An interaction between NDE1 and high birth weight increases schizophrenia susceptibility

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ABSTRACT

Pre- and perinatal environmental factors have been shown to increase schizophrenia risk particularly when combined with genetic liability. The investigation of specific gene environment interactions in the etiology of psychiatric disorders has gained momentum. We used multivariate GEE regression modeling to investigate the interaction between genes of the DISC1 pathway and birth weight, in relation to schizophrenia susceptibility in a Finnish schizophrenia family cohort. The study sample consisted of 457 subjects with both genotype and birth weight information. Gender and place of birth were adjusted for in the models. We found a significant interaction between birth weight and two NDE1 markers in relation to increased schizophrenia risk: a four SNP haplotype spanning NDE1 ($b=1.26$, $SE=0.5$, $p=0.012$) and one of its constituent SNPs rs4781678 ($b=1.33$, $SE=0.51$, $p=0.010$). Specifically, high birth weight (>4000 g) was associated with increased schizophrenia risk among subjects homozygous for the previously identified risk alleles. The study was based on a family study sample with high genetic loading for schizophrenia and thus our findings cannot directly be generalized as representing the general population. Our results suggest that the functions mediated by NDE1 during the early stages of neurodevelopment are susceptible to the additional disruptive effects of pre- and perinatal environmental factors associated with high birth weight, augmenting schizophrenia susceptibility.

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1. Introduction

The heritability of schizophrenia is high, with estimates from family and twin studies ranging from 64% to 81%, emphasizing the role of both genetic and environmental factors in the etiology of the disorder (Sullivan et al., 2003; Lichtenstein et al., 2009). Pre- and perinatal environmental adversities represent a widely replicated group of environmental risk factors associated with the neurodevelopmental trajectory of schizophrenia (Cannon et al., 2002).

Recently it has become possible to investigate the interaction between specific biologically relevant gene variants and defined environmental exposures in relation to future psychiatric morbidity (Caspi et al., 2002; Caspi et al., 2003; Caspi et al., 2005; Dick,

2011). Some studies have set out to investigate the interaction between specific schizophrenia susceptibility conferring genes and defined pre- and perinatal environmental factors in relation to subsequent schizophrenia risk (Modinos et al., 2013). Polymorphisms of proposed schizophrenia susceptibility genes AKT1, BDNF, DTNBP1 and GRM3 (G protein-coupled metabotropic glutamate receptor) have been found to interact with severe obstetric complications, augmenting schizophrenia susceptibility (Nicodemus et al., 2008). Of these genes, GRM3 has been suggested to interact with hypoxia, in association with changes in hippocampal volume (Haukvik et al., 2010).

It has been suggested that any adverse environmental factor acting on the developing fetus will affect its growth (Rapoport et al., 2005; Galjaard et al., 2013; O'Connor et al., 2013). Population based studies have shown a robust association between low birth weight (LBW) (<2500 g) and psychotic disorders including schizophrenia (Cannon et al., 2002; Abel et al., 2010; Byars et al., 2014). Increasing birth weight has been associated with neurodevelopmental disorders (Byars et al., 2014). Accumulating evidence also

points to an association between high birth weight (HBW) (4000–4500 g) and increased schizophrenia risk (Hultman et al., 1997; Gunnell et al., 2003; Bersani et al., 2007; Moilanen et al., 2010; Wegelius et al., 2011; Keskinen et al., 2013).

In the Finnish population consistent evidence has emerged for the independent roles of both birth weight and a network of neurodevelopmental genes in relation to schizophrenia susceptibility. In a study on the Northern Finland 1966 Birth Cohort, both LBW (<2500 g) and HBW (>4500 g) were found to increase schizophrenia risk (Moilanen et al., 2010). Further investigation of the same cohort found that HBW (>4500 g), in contrast to LBW (<2500 g), was associated with augmented schizophrenia risk specifically among offspring presenting with a history of parental psychosis, suggestive of a gene-environment interaction mediated by HBW (Keskinen et al., 2013). Recently, both low and high birth weight have been found to associate with increased cognitive impairment among subjects with schizophrenia and their non-affected first-degree relatives, suggesting that the interaction between genetic liability and birth weight could have the propensity to influence the neurodevelopmental process (Torniainen et al., 2013). One of the most consistent genetic observations on the Finnish population with respect to schizophrenia is linkage and association at the 1q42/DISC1 locus (Ekelund et al., 2001; Hennah et al., 2003; Ekelund et al., 2004; Hennah et al., 2009). DISC1 has been found to have various functional roles in relation to the neurodevelopmental process, including mediating cell proliferation, cell migration and synaptic transmission (Soda et al., 2013). DISC1 has been found to play a role in the integration of cortical and hippocampal neuronal networks during the maturation of the prefrontal cortex (El-Hassar et al., 2014). Suppression of the expression of DISC1 during the neurodevelopmental process has been found alter dopamine transmission, with subsequent behavioral abnormalities (Niwa et al., 2013). Obstetric complications such as hypoxia have been found to increase the degradation of DISC1 (Barodia et al., 2015). Furthermore, DISC1 has been associated with visual memory in the Finnish schizophrenia family cohort (Hennah et al., 2005).

Since the identification of an association between DISC1 and schizophrenia in the Finnish schizophrenia family cohort (Hennah et al., 2003; Ekelund et al., 2004), additional genes interacting with DISC1 have also being noted to associate with increased schizophrenia susceptibility in the same study sample (Hennah et al., 2007, Tomppo et al., 2009). NDE1, a DISC1 interacting partner, was identified to associate with schizophrenia when its chromosomal locus was highlighted through genome-wide linkage analysis conditioned on DISC1 (Hennah et al., 2007). This observation of two genes from the same network associating with schizophrenia in our cohort has led to the identification of 11 additional DISC1 network genes associating with schizophrenia in the cohort (Tomppo et al., 2009).

Based upon these previous independent observations from the Finnish schizophrenia family cohort implicating a role for both (1) genes of the DISC1 network and (2) HBW in the early stages of the neurodevelopmental process we set out to investigate the potential interaction between HBW and specific DISC1 pathway genes in relation to schizophrenia risk.

2. Methods

2.1. Study sample

The characteristics of the Finnish schizophrenia family cohort have been described in detail previously (Wegelius et al., 2011; Ekelund et al., 2001; Paunio et al., 2004). The register-based sample consisted of 33 371 subjects, born between 1940 and 1976, who had been hospitalized, had received disability pension or had been granted entitlement to free outpatient antipsychotic medication for the treatment of schizophrenia between 1969 and 1998. First-degree relatives of probands were identified from the Population Register Centre. Information concerning the psychiatric diagnoses of relatives was obtained from the health care register. Two subsamples with a high genetic risk of schizophrenia were drawn from the identified families: (1) families originating from an internal isolate region (IS) with at least one sibling with schizophrenia and with at least one parent having been born in the isolate region and (2) families from the rest of Finland (AF) with at least two siblings with a schizophrenia spectrum diagnosis (Wegelius et al., 2011). Obstetric practice in Finland evolved dramatically after the 1940 s and the number of deliveries, which took place in maternity hospitals increased from 31.0% to 92.5% during the years 1940–1960 (Hemminki, 1983). The isolate region represented a socio-economically disadvantaged area, in which the availability of obstetric care was limited and infant mortality higher in comparison to other regions (Palmgren, 1964). Place of birth with respect to the IS-region vs. the AF- region was adjusted for in our model.

The study was approved by the Ministry of Social Affairs and Health of Finland, the Ethics Committee of the National Public Health Institute of Finland (since January 1st 2009 National Institute for Health and Welfare) and the Ethics Committee of the Hospital District of Helsinki and Uusimaa. Probands were contacted by their treating physicians. Family members were contacted only if the respective proband gave permission. Written informed consent was obtained from each participant.

2.2. Birth records

The birth weight data from a total of 1051 subjects, was obtained from obstetric records, of which 589 subjects were interviewed using the Structured Clinical Interview for DSM-IV Axis I Diagnosis (First et al., 1996), while the rest were diagnosed on the basis of information obtained from medical records (Wegelius et al., 2011). HBW, or macrosomia, is commonly defined as a birth weight >4000 g, after which increasing birth weight is associated with increasing neonatal morbidity (Boulet et al., 2003; Henriksen, 2008; Koyanagi et al., 2013). The present study consisted of a total of 457 subjects with both genetic and birth weight data: 204 females (44.6%) and 253 males (55.4%). 142 subjects had a diagnosis of schizophrenia. For information concerning the general characteristics of the study sample see Table 1.

2.3. Genetic data

Five DISC1 pathway genes (DISC1, NDE1, NDEL1, PDE4B, PDE4D), which had previously demonstrated association with schizophrenia risk in the cohort were examined (Hennah et al., 2003; Ekelund et al., 2004; Hennah et al., 2007; Tomppo et al., 2009). The markers used were significant SNPs or haplotypes, which had previously been genotyped and analyzed by this research group in the prior studies mentioned above. A total of 20 significant markers from the five genes were available for analysis. Due to the fact that in our cohort only 457 subjects had both genetic and birth weight data available we imposed an allele frequency threshold to ensure that analysis of the interaction model would be statistically feasible, by defining that minor allele homozygotes should occur at a frequency $\geq 10\%$. After application of this cut-off criterion, 7 of the original 20 variants, from NDE1 (NDE1 haplotype, rs4781678, rs2242549, rs881803, rs2075512), PDE4B (rs7412571) and PDE4D (PDE4D haplotype), were taken forward for analysis. The NDE1 haplotype, corresponding to a specific CGCC allele was composed of the combination of

Table 1
Characteristics of the study sample (N=457).

	Whole sample	Schizophrenia (31.1%)	Others (68.9%)
Gender: N (%)			
Female	204 (44.6)	45 (31.7)	159 (50.5)
Male	253 (55.4)	97 (68.3)	156 (49.5)
Birthweight: N (%)			
< 2500 g	22 (4.8)	7 (4.9)	15 (4.8)
2500–3000 g	71 (15.5)	25 (17.6)	46 (14.6)
3000–4000 g	307 (67.2)	87 (61.3)	220 (69.8)
> 4000 g	57 (12.5)	23 (16.2)	34 (10.8)
Birthweight: mean (SD)	3440 g (570 g)	3460 g (620 g)	3430 g (550 g)
Geographical distribution: N (%)			
Rest of Finland	238 (52.1)	90 (63.4)	148 (47)
Internal isolate	219 (47.9)	52 (36.6)	167 (53)

individual SNPs: rs4781678, rs2242549, rs881803 and rs2075512. For a depiction of the allele frequencies of the gene variants investigated see Table 2.

2.4. Statistical analysis

We used logistic regression modeling to test for gene environment interactions between birth weight and the specific genotypes in relation to schizophrenia risk. Since our study sample comprised of individuals drawn from families, we used a generalized estimating equation (GEE) framework to account for any intra-family correlation (Liang and Zeger., 1986). The model included birth weight (≤ 4000 g vs. > 4000 g), genotype and their interaction (birth weight x genotype) as explanatory variables. An additive genetic mechanism was presumed in the model. Place of birth (isolate vs. rest of Finland) and gender were adjusted for in the model.

Correction for multiple testing was performed and the level of statistical significance was set at p=0.017 (0.05/3), in regard to the fact that three hypothesized genes were taken forward for analysis with variants within each gene locus that are to some extent non-independent. In order to further characterize which genotype-phenotype pairings were driving any of the observed interactions, the association between birth weight and schizophrenia risk was investigated individually with respect to each genotype using Fischer's exact test. All analyses were performed using the R-program version 3.0.2 (R Development Core Team., 2013).

3. Results

A statistically significant interaction was observed between birth weight and NDE1 SNPs in relation to increased schizophrenia

risk among subjects with the NDE1 haplotype ($b=1.26$, SE=0.5, $p=0.012$) and one of its constituent SNPs rs4781678 ($b=1.33$, SE=0.51, $p=0.010$) (Table 3) (Fig. 1). The interaction between birth weight and the other investigated NDE1 SNPs rs2242549, rs881803, rs2075512 in relation to schizophrenia risk demonstrated borderline statistical significance. An interaction between birth weight and the other investigated DISC1 pathway variants in relation to schizophrenia risk was not observed: PDE4B [rs7412571 ($b=-0.21$, SE=0.46, $p=0.648$)] and PDE4D [PDE4D Haplotype ($b=-0.33$, SE=0.46, $p=0.481$)] (Table 3).

In order to further understand this interaction model, the association between HBW and schizophrenia was analyzed with respect to each separate NDE1 genotype. A statistically significant association between HBW and schizophrenia was observed specifically among minor allele homozygotes of the NDE1 haplotype, and its constituent SNPs: rs4781678 and rs2075512 ($p < 0.017$, Fisher's exact test). Schizophrenia susceptibility being increased among HBW subjects homozygous for NDE1 indicates that a recessive genetic model was driving the significance within our interaction model.

4. Discussion

We set out to characterize a potential gene environment interaction between birth weight and genes of the DISC1 pathway in relation to schizophrenia susceptibility in a Finnish schizophrenia family cohort. We found an interaction between variants in the NDE1 gene and HBW associating with increased schizophrenia risk. Further identifying a potential recessive genetic effect in HBW (> 4000 g) subjects, but not in subjects with a birth weight ≤ 4000 g.

Two previously conducted separate studies on the same Finnish schizophrenia family cohort have identified independent associations between increased schizophrenia risk and both HBW and NDE1 emphasizing the hypothesis driven rationale behind examining the potential interaction between these two variables (Wegelius et al., 2011; Hennah et al., 2007). In the present study sample a marked statistically significant association between the NDE1 haplotype and schizophrenia was not detected, which was attributed to the reduced size of the present sample in relation to the original study, due to the exclusion of subjects without both genotype and birth weight data. A statistically significant association between HBW and schizophrenia was detected in the present study sample despite the reduced size of the study sample (OR 1.71 95% CI 1.04–2.82, $p < 0.05$).

Our study focused on the DISC1 network of genes, not just due to their prior evidence of association with schizophrenia in the Finnish population, but also because DISC1 network of genes have been known to mediate prenatal neurodevelopment, which has also been hypothesized to represent a period of elevated

Table 2
The allele frequencies of gene variants.

Gene	Variant	Genotype					
		Genotype	N (%)	Genotype	N (%)	Genotype	N (%)
NDE1	rs4781678	A/A	155 (37)	A/C	207 (49)	C/C	60 (14)
	rs2242549	G/G	141 (34)	G/T	202 (49)	T/T	72 (17)
	rs881803	C/C	147 (38)	C/T	186 (48)	T/T	51 (13)
	rs2075512	C/C	132 (33)	C/T	193 (49)	T/T	73 (18)
	NDE1 haplotype	other[1]/other[1]	195 (50)	CGCC/other[1]	157 (40)	CGCC/CGCC	38 (10)
PDE4B	rs7412571	C/C	113 (29)	C/T	205 (53)	T/T	70 (18)
PDE4D	PDE4D haplotype	other[1]/other[1]	141 (36)	GGACA/other[1]	183 (47)	GGACA/GGACA	67 (17)

[1] The term "other" refers to all other haplotype alleles combined i.e. those not the hypothesized allele.

Table 3
The interaction between birth weight (≤ 4000 g vs. > 4000 g) and DISC1 network gene variants (MAF $\geq 10\%$) in relation to schizophrenia risk. Gender and place of birth were adjusted for in the models. The threshold of statistical significance was set at $p = 0.017$. Statistically significant interactions were observed between birth weight and the NDE1 haplotype and its constituent SNP rs4781678. The interaction between birth weight and the other NDE1 markers rs2242549, rs881803, rs2075512 was of borderline statistical significance.

Gene	Variant used in the model	Predictor variables									
			HBW			Variant[1]			HBW $\times$ Variant[1]		
		Intercept	b	SE	p	b	SE	p	b	SE	p
NDE1	NDE1 haplotype	−0.45	−1.66	0.98	0.092	−0.18	0.18	0.335	1.26	0.5	0.012**
	rs4781678	−0.64	−1.72	1.02	0.09	−0.18	0.18	0.323	1.33	0.51	0.010**
	rs2242549	−0.89	−1.19	1.07	0.266	0.00	0.17	0.981	0.96	0.51	0.061
	rs881803	−0.84	−1.47	1.08	0.172	0.00	0.17	0.988	1.07	0.53	0.043*
	rs2075512	−0.82	−1.92	1.28	0.131	−0.04	0.16	0.813	1.29	0.61	0.035*
PDE4B	rs7412571	−0.72	0.94	0.82	0.251	−0.09	0.17	0.589	−0.21	0.46	0.648
PDE4D	PDE4D haplotype	−1.05	1.23	0.96	0.201	0.09	0.17	0.569	−0.33	0.46	0.481

[1] Shown in the corresponding row.
** $p < 0.017$.
* $p < 0.050$.

susceptibility with respect to the effects of various environmental factors acting on the developing fetus. Functional alterations in the NDE1 gene have been associated with clinically significant neurodevelopmental morbidity, associated with both a failure of neurogenesis and a deficiency in cortical lamination, implicating a central role for NDE1 in the early stages of brain development (Bakircioglu et al., 2011; Paciorkowski et al., 2013).

Both low and high birth weight, have been associated with increased susceptibility to disorders of neurodevelopmental origin, including autism spectrum disorders and schizophrenia (Hultman et al., 1997; Cannon et al., 2002; Gunnell et al., 2003; Bersani et al., 2007; Abel et al., 2010; Moilanen et al., 2010; Wegelius et al., 2011; Abel et al., 2013; Keskinen et al., 2013; Byars et al., 2014). The causal mechanisms mediating the observed association between birth weight and neurodevelopment remain hypothetical. Schizophrenia is highly heterogenous with respect to clinical presentation, suggestive of a multifactorial etiology (Insel, 2010). Our results corroborate findings implicating a role for NDE1 in the neurodevelopmental process in relation to schizophrenia risk and suggest that NDE1 conferred genetic susceptibility is further augmented by factors associating with HBW. For example gestational diabetes, one of the strongest triggers of HBW, is associated with maternal obesity, fetal hypoxia, all of which have been suggested to associate with cognitive impairment and increased schizophrenia risk among offspring (Henriksen, 2008; Van Lieshout and Voruganti., 2008; Nielsen et al., 2010; Ornoy., 2011; Vambergue & Fajardy, 2011; Anastario et al., 2012; Koyanagi et al., 2013).

Our study sample is not a conventional case-control study due to the fact that the control group, which consisted of the unaffected siblings of the schizophrenia probands, was also understood to have an elevated genetic risk of developing schizophrenia. Due to the high genetic loading for schizophrenia our study sample is not considered as being representative of the general population and thus the generalizability of our findings with respect to the general population is not self-evident. From a methodological perspective, it is also possible that the risk factors associated with pre- and perinatal complications are different in older, in comparison to younger birth cohorts. For example, it has been noted that the effect of rural birth as a risk factor for schizophrenia in Finland decreases in younger cohorts (Haukka et al., 2001). In Finland the number of births that took place in hospitals increased from 31.0% to 92.5% between years 1940 to 1960 respectively (Hemminki, 1983). It is probable that the risk of complications associated with the delivery of a large fetus is greater among subjects born at home in comparison to subjects born in a

hospital. The increased capacity to perform cesarean sections can be postulated to have reduced the frequency and severity of potential HBW associated obstetric complications in younger cohorts (Henriksen, 2008; Koyanagi et al., 2013). Of note, there were also only 22 people with a birth weight below 2500 g, reflecting the high mortality of LBW infants in Finland before the 1960s (Rantakallio., 1968). A limitation regarding the genetic analysis is attributed to fact that the number of individuals in the genotype specific subsamples is small. Some preliminary gene environment interaction findings have been difficult to replicate due to methodological considerations, which has led to caution regarding the interpretation and generalizability of findings (Risch et al., 2009; Duncan and Keller, 2011). Proponents have emphasized the need to accurately define the quality and duration of the environmental exposure under consideration (Caspi et al., 2010). The use of birth weight as a proxy measure reflective of the pre- and/or perinatal environment is proposed to represent a clearly defined and retrospectively unbiased variable.

Our results suggest a putative gene environment interaction between the DISC1 network gene NDE1 and HBW in relation to augmented schizophrenia risk. Our observation corroborates recent findings implicating an interaction between genetic susceptibility and HBW in relation to increased schizophrenia risk (Keskinen et al., 2013). We suggest that the role of NDE1 during the pre- and perinatal stages of the neurodevelopmental process is susceptible to the influence of environmental factors associated with HBW. Our results implicate the necessity to further our understanding of the interaction between genes and the prenatal environment in relation to psychiatric morbidity.

Competing interests

The authors report no competing interests.

Contributors

J. Suvisaari, U. Lehto, T. Paunio, J. Lönnqvist, L. Tomppo, and W. Hennah collected the data. A.Wegelius, M. Pankakoski, J. Suvisaari, T. Paunio and W. Hennah designed the study. A. Wegelius, M. Pankakoski and W. Hennah performed the analyses. A. Wegelius, M. Pankakoski and W. Hennah wrote the paper, which all authors reviewed and approved for publication.
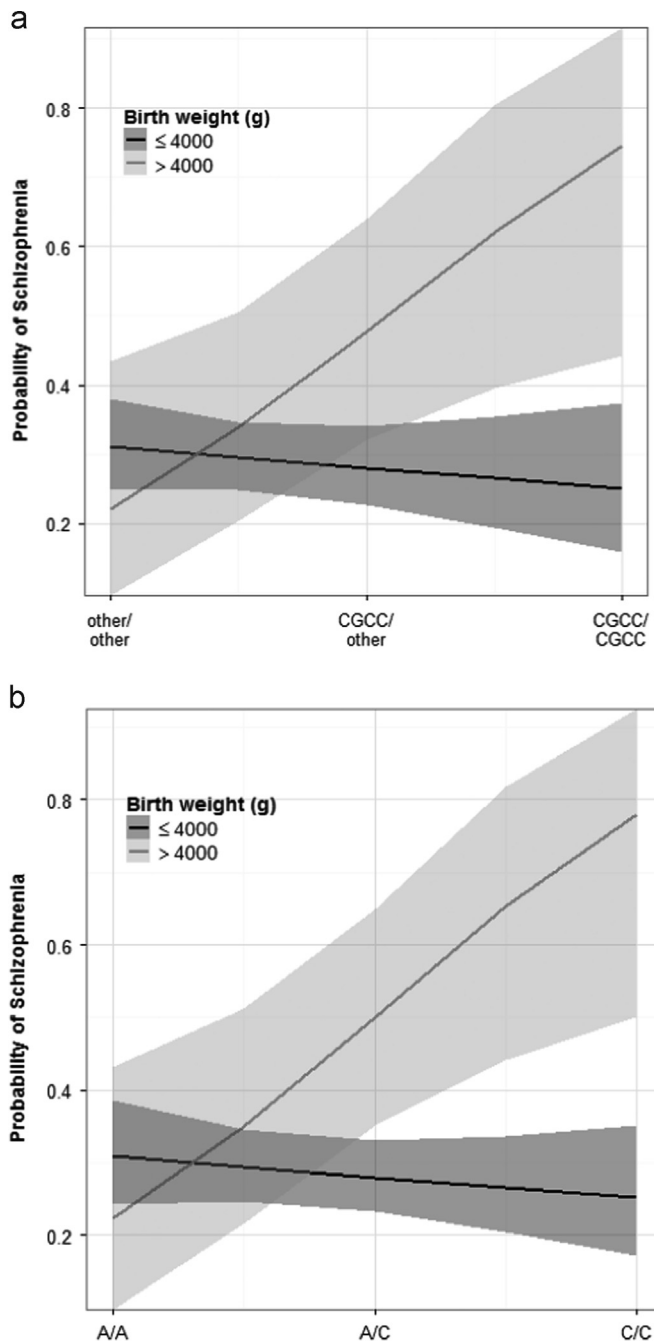
Fig. 1. A graphical depiction demonstrating the significant interaction between birth weight and NDE1 variants on schizophrenia: (a) the NDE1 haplotype and (b) its constituent rs4781678 SNP. The shaded regions represent respective 95% confidence intervals.

Acknowledgment

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