusting for gestational age and sex. The OXTR rs2268490 polymorphism was significantly associated with brain network metrics, including global (p=0.038) and local efficiency (p=0.042) and small-worldness (p=0.012).
Conclusion: OXTR and COMT polymorphisms may interact with environmental factors, influencing neurodevelopmental outcomes in preterm infants.

Introduction

OXTR polymorphism could influence preterm infants' sensitivity, indirectly impacting brain development and subsequent social and emotional development.
COMT polymorphism could potentially influence brain development in preterm infants by affecting dopamine regulation, cognitive development, and stress responses.
GRIN2B polymorphism could affect NMDA receptor functioning, a critical component for synaptic plasticity during early brain development.



Materials and Methods

- **DNA sample collection and extraction / SNP microarray and imaging**

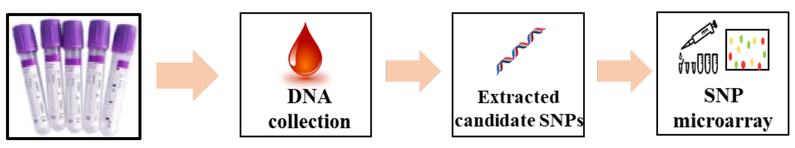
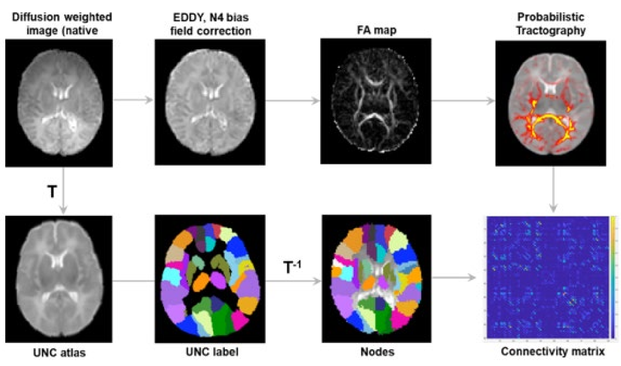


Table 1. Allele frequencies, coding information, linkage disequilibrium details, and location of SNP

Gene	SNP Name	Chromosome	Coordinate (Position)	Source	Variant (major/minor)	Korean MAF	Population MAF	HWE Unaffected, *p*
OXTR	rs1042778	3	8794545	dbSNP	G/T	0.087	0.076	0.504
OXTR	rs2268490	3	8797085	dbSNP	C/T	0.494	0.492	0.856
OXTR	rs2268493	3	8800840	1000_genomes	T/C	0.161	0.139	0.465
GRIN2B	rs2268116	12	13870080	1000_genomes	A/G	0.368	0.349	0.687
GRIN2B	rs2284411	12	13866172	dbSNP	C/T	0.186	0.164	0.736
COMT	rs174690	22	19939432	1000_genomes	G/A	0.283	0.290	0.824
COMT	rs4818	22	19951207	dbSNP	C/G	0.334	0.277	0.106
COMT	rs740603	22	19945177	dbSNP	A/G	0.423	0.357	0.548

- **Brain MRI scan image processing**



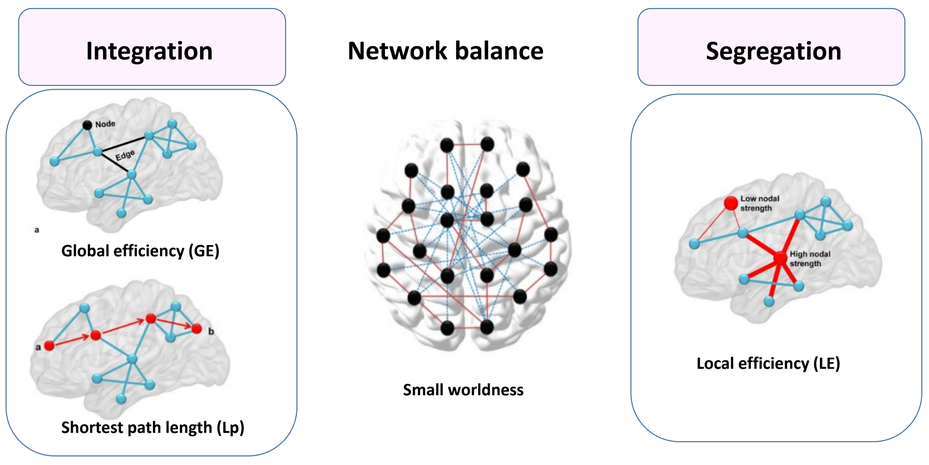
MRI and DTI image processing

- FMRIB Software Library (FSL) – Jenkinson 2012.
- Eddy correction tool – Andersson 2016.
- Advanced Normalization Tools (ANTs) – Avants 2010

Network Construction and Global network analysis

- University of North Carolina (UNC) neonate atlas – Shi 2011

- **Brain Network analysis**



- **Brain volume analysis**
  - **MANTis toolbox (Beare 2016)**

- **Neurodevelopmental assessment**
  - **The Korean developmental screening test for Newborns and Children (K-DST)**
  - **The Bayley Scales of Infant and Toddler Development (BSID-III)**

- **Statistical analysis**
  - To investigate the association between SNP and brain network, multiple regression models were performed, categorizing groups based on the presence or absence of the minor allele.
  - Adjusted by gestational age, sex, or PMA .
  - For multiple correction, the Benjamini and Hochberg method to control FDR using R.

Results

- **Association of allele frequency with Brain Network in preterm infants**

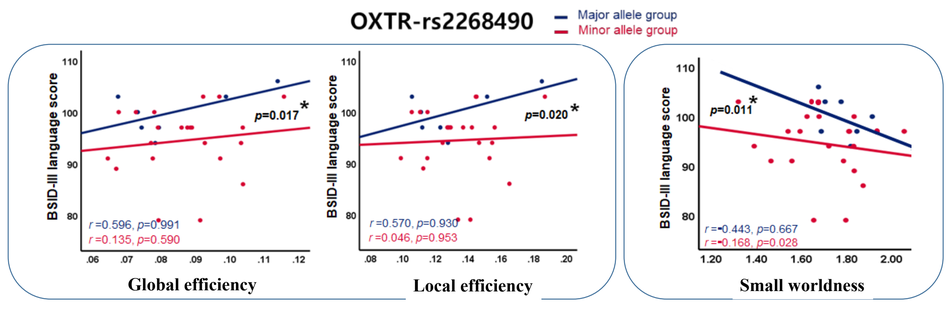
Gene	SNP Name	GE B (95% CI)	GE *p*	LE B (95% CI)	LE *p*	SW B (95% CI)	SW *p*	L_p B (95% CI)	L_p *p*
OXTR	rs1042778	-0.014 (-0.027 to -0.002)	**0.030**	-0.020 (-0.041 to 0.000)	0.058	0.183 (0.050 to 0.316)	**0.009**	2.101 (0.360 to 3.842)	**0.022**
OXTR	rs2268490	-0.006 (0.001 to 0.022)	0.241	0.018 (0.001 to 0.034)	**0.042**	-0.145 (-0.254 to -0.035)	**0.012**	-1.912 (-3.331 to -0.512)	**0.010**
OXTR	rs2268493	0.011 (-0.016 to 0.004)	0.038	-0.010 (-0.026 to 0.006)	0.226	-0.061 (-0.167 to 0.0451)	0.264	0.747 (-0.622 to 2.116)	0.290
GRIN2B	rs2268116	-0.000 (-0.010 to 0.009)	0.942	-0.008 (-0.019 to 0.012)	0.664	0.010 (-0.093 to 0.112)	0.854	0.187 (-1.129 to 1.502)	0.782
GRIN2B	rs2284411	-0.005 (-0.015 to 0.005)	0.369	-0.003 (-0.024 to 0.008)	0.308	0.052 (-0.055 to 0.160)	0.342	0.557 (-0.827 to 1.941)	0.434
COMT	rs174690	0.004 (-0.005 to 0.014)	0.386	0.008 (-0.008 to 0.023)	0.334	-0.046 (-0.148 to 0.056)	0.380	-0.824 (-2.128 to 0.481)	0.221
COMT	rs4818	-0.002 (-0.011 to 0.008)	0.699	-0.002 (-0.017 to 0.013)	0.785	-0.005 (-0.107 to 0.097)	0.923	0.495 (-0.815 to 1.806)	0.462
COMT	rs740603	-0.004 (-0.006 to 0.013)	0.426	0.006 (-0.009 to 0.021)	0.459	-0.084 (-0.183 to 0.016)	0.105	-0.226 (-1.536 to 1.084)	0.737

- **Association of allele frequency with Brain Volume in preterm infants**
  - **No significant association was observed between minor allele frequency and brain volume in premature infants.**

- **Association of allele frequency with Neurodevelopment in preterm infants**

Gene	SNP Name	Cognition B (95% CI)	Cognition *p*	Language B (95% CI)	Language *p*	Motor B (95% CI)	Motor *p*	Socio-Emotional B (95% CI)	Socio-Emotional *p*	Adaptive behavior B (95% CI)	Adaptive behavior *p*
OXTR	rs1042778	-5.881 (-13.25 to 1.488)	0.125	-2.05 (-8.939 to 4.839)	0.563	-2.643 (-12.17 to 6.883)	0.589	-0.842 (-13.97 to 12.28)	0.900	7.171 (-3.501 to 17.84)	0.194
OXTR	rs2268490	-2.605 (-9.212 to 4.002)	0.444	-6.51 (-12.1 to -0.924)	0.027	-4.03 (-12.2 to 4.139)	0.339	-1.446 (-12.87 to 9.982)	0.805	-10.23 (-18.95 to -1.515)	0.026
OXTR	rs2268493	-2.073 (-8.215 to 4.069)	0.512	-2.455 (-7.874 to 2.964)	0.379	-0.197 (-7.852 to 7.459)	0.960	-2.566 (-13.15 to 8.021)	0.637	-1.675 (-10.2 to 6.846)	0.702
GRIN2B	rs2268116	0.121 (-6.017 to 6.258)	0.970	1.205 (-4.219 to 6.63)	0.665	-3.544 (-11.09 to 4.004)	0.362	-0.083 (-10.64 to 10.47)	0.988	-1.371 (-9.853 to 7.11)	0.753
GRIN2B	rs2284411	-0.862 (-7.34 to 5.616)	0.795	2.396 (-3.303 to 8.095)	0.414	-2.652 (-10.66 to 5.355)	0.519	2.338 (-8.791 to 13.47)	0.682	4.966 (-3.888to 13.82)	0.277
COMT	rs174690	2.583 (-3.372 to 8.539)	0.400	0.043 (-5.272 to 5.357)	0.988	5.654 (-1.615 to 12.92)	0.134	6.722 (-3.419 to 16.86)	0.200	0.232 (-8.069 to 8.534)	0.957
COMT	rs4818	4.516 (-1.333 to 10.36)	0.137	4.032 (-1.145 to 9.209)	0.134	3.679 (-3.677 to 11.04)	0.332	-12.25 (-21.94 to -2.568)	0.017	-3.309 (-11.54 to 4.922)	0.435
COMT	rs740603	3.836 (-2.084 to 9.756)	0.210	-0.086 (-5.418 to 5.246)	0.975	-4.197 (-11.57 to 3.177)	0.270	-11.55 (-21.36 to -1.734)	0.026	-7.07 (-15.15 to 1.009)	0.093

- **Interaction effect between language development and brain network of OXTR-rs2268490 variant**



Conclusion

- OXTR gene variants showed a negative correlation in the domain of language and adaptive behavior development.
- COMT gene variants showed a negative correlation in the domain of social-emotional development .
- The OXTR-rs2268490 minor allele group showed increased local efficiency and decreased small worldness.
- In the OXTR-rs2268490 major group, later language development increased as local efficiency or global efficiency increased, that is, as the efficiency of brain connectivity increased, but the minor group did not show a significant increase.
- Single nucleotide polymorphisms in OXTR and COMT genes may affect neurodevelopmental scores or brain connectivity in premature infants affected by prematurity.
- In particular, OXTR-rs2268490 variation showed an association with both, suggesting that further studies are needed to determine whether it can be used as an early candidate biomarker for late developmental disorders in premature infants.

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