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Original article

Child apolipoprotein E gene variants and risk of cerebral palsy: Estimation from case–parent triads

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ABSTRACT

Objective: To use case–parent triad data to investigate if cerebral palsy (CP) is associated with variants of the *APOE* gene, the rs59007384 SNP of the *TOMM40* gene or combined haplotypes of the two genes.
Study design: DNA was analyzed in buccal swabs from 235 children with CP, their parents and a sibling. The relative risks (RR) with 95% confidence intervals (CI) that the children would have a distribution of *APOE* genotypes, rs59007384 variants or combined haplotypes deviating from Mendelian inheritance were estimated.
Results: Children with CP were more likely than expected to carry the *APOEε3* allele (RR 7.5; CI: 0.99–53.7 for heterozygotes and 10.3; CI: 1.4–79.6 for homozygotes), and to have the haplotype of *APOEε3* and rs59007384 G (RR 2.4; CI: 1–5.7 for heterozygotes, RR 3.7; CI: 1.4–9.5 for homozygotes) whereas the distribution was as expected for rs59007384 alone. In the subgroup analyses the findings were confined to children born preterm. Among siblings the distribution of these genes was as expected according to Mendelian inheritance.
Conclusion: We speculate that children with *APOEε2/APOEε4* alleles are more likely to die following cerebral injury in utero, resulting in a higher than expected proportion of children with CP carrying the *APOEε3* allele.
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Abbreviations: AD, Alzheimer disease; *APOE*, apolipoprotein E (gene); apoE, apolipoprotein E (protein); BFMF, Bimanual Fine Motor Function; CP, cerebral palsy; CPRN, Cerebral Palsy Register of Norway; GMFCS, Gross Motor Function Classification System; HWE, Hardy–Weinberg equilibrium; LD, linkage disequilibrium; MBRN, Medical Birth Registry of Norway; REC, Regional Ethics Committee; SNP, single-nucleotide polymorphism; TBI, traumatic brain injury.

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1. Introduction

We have in an earlier study shown that cerebral palsy (CP) may be the result of a number of risk factors.[1] However, few children shared the same risk factors suggesting individual susceptibility to ante- or peri-natal brain injuries. This individual susceptibility may partly be explained by variations of genes encoding factors involved in repair processes or responses to early brain insults.[2]

The apolipoprotein E gene (*APOE*), located on chromosome 19, is a gene where variants in single nucleotides may lead to different susceptibility to an early brain injury.[2] Three alleles, ε2, ε3 and ε4, of this gene have been identified and described, resulting in corresponding differences in protein structure. The presence of the ε4 allele has in earlier studies been associated with Alzheimer disease (AD) and poor long-term recovery after traumatic brain injury (TBI).[3–7] However, whereas *APOE* association studies have been inconclusive regarding the etiology of CP[8,9] we have in an earlier study shown that presence of the *APOE*ε4 allele was associated with more severe clinical manifestations of CP.[2]

In addition, we have reported that the presence of the T allele of the rs59007384 SNP (single-nucleotide polymorphism) in the *TOMM40* gene influencing the production of apoE was associated with more severe manifestation of CP.[10] The *TOMM40* gene is located centromeric and adjacent to *APOE*. The results of our two previous studies therefore suggest that both the structure as well as the amount of apoE produced may play a significant role in the pathophysiology leading to various clinical manifestations of CP.

Studies using case–parent triad data are considered more robust than the classical case–control design that so far has been used in studies of the etiology of CP.[11] By genotyping both the children and their parents it is possible to assess whether children with a specific disease have a genotype distribution deviating from what would be expected assuming Mendelian transmission. To our knowledge, such case–parent triads have not been applied in studies of the etiology leading to CP.

The aim of the present study was therefore to use case–parent triad data to investigate if CP is associated with specific *APOE* alleles and/or specific variants of the rs59007384 SNP in *TOMM40*. We hypothesized that the proportion of children with the *APOE*ε4 allele, the T allele of the rs59007384 SNP or with the haplotype of *APOE*ε4 and rs59007384 T would be higher in children with CP than expected according to Mendelian inheritance.

2. Materials and methods

2.1. Study design

This study is a case–parent triad study including children diagnosed with CP in Norway born between 1996 and 2003 and recorded with detailed information in the Cerebral Palsy Register of Norway (CPRN). Genotyping was performed on DNA from buccal epithelial cells in children with CP and their parents, as well as one sibling. The complete process from collecting these cells to the DNA analysis has been described in detail in an earlier study.[2]

The CPRN[12] provided clinical data on the children diagnosed with CP. Written informed consent comprising detailed data registration in the CPRN and linkage with MBRN (Medical Birth Registry of Norway) was obtained from the parents. The CP register is an informed consent based register recording detailed information from all the pediatric habilitation centers in Norway. We did not collect any information on the mothers, fathers or siblings.

2.2. Participants

In total, 703 children and families recorded in the CPRN were invited to participate, and 281 (40%) returned swabs. Of these, 26 were of poor quality and could not be used, resulting in a final population of 255 (36.3%) children with reliable *APOE* and *TOMM40* genotyping. In this population of 255 children DNA was available for 235 triads, i.e. the child and its parents, and in addition, DNA was available in 208 siblings. Due to Mendelian inconsistencies 20 triads were removed, leaving 215 triads for further analyses. Among the siblings, 192 triads remained after 16 were removed due to Mendelian inconsistencies. We have, in a previous study, described that participants (those who returned swabs) and non-participants (those who did not return swabs) with CP did not differ in terms of CP subtype, GMFCS and BFMF levels.[2]

2.3. Study variables

Clinical information regarding CP subtypes and severity were abstracted from CPRN. Cerebral palsy was diagnosed and classified according to the recommendations by the Surveillance of Cerebral Palsy in Europe in 1999.[13] Severity of CP was defined by the Bimanual Fine Motor Function (BFMF) and the Gross Motor Function Classification System (GMFCS). The GMFCS describes gross motor function within five levels. Level I corresponds to walking without limitations, whereas Level V corresponds to transportation by manual wheelchair.[14,15] The BFMF describes fine motor function, also within five levels, where Level V corresponds to only ability to hold or worse.[16] In the present study both GMFCS and BFMF were used as dichotomous variables by contrasting levels I and II with levels III to V. Another indicator of severity of CP is epilepsy, in this study defined as current use of antiepileptic drugs.

2.4. Ethics

The present study was approved by the Regional Ethics Committee (REC) for medical research in Mid-Norway (reference number 2010/398). Written informed consent was obtained from the parents for participants younger than 16 years, or from the participants themselves if they were older.

2.5. Statistical analysis

We estimated relative risks (RR) with 95% confidence intervals (CI) of child *APOE* genotypes, rs59007384 variants and

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