Mannose-binding lectin (MBL) is an acute-phase reactant that activates the complement system. A genetic variant of MBL2, rs1800450, with a minor allele frequency of approximately 14%, is associated with the protein change MBL2Gly54Asp and causes autosomal dominant MBL deficiency. We recently reported in this Journal that rs1800450 was associated with increased pervasive developmental problems after cardiac surgery at 4-year follow-up.1 Most initial reports of genotype-phenotype associations are not subsequently validated. Ideally, validation should be performed in a similar population. The phenotype assessed in the validation study should be the same as in the initial report, and similar covariates should be measured. We were previously able to validate our findings related to MBL2Gly54Asp.

We used data from 231 subjects from the combined Infant Single Ventricle (ISV) and Single Ventricle Reconstruction (SVR) trials and performed separate linear regressions on the outcomes of Psychomotor Developmental Index and Mental Developmental Index, with adjustment for other known risk factors (see Table 1 for a full list of variables). We found a marginally significant association (α = 0.01 or 0.05/5, adjusting for 5 total statistical tests) between MBL2Gly54Asp and Psychomotor Developmental Index (P = .076) at 14 months of follow-up after cardiac surgery. The direction of effect for MBL2Gly54Asp (β = 5.11) was opposite that of APOE ε2 allele2 with data from the Pediatric Heart Network (PHN),3 and sought to similarly validate our findings related to MBL2Gly54Asp.

We also performed an analysis of a subset of the Single Ventricle Reconstruction trial (N = 189) for the outcome of Functional Status II-R at 2 to 3 years of age (FSII-R). We found marginally significant associations for MBL2Gly54Asp with decreased FSII-R General (β = −3.91; P = .037) and FSII-R Total (β = −3.41; P = .074) scores in multivariable analysis. We found no association between MBL2Gly54Asp and FSII-R Activity score (β = −3.11; P = .14). We again note that the direction of effect is opposite that of APOE ε2 (Table 1) and reflects a consistent neuroprotective effect for MBL2Gly54Asp across all FSII-R domains tested.

In summary, we could not validate our previous finding that MBL2Gly54Asp is associated with poorer neurodevelopmental outcomes.1 In the PHN data, we do not find significant associations after correction for multiple comparisons. The findings do, however, suggest a neuroprotective effect across tested domains. These results could reflect underlying differences between cohorts, because data from the Child Behavior Checklist, from which the variable of pervasive developmental problems (the primary outcome from our previous study) was defined, was not available in the PHN cohorts. In addition, these results may reflect differential effects of MBL deficiency at varying stages of neurodevelopment.4 Alternatively, this MBL2 variant may reflect the effects of another, closely correlated, causal variant in this region. Regardless of the underlying reason for our lack of validation, further investigation is needed into the molecular mechanism of effect for MBL deficiency on neurodevelopment the better to understand and prevent sequelae of cardiac surgery in infancy.

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should: Include no more than 500 words of text, three authors, and five references. Type with double-spacing. See http://jtcvs.ctsnetjournals.org/misc/ifora.shtml for detailed submission instructions. Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given the opportunity of offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

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**TABLE 1. Summary of associations for APOE ε2 and MBL2Gly54Asp with neurodevelopmental outcomes in the Pediatric Heart Network data**

<table>
<thead>
<tr>
<th>Outcome*</th>
<th>N</th>
<th>APOE ε2</th>
<th>MBL2Gly54Asp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P value</td>
<td>β</td>
</tr>
<tr>
<td>MDI</td>
<td>231</td>
<td>−3.49</td>
<td>.31</td>
</tr>
<tr>
<td>PDI</td>
<td>231</td>
<td>−9.23</td>
<td>.014</td>
</tr>
<tr>
<td>FSII-R General</td>
<td>189</td>
<td>4.05</td>
<td>.18</td>
</tr>
<tr>
<td>FSII-R Total</td>
<td>189</td>
<td>2.92</td>
<td>.35</td>
</tr>
<tr>
<td>FSII-R Activity</td>
<td>189</td>
<td>2.93</td>
<td>.39</td>
</tr>
</tbody>
</table>

MDI: Mental Development Index at 14 months of follow-up; PDI: Psychomotor Development Index at 14 months of follow-up; FSII-R: Functional Status II-R at 2 to 3 years of age. *Analyses adjusted for clinical site, sex, ethnicity (as a factor variable), birth weight, gestational age, presence of genetic anomaly, type of congenital heart disease (as a factor variable), age at first surgery, total cardiopulmonary bypass time, total aortic crossclamp time, total deep hypothermic circulatory arrest time, medical insurance, socioeconomic status, poverty, number of severe adverse events, and postoperative stay in days.
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References