Evaluation of Autism Gene Link Evidence (EAGLE)

Curation Process


OVERVIEW: At present, there is no standardized approach for evaluating a gene’s etiological relationship to autism spectrum disorder (ASD). Given the increasing use of genetic testing for individuals with ASD and other neurodevelopmental disorders, this creates inconsistencies in the evaluation of individuals with ASD, and may hamper uniform interpretation of genetic results. First presented in Schaaf et al. (2020)1, the EAGLE scoring system implements and expands on pre-existing frameworks (primarily the ClinGen (Clinical Genome Resource) framework) with the objective to evaluate evidence regarding the relevance of a gene with respect to ASD, rather than potentially with a broad range of neurodevelopmental phenotypes (see figure).

AIMS/OBJECTIVES: To implement a multi-disciplinary consensus-based method for the curation of genes putatively associated with likelihood to develop ASD. This, in turn, will enable development of a comprehensive evidence-based list of genes involved in ASD.

CURATION PROCESS:

Evidence Collection: Genotype information. Curators first conduct an extensive literature search to gather all available clinical cases, and document genotype information for each case. Information collected includes the genotyping method (in particular, whole-exome/genome versus more targeted approaches); variant(s) reported (including genomic coordinates; genome build; c. and p. nomenclature; and transcript number, if available); variant impact (e.g. missense, frameshift, nonsense, etc.); presence/absence in gnomAD; and inheritance.

Any evidence, functional or otherwise, that supports pathogenicity of the reported variant, is used to score the case, not scored separately under experimental evidence2.

Evidence Collection: Phenotype information. Curators must also extract any reported phenotype information from each case. This includes the identification number/code provided to the subject (in some cases, this may simply be reported as “proband”); sex; and additional phenotypes (e.g. intellectual disability, epilepsy, dysmorphic features, etc.). Information regarding ASD phenotyping and cognition should also be recorded, including specific assessments used to diagnose ASD in the subject, IQ scores, and any other such relevant information. (See figure)

Scoring: System. Following collection of all available case level information, curators then score each case, taking into account genotype and phenotype information. While default scores are set for each variant type, based on the ClinGen scoring framework (see Section X, EAGLE Standard Operating Procedure), these default scores may be adjusted based on a holistic assessment of the case. For instance, low confidence ASD phenotyping (i.e. only mention of “ASD,” without description of diagnostic methods) will result in a downgraded score, as would a high frequency in the gnomAD database (see Section X, EAGLE Standard Operating Procedure). Curators must assess each score on a case-by-case basis, while also considering the gene in question (e.g. certain domains of the protein are more susceptible to pathogenicity; disease mechanism is not loss of function, etc.).

Scoring: Category Assignment. Once scores have been assigned to all cases, curators sum individual scores to arrive at a total. Care must be taken to ensure cases are not double-scored, should the subject appear in multiple publications (sometimes under different identifiers). Based on the score ranges provided in the scoring matrix, genes will be given a limited, moderate, or strong/definitive classification (also see Section X, EAGLE Standard Operating Procedure). Experimental evidence may also be included in the total score, if applicable.
EAGLE SCORE INTERPRETATION

1. Note that for the EAGLE Curation process, all unique cases are taken into account in calculating the total score, with a threshold (12), but not a ceiling for definitive scores. Consequently, while any gene accumulating 12 points or more is considered definitive, the degree with which a score exceeds 12 can be interpreted as a measure of additional strength of the underlying evidence.

<table>
<thead>
<tr>
<th>POINTS</th>
<th>0.1-6</th>
<th>7-11</th>
<th>12+</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLASSIFICATION</td>
<td>Limited</td>
<td>Moderate</td>
<td>Definitive</td>
</tr>
</tbody>
</table>

2. The interpretation of the EAGLE score (evaluating evidence for ASD) compared to existing curation frameworks evaluating evidence of association with the broader neurodevelopmental phenotype can be summarized in these two statements (and figure):

   I. A high evidence score resulting from curation in the existing frameworks can, but does not necessarily imply that the gene is also related to ASD.

   II. A high evidence score resulting from curation with the EAGLE scoring framework confirms a gene’s relationship with ASD, but does not rule out a relationship with any other neurodevelopmental phenotypes.

3. From the preceding follows that EAGLE curation of evidence of association with ASD does not necessitate nor imply the existence of “ASD-specific” genes.
Author affiliations

1 Institute of Human Genetics, Heidelberg University, Heidelberg, Germany.
2 Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA.
3 Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX, USA.
4 Neuroscience Paris Seine, Institut de Biologie Paris Seine, Sorbonne Université, INSERM, CNRS, Paris, France.
5 The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada.
6 Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada.
7 Population Health Science Institute, Sir James Spence Institute, Newcastle University, Royal Victoria Infirmary, Newcastle, UK.
8 Institute of Child Health, University College London, London, UK.
9 Department of Psychiatry & Neuropsychiatric Genetics Research Group, School of Medicine, The Trinity Centre for Health Sciences, Trinity College Dublin, Dublin, Ireland.
10 Department of Psychiatry and Behavioral Sciences, University of Washington, Center for Child Health, Behavior, and Disabilities, Seattle, WA, USA.
11 Children’s Autism Center, Seattle, WA, USA.
12 Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
13 Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
14 Translational Neuroscience Center, Department of Neurology, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA.
15 Montreal Neurological Institute, Azrieli Centre for Autism Research, McGill University, Montreal, QC, Canada.
16 Department of Clinical Genetics, Cambridge University Hospitals NHS Foundation Trust & Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK.
17 Autism Speaks, Cleveland, OH, USA.
18 CHU Sainte-Justine Research Center, University of Montreal, Montreal, QC, Canada.
19 Department of Psychiatry, Hospital for Sick Children, Toronto, ON, Canada.
20 Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada.
21 Department of Pediatrics (in Medicine), Columbia University Medical Center, New York, NY, USA.
22 Institute of Psychiatry, King’s College London, London, UK.
23 Department of Psychiatry, University of Illinois at Chicago, Chicago, IL, USA.
24 The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada. stephen.scherer@sickkids.ca.
25 Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada. stephen.scherer@sickkids.ca.
26 McLaughlin Centre, University of Toronto, Toronto, ON, Canada. stephen.scherer@sickkids.ca.
27 The Centre for Applied Genomics, Program in Genetics and Genome Biology, The Hospital for Sick Children, Toronto, ON, Canada. jacob.vorstman@sickkids.ca.
28 Department of Psychiatry, Hospital for Sick Children, Toronto, ON, Canada. jacob.vorstman@sickkids.ca.
29 Department of Psychiatry, University of Toronto, Toronto, ON, Canada. jacob.vorstman@sickkids.ca.