Associations between genes associated with syndromic cerebral visual impairment (CVI) with CVI-related vision tests in a community-based sample of children

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Introduction

- Cerebral visual impairment (CVI) comprises a spectrum of verifiable visual impairments caused by central (retrogeniculate) visual pathway malfunction (1). CVI is frequently present in children or adults with neurological or neurodevelopmental problems, both congenital and/or acquired (2).
- Bosch *et al* recently described genes associated with CVI in children with *rare genetic syndromes* (3)
- We aimed to explore whether these genes might also be associated with brain-related visual functions in children *without known syndromes*. We used a dataset already assembled for a project investigating associations between neuroprotection-related genes and brain-related visual functions, in the Avon Longitudinal Study of Parents and Childhood (ALSPAC) (4)

Objective

To investigate associations between the CVI genes reported by Bosch et al and brain-related visual functions assessed in children at ages 7yr-12yr, in the early 2000s, as part of the ALSPAC birth cohort study.

Methods

Visual function data (including acuity, autorefraction) were collected in research clinics to which the ALSPAC children were invited at ages 7, 10, 11, 12 and 15 and a shortened INSIGHT questionnaire (8) was asked when they were aged 13 yr. Novel tests of **mid-level visual processing** were included at ages 11, 12 and/or 15yr, *if time allowed*. These were (i) **contour detection threshold cards** (5), (ii) **Shape Discrimination Hyperacuity test** (6) and (iii) **a vernier acuity test** (7).

(i) Contour detection)



(ii) Shape Deformation Hyperacuity (SDH)



(iii) Vernier acuity



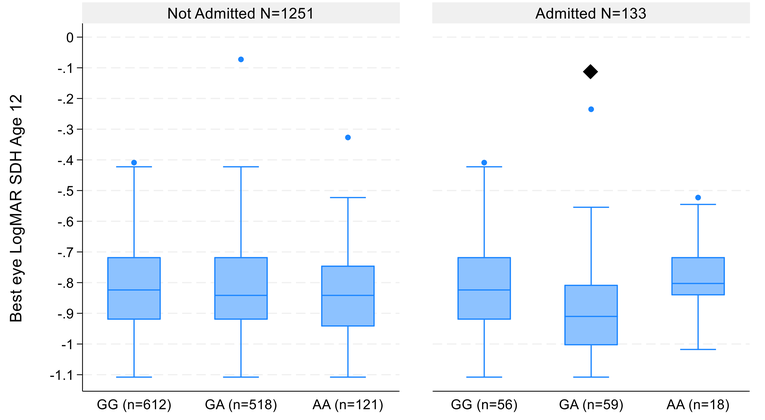
We examined results for **pursuits, contour cards, SDH**, recognition and Resolution **Vernier acuity,** and the INSIGHT scores (= 9 outcomes) by genotypes for the 5 available SNPs relating to the genes Bosch el al reported **GRIN1, GRIN2B, GRIN2A, GRIN3, DLG4** (= 5 predictors) using non-parametric Kruskal Wallis (KW) test. For the 8 tests where KW $p < 0.05$, we carried out linear regressions using genotype as continuous (additive models) or discrete (genotype models) predictors, in (a) all participants with data and (b) participants admitted to hospital in the first month of life.

Results

- Results were available for 54 - 3133 children, dependent on the data available.
- No associations with $p<0.05$ were seen using **additive** models
- Four of the five SNPs were associated with SDH or Contours using **genotype** models:

  All children with data
  - **GRIN2A** (SDH results: AA vs AC, p=0.048)
  - **GRIN1** (SDH results: GA vs GG, p=0.045)

  Children admitted to hospital perinatally
  - **DLG4** (SDH results: GA vs GG, p=0.045)
  - **GRIN3A** (Contour detection results: CT vs CC, p=0.023).
- No associations of $p<0.05$ were seen with these SNPs and the oculomotor or vernier results or with GRIN2B genotypes
- An example of the SDH results expressed as LogMAR units, by DLG4 genotype, is shown in Figure 1



Graphs by Admission to SCBU/NICU/hospital ward in the first 4 weeks of life

Fig. 1 LogMAR SDH (better-seeing eye) results by genotype for a SNP in DLG4, across patients based on their admission status to hospital within the first four weeks of life, in children aged 12 participating in the ALSPAC study. Diamond denotes $p < 0.05$ (GG vs GA)

Conclusions

These **preliminary** findings from an **opportunistic, exploratory** study using historic data suggest potential links between the GRIN and DLG4 genes, which are involved with **NMDA (N-methyl-D-aspartate) receptor functioning**, and **SDH** and **Contour detection** in children. Dedicated studies to investigate this could contribute to our understanding of mechanisms leading to CVI and inform the development of targeted treatment strategies.

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