Cognitive Function in Adolescence: Testing for Interactions Between Breast-Feeding and *FADS2* Polymorphisms

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Objectives: Breast-fed C-allele carriers of the rs174575 single nucleotide polymorphism in the fatty acyl desaturase 2 (*FADS2*) gene have been reported to show a 6.4 to 7 IQ point advantage over formula-fed C-allele carriers, with no effect of breast-feeding in GG carriers. An Australian sample was examined to determine if an interaction between breast-feeding and the rs174575 single nucleotide polymorphism had any effect on IQ. **Method:** This hypothesis was tested in more than 700 families of adolescent twins assessed for IQ and breast-feeding, birth weight, and *FADS2* polymorphisms, and parental socioeconomic status and education, and maternal *FADS2* status. **Results:** No significant evidence for a moderating effect on IQ of rs174575 C-carrier status and breast-feeding was found, and there no effects of maternal *FADS2* status on offspring IQ. In addition, no main effects of any *FADS2* polymorphisms on IQ were found when the genotype was kept as two-homozygote and one-heterozygote categories and indeed no evidence for effects of breast-feeding on IQ scores after controlling for parental socioeconomic status and education. The investigation was extended to two additional *FADS2* polymorphisms (rs1535 and rs174583), but again, although these polymorphisms code alleles affecting fatty acid metabolism, no main or interaction effects were found on IQ. **Conclusion:** These results support the view that apparent effects of breast-feeding on IQ reflect differential likelihood of breast-feeding as a function of parental education and did not support the predicted interaction effect of *FADS2* and breast-feeding on IQ. J. Am. Acad. Child Adolesc. Psychiatry, 2011; 50(1):55–62. **Key Words:** Breast-feeding, IQ gene-environment interactions, fatty acid metabolism, *FADS2*

A core topic in the fields of pediatric medicine, developmental psychology, and cognitive science is the potential benefit of breast-feeding. Initial support for a beneficial effect of breast-feeding on IQ has been provided by observational studies showing evidence of higher IQ in children who were breast-fed.[1-7] This apparent effect of breast-feeding on cognitive development has been supported by biological studies indicating that breast milk components including long-chain polyunsaturated fatty acids (LC-PUFAs) may influence early brain development.[8] Breast-feeding, however, is confounded by background factors such as socioeconomic status (SES) and parental education, which are associated with IQ and the decision to breast-feed, and a series of studies has suggested that these confounders account for all or most of the association of breast-feeding with cognitive ability.[9-15] Critically, Der et al.[9] conducted a meta-analysis of previous studies finding that maternal IQ alone accounted for 72% of the apparent effects of breast-feeding on IQ. This group also presented data indicating that when maternal IQ was taken into account, there was no longer any significant association of breast-feeding with IQ.

Recently, Caspi et al.[16] suggested a moderating effect of genetics on breast-feeding effects, such that the effect of breast-feeding would be contingent on the allelic status of genes involved in fatty acid metabolism, with some children showing an effect of breast-feeding, whereas oth-

Supplemental material cited in this article is available online.

ers, with different fatty acid metabolisms, would show no effect of milk versus formula feeding. They investigated two single nucleotide polymorphisms (SNPs), rs174575 and rs1535, which are in strong linkage disequilibrium with SNPs in the promotor and 5′ regions of the fatty acyl desaturase 2 gene (*FADS2*) and the very similar adjacent gene *FADS1*. Their key finding was an IQ advantage of 6.4 to 7 IQ points for breast-fed versus non-breast-fed infants among children carrying one or more C allele of the rs174575 SNP, but with no main effect of carrier status and no effect of breast-feeding among GG homozygotes. Since Caspi et al.[16] reported this finding, one attempt to replicate has been reported. In a study of 5,934 children 8 years old, Steer et al.[17] found no main effect of rs174575 on childhood IQ but did find a significant interaction such that breast-fed children homozygous for the G allele of rs174575 performed better than formula-fed GG-homozygous children by 5.8 IQ points. This study, then, failed to replicate the sensitivity of C-allele carriers to breast-feeding.

FADS2 is one of three members of the *FADS* gene cluster[18] that encode for rate-limiting enzymes in the synthesis of ω-3 LC-PUFAs[18-23] that are involved in a wide range of cellular processes including docosanoid and eicosanoid synthesis and gene expression regulation.[21,24-26] An accumulation of these LC-PUFAs takes place in the brain during the first months after birth,[27] and this is positively associated with better development of neural function.[25,27-32] It has also been shown that children who are breast-fed have a higher concentration of LC-PUFAs than children fed unsupplemented formula.[33,34] Breast-feeding may also affect IQ through maternal effects on LC-PUFA metabolism, which influence the fatty acid composition of breast milk. Xie and Innis[23] reported an association of polymorphisms in the *FADS* gene cluster (including rs174583 tested in the present study) with altered ω-6 and ω-3 essential fatty acid components in breast milk.

In the present study, we examined the effect of breast-feeding and confounding factors on IQ in our Australian twin sample (N = 1431), testing for a predicted gene-by-environment interaction of *FADS2* polymorphisms rs174575, 174583, and rs1535 on cognitive development in breast-fed and nonbreast-fed children. In addition, we extended this investigation to examine main effects and effects of duration of breast-feeding on offspring IQ and testing for effects of maternal *FADS2* genotypes on IQ variation in offspring.

METHOD

Participants

Twins and their siblings were initially recruited as part of ongoing population studies of melanoma risk factors and cognition in the greater Brisbane area.[35] Data examined in the present study were collected before July 2008 as part of the cognition study (since 1996; e.g., Luciano et al.[36]). This sample has previously been shown to have adequate power for detecting gene effects on cognition in linkage[37] and association[38] studies. At the time the study was performed 1,838 individuals had been assessed for full-scale IQ (FSIQ). Breast-feeding data were available for 1,431 of the 1,838 participants (678 male and 753 female) comprising 720 twin pairs (278 monozygotic pairs and 442 dizygotic pairs) ranging in age from 15 to 22 years (mean ± standard deviation [SD] = 16.28 ± 0.45 years). A range of other measurements (including SES, paternal education, maternal education, gestational age, and birth weight) were available for more than 99% of the sample and 76% of these individuals have been genome-scanned on the Illumina 610-QUAD SNP (Illumina Inc., San Diego, CA) array (monozygotic and dizygotic twin pairs due to a current project examining copy number variations in monozygotic twins). No major differences in FSIQ, breast-feeding, and confounders were found between genotyped and nongenotyped individuals (Table S1, available online).

Zygosity for twin pairs of the same sex was initially determined by genotyping nine polymorphic microsatellite markers (AmpF1STR Profiler Plus Amplification kit; Applied Biosystems, Foster City, CA) and subsequently confirmed by genomewide association scan of most pairs. Exclusion criteria for the cognition study included a significant head injury, neurological or psychiatric conditions, history of substance abuse/dependence, and/or taking medications with significant central nervous system effects. This information was obtained through parental report. Informed written consent for all measurements was obtained from participants and their parents/guardian if participants were younger than 18 years. Ethics approval for these studies was obtained from the human research ethics committee of Queensland Institute of Medical Research.

Measurements

IQ. The FSIQ was assessed using the Multi-dimensional Aptitude Battery (MAB).[39] The MAB is a general intelligence test designed to mirror the Wechsler Adult Intelligence Scale–Revised[40] and presented in a multiple-choice format. Participants completed three verbal (information, arithmetic, vocabulary) and two