



## Original Article

## Strabismus in Children With Intellectual Disability: Part of a Broader Motor Control Phenotype?



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## ABSTRACT

**Purpose:** Intellectual disability (ID) results from a heterogeneous group of disorders and affects 1% to 2% of children. ID frequently occurs in association with other clinical features such as seizures or malformations. We suspected that strabismus might also be unusually frequent in this population and that it might be associated with ID groups affecting motor control.

**Methods:** We reviewed phenotypic descriptors, extracted from medical records, for a heterogeneous series of 222 probands with ID who had been enrolled in a study of clinical application of exome sequencing. We estimated the frequency of strabismus and other common clinical features and explored statistical associations between them. Data from Population Data British Columbia and Online Mendelian Inheritance in Man were also examined for confirmation of our observations.

**Results:** Strabismus had a higher prevalence among probands with ID than in the general population (odds ratio = 5.46). Moreover, probands with both ID and strabismus were more likely to have problems affecting motor control than those with ID and no strabismus (odds ratio = 2.84). Hypotonia was one of the most common motor control subgroups affecting the ID probands, and a frequent co-occurrence of strabismus and hypotonia was also observed (odds ratio = 2.51) and supported by related gene literature review. There was no evidence for associations between strabismus and other frequent clinical features.

**Conclusion:** Strabismus is a frequent feature in individuals with ID. The frequent co-occurrence of strabismus and motor control phenotypes, in particular hypotonia, suggests that a common cerebellar mechanism or pathway may underlie these phenotypes.

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## Introduction

Intellectual disability (ID) results from a very large and heterogeneous group of disorders or exposures and is diagnosed on the basis of limitations affecting both cognitive and adaptive domains.<sup>1</sup> The US Centers for Disease Control and Prevention currently estimate that 1.14% of children aged three to 17 years have been diagnosed with ID.<sup>2</sup>

Strabismus is a broad phenotype of ocular misalignment affecting 2% to 4% of children.<sup>3</sup> Multiple mechanisms can lead to strabismus, including abnormalities of the brain, the cranial nerves, or the extraocular muscles, although in most children the underlying pathology remains obscure.<sup>4,5</sup> Recognized risk factors for strabismus

include low birth weight, cicatricial retinopathy of prematurity, prematurity, smoking throughout pregnancy, anisometropia, hyperopia, and inheritance.<sup>6</sup> Motor problems often occur in children with ID, and we suspected that strabismus, which may reflect a functional abnormality of ocular movement, might also be more frequent than expected in this population. We analyzed the phenotypes in a heterogeneous series of children with ID to (1) document the prevalence of strabismus and (2) test the hypothesis that strabismus may be part of a broader motor control phenotype, as evidenced by correlation with motor subgroups such as hypotonia.

## Methods

## Clinical characterization of CAUSES subjects

Clinical phenotypic information was extracted from electronic and hard copy health records (dating up to the end of 2017) for

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probands enrolled in a study of exome sequencing: the CAUSES (Clinical Assessment of the Utility of Sequencing and Evaluation as a Service) project at BC Children's & Women's Hospital in Vancouver, British Columbia, Canada. The study used genome-wide sequencing (exome or whole genome) and analyzed subject families as trios. Not all the probands in the CAUSES study were affected by ID, so only a subset of the series was included for this study.

Individuals described as having either intellectual or cognitive disabilities were identified for inclusion in our analysis. The team identified causal or probable causal variants for 46.4% of these CAUSES-ID probands. Within this CAUSES-ID series, those with at least one of the following were considered to have a "motor control" phenotype: hypotonia, hypertonia, dystonia, cerebral palsy, spasm, tremor, any movement defect, or any coordination defect.

Clinical features were obtained from close inspection of phenotypic descriptors compiled by CAUSES study investigators after review of free-text medical records from various specialists. To identify the most common phenotypes, appropriate for inclusion in our study, we first used a text mining and visualization approach with R (v3.4) packages *tm* (text mining), *wordcloud*, and *RColorBrewer*, followed by a manual curation step. We manually inspected the results, focusing on the most frequently presented words ( $\geq 25$  subjects). During the manual inspection process, synonymous clinical features were identified, and the ones associated with the most common words were combined to obtain more accurate frequencies of the phenotypes. Contingency analysis with two-sided Fisher's exact tests (R package "exact2x2") was then applied to detect associations between strabismus and other phenotypes.

#### Analyses based on Population Data BC and OMIM

Additional data were obtained from two independent sources to determine if our observation replicated with different datasets. BC Data Scout is a service of Population Data British Columbia that provides aggregate numbers of people with specific International Classification of Diseases diagnoses recorded in billings submitted to the Medical Service Plan records in British Columbia (BC), Canada.<sup>7</sup>

An International Classification of Diseases code for "specific motor retardation" was used to select subjects with motor control phenotypes, despite the possibility that motor delays related to peripheral neuromuscular disorders could be included. Hypotonia was not significantly represented in billing records and could not be reliably analyzed. To further assess the relationship between strabismus and hypotonia, the Online Mendelian Inheritance in Man (OMIM) database was used to compile entities featuring ID, strabismus, and hypotonia. The search was limited to the OMIM Clinical Synopsis, which provides systematic phenotypic descriptions of monogenic disorders and some chromosomal disorders such as Down syndrome. Datasets and detailed search strategies for both sources are described in the [Supplementary Methods](#).

#### Analysis of genes from CAUSES-ID-strabismus probands

Causal or probably causal genes from CAUSES-ID probands presenting with strabismus were compiled and subjected to literature review. Only genes supported by two or more probands demonstrating the association between strabismus and motor control defects, including the probands in this study, were further analyzed to explore enriched properties by using STRING.<sup>8</sup>

## Results

### *Strabismus frequently affects children with ID*

To study the prevalence of strabismus and its association with other phenotypes, we reviewed clinical information for 479 individuals enrolled in the CAUSES study, 222 (46.3%) of whom were affected by ID. An additional 106 subjects had global developmental delay, which frequently precedes receiving a diagnosis of ID once children were old enough for intellectual assessment; these were not included in the current analysis. Analysis of phenotypic records in the CAUSES-ID series revealed six phenotypes occurring in at least 25 subjects (Table 1). Among these, strabismus occurred in 14.4% of the cohort and hypotonia occurred in 17.6%.

To compare the prevalence of strabismus in ID to that of the rest of the population, we generated a report through the BC Data Scout service.<sup>9</sup> We identified a total of 754,125 children aged four to 17 years, 3540 of whom (0.47%) had been reported as having ID via billing codes. Strabismus occurred more often in the ID group (30.4%) than in the rest of the population (7.4%; odds ratio [OR] = 5.46, 95% confidence interval [CI] [5.08, 5.86]; Fig B).

### *Motor control phenotypes are associated with strabismus in ID*

To explore an association between motor control phenotypes and strabismus, we further sub-classified the CAUSES-ID series into an ID-motor group (77 individuals) and an ID-non-motor group (145 individuals). Strabismus was reported more often in the ID-motor group (18 of 77 = 23.4%) than in the ID-non-motor group (14 of 145 = 9.7%; OR = 2.84, 95% CI [1.24, 6.63]; Fig A). As a comparison, we also tested for associations between strabismus and other frequent phenotypes in ID. The occurrence of strabismus was not significantly higher in groups with dysmorphisms, autism, seizures, or microcephaly compared with the corresponding non-affected groups (Fig A, Table 2).

Although hypotonia was included within the ID-motor group analysis, it is, by itself, among the most frequent phenotypes in ID. Therefore we also examined strabismus prevalence in the ID-hypotonia group. Strabismus prevalence is more common than in the ID group without hypotonia (OR = 2.51, 95% CI [1.07, 6.04]; Fig A).

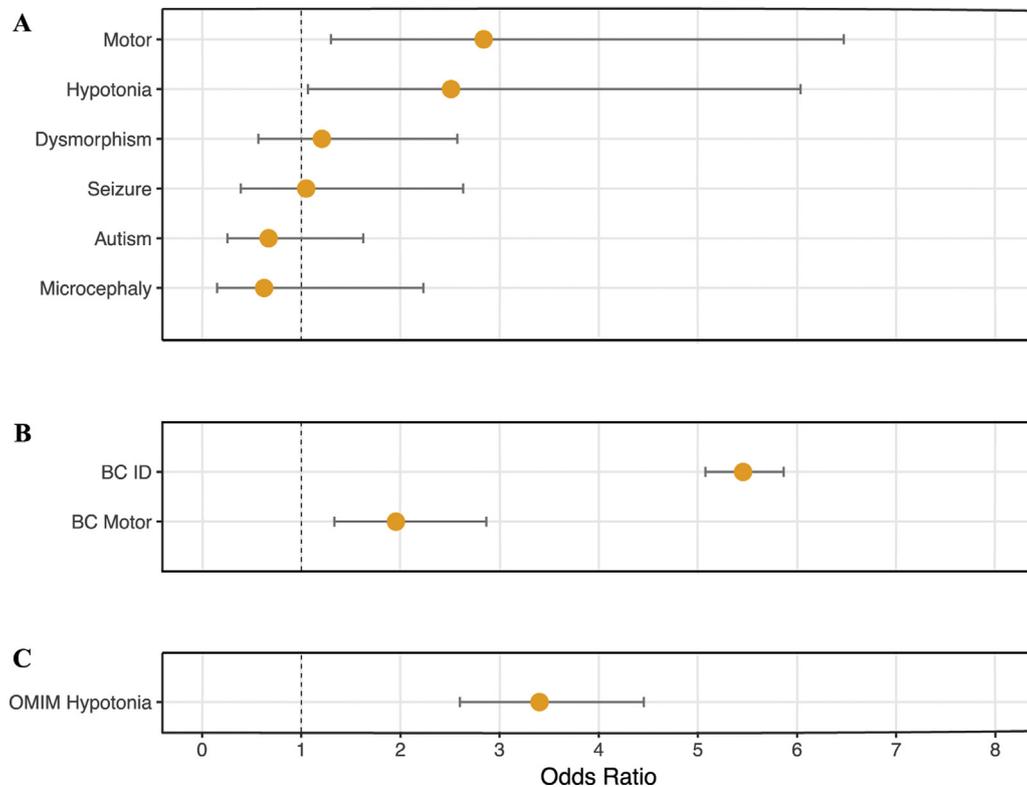
To replicate the association between strabismus and motor control within ID, we analyzed 3540 individuals with ID from

**TABLE 1.**  
Prevalence of Clinical Features in CAUSES-ID Probands

Clinical Feature	Number (%) (Total 280)
Dysmorphism	
Including "dysmorphic," "unusual morphological features," "morphological difference," "hypertelorism," "down slanting palpebral fissures," abnormally formed external ears	102 (45.9)
Autism	
Including "autism spectrum disorder," "Asperger"	63 (28.4)
Seizure	
Including "epilepsy"	47 (21.2)
Hypotonia	
Including "low muscle tone" and "low tone"	39 (17.6)
Strabismus	
Including "esotropia," "exotropia," "hypertropia," "hypotropia"	32 (14.4)
Microcephaly	
Including "small head"	30 (13.5)

Abbreviation:

CAUSES-ID = Clinical Assessment of the Utility of Sequencing and Evaluation as a Service



**FIGURE.** Odds ratios and 95% confidence intervals (x-axis) for the association of different clinical features (y-axis) with strabismus versus nonstrabismus ID groups. Odds ratio represents the odds that a clinical feature co-occurs with strabismus, compared with the odds that the clinical feature occurs in the absence of strabismus. (A) Data from the CAUSES series with ID. (B) Data from the British Columbia population. BC ID represents odds ratio between odds of having strabismus in the presence of ID and odds of having strabismus in the absence of ID in British Columbia, as determined by ICD codes used in billing. (C) Data from OMIM records. BC, British Columbia; CAUSES, Clinical Assessment of the Utility of Sequencing and Evaluation as a Service; ICD, International Classification of Diseases; ID, intellectual disability; OMIM, Online Mendelian Inheritance in Man. The color version of this figure is available in the online edition.

Population Data BC. Strabismus occurred more often in the ID-motor group (50 of 110, 45.5%) than in the ID-non-motor group (1025 of 3430, 29.9%; OR = 1.95, 95% CI [1.33, 2.87]) (Fig B). As the Population Data BC records do not report on hypotonia, we could not use this dataset to replicate the strabismus-hypotonia association observed in the CAUSES-ID series. Instead, we examined this association using phenotypic descriptions from OMIM records. A total of 1481 entities featuring ID and 433 entities featuring strabismus were identified. Strabismus occurred in 174 records together with hypotonia and showed a significant co-occurrence compared with records without hypotonia (OR = 3.40, 95% CI [2.60, 4.46]; Fig C).

#### *The biological roles of genes altered in the CAUSES-ID-strabismus series support the association between strabismus and motor control defects*

To explore the underlying genetics of the probands with strabismus and ID, we compiled the list of causal genes for CAUSES-ID probands with strabismus. A total of 19 causal genes were identified for 32 probands, with a diagnostic rate of 59.4% (Table 3). Literature reviews revealed that 14 of 19 genes have been previously associated with both strabismus and motor control defects, three of which (*MECP2*, *ARID1B*, and *SETD5*) have been included in a curated strabismus gene set.<sup>10</sup> An association (or the lack of it) is still inconclusive for *TRRAP*, *PIK3CA*, *WINT10A*, *WWOX*, and *DYRK1A* due to few reports on these syndromes. Many of the 14 genes with evidence for both strabismus and motor control defects have DNA-binding and chromatin remodeling functions, and as a set are

enriched for “DNA-templated transcription” (10 genes), “regulation of synapse organization” (four genes), and “chromosome organization” (six genes). (The top 10 enriched GO Biological Process terms can be found in Supplementary Table 1.)

#### **Discussion**

While independent datasets and literature reviews support our finding of an independent association between hypotonia and strabismus in children with ID, we report and interpret our observations with two challenges in mind. First, free-text was used to record proband phenotypes upon assessment in the CAUSES study, and the use of uncontrolled vocabularies poses a challenge for deep and precise analysis of all the phenotypes because different terminology can be used to describe the same feature.<sup>11</sup> Future improvement will come from the systematic use of controlled vocabularies, such as the Human Phenotype Ontology, during data collection.<sup>11</sup> A more significant limitation of the current study is rooted in the fact that the original data are not recorded for the purpose of studying the associations explored here. Misclassification, over- or underascertainment of ID, strabismus, hypotonia, or motor control phenotype can be potential confounding factors.

In a study specifically designed to describe ocular findings and refractive errors in a cohort with ID, Akinci and colleagues prospectively performed ophthalmologic examinations and reported a similar strabismus prevalence of 14.0% with both idiopathic and syndromic ID compared with 1.3% of the control group.<sup>12</sup> We used population-based health data (BC billing information)—a larger sample size—to show that strabismus occurs more frequently in

**TABLE 2.**  
Co-occurrence of Strabismus With Other Clinical Features in CAUSES-ID Series

Clinical Feature	Proband with Strabismus	Odds Ratio
Dysmorphism	16	1.21
Autism	7	0.67
Seizure	7	1.05
Hypotonia	10	2.51
Microcephaly	3	0.63
Motor control phenotypes	18	2.84

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children with ID than in control individuals. Both rates are, however, approximately twice as high as in previous reports: 30% vs 14% and 7% versus 4%, respectively.<sup>3,12</sup> We also noticed that the reported ID prevalence in BC is approximately half of the expected frequency of 1.14%.<sup>2</sup> These observed discrepancies are likely nonrandom: the inclusion of referrals to ophthalmologists for ruling out strabismus likely increases the strabismus rates, and the underrepresentation of individuals with mild ID in the billing data may be a cause for reduced ID prevalence. Replicating this association in a dataset that ascertains and classifies ID, strabismus, and various motor problems more rigorously and consistently would be an important next step.

**TABLE 3.**  
Genes Identified for CAUSES-ID-Strabismus Proband and Relevant Annotations

Gene Name	Gene Description	Gene Stable ID	Related Phenotype Description	CAUSES Subgroup	Strabismus Reported (≥2 Cases)	Motor Control Defect Reported (≥2 Cases)
<i>ADNP</i>	Activity-dependent neuroprotector homeobox	ENSG00000101126	Helsmoortel-VanDerAa syndrome	Non-motor	Y	Y
<i>AHDC1</i>	AT-hook DNA-binding motif-containing 1	ENSG00000126705	Xia-Gibbs syndrome	Motor	Y	Y
<i>ARID1B</i>	AT-rich interaction domain 1B	ENSG00000049618	Coffin-Siris syndrome	Motor	Y	Y
<i>CAMK2B</i>	Calcium/calmodulin-dependent protein kinase II beta	ENSG00000058404	Intellectual disability	Motor	Y	Y
<i>CTNNB1</i>	Catenin beta 1	ENSG00000168036	Severe intellectual disability-progressive spastic diplegia syndrome	Motor	Y	Y
<i>DDX3X</i>	DEAD-box helicase 3 X-linked	ENSG00000215301	X-linked intellectual disability-hypotonia-movement disorder syndrome	Motor	Y	Y
<i>DYRK1A</i>	Dual specificity tyrosine phosphorylation regulated kinase 1A	ENSG00000157540	Intellectual disability syndrome due to a <i>DYRK1A</i> point mutation	Non-motor	NA	NA
<i>EBF3</i>	EBF transcription factor 3	ENSG00000108001	Hypotonia ataxia and delayed development syndrome	Motor	Y	Y
<i>KCNQ2</i>	Potassium voltage-gated channel subfamily Q member 2	ENSG00000075043	Epileptic encephalopathy early infantile 7	Non-motor	Y	Y
<i>MECP2</i>	Methyl-CpG binding protein 2	ENSG00000169057	Rett syndrome	Motor	Y	Y
<i>NEUROD2</i>	Neuronal differentiation 2	ENSG00000171532		Motor	Y	Y
<i>PIK3CA</i>	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	ENSG00000121879	CLOVE syndrome: congenital lipomatous overgrowth vascular malformations, and epidermal nevi	Motor	Y	NA
<i>PHF6</i>	PHD finger protein 6	ENSG00000156531	Borjeson-Forsman-Lehmann syndrome	Motor	Y	Y
<i>PYCR1</i>	Pyrroline-5-carboxylate reductase 1	ENSG00000183010	Cutis laxa autosomal recessive type IIb	Motor	Y	Y
<i>SETD5</i>	SET domain-containing 5	ENSG00000168137	Cornelia de Lange syndrome	Motor	Y	Y
<i>TRRAP</i>	Transformation/transcription domain-associated protein	ENSG00000196367		Motor	NA	NA
<i>WAC</i>	WW domain-containing adaptor with coiled-coil	ENSG00000095787	Desanto-Shinawi syndrome	Non-motor	Y	Y
<i>WNT10A</i>	Wnt family member 10A	ENSG00000135925	Schopf-Schulz-Passarge syndrome	Motor	NA	NA
<i>WWOX</i>	WW domain-containing oxidoreductase	ENSG00000186153	Epileptic encephalopathy early infantile 28	Non-motor	NA	NA

Abbreviation:

CAUSES-ID = Clinical Assessment of the Utility of Sequencing and Evaluation as a Service-intellectual disability

The co-occurrence of strabismus and motor control defect suggests involvement of cerebellum. How the cerebellum controls movement is still poorly understood, but it is known to contribute to control of both the oculomotor systems and tone.<sup>13,14</sup> Experimental lesions of the cerebellar dorsal vermis in monkeys led to esodeviation and impaired vergence adaptation, and GABA<sub>A</sub> agonist inactivation of the fastigial nucleus or interposed nucleus of the cerebellum results in impaired vergence responses in monkeys. These observations suggest that the cerebellum is important for the maintenance of proper eye alignment.<sup>15</sup> It has been shown that ablation of the cerebellum results in hypotonia in monkeys, supporting the role of cerebellar defect in hypotonia.<sup>14</sup> The absence of specific peripheral neuromuscular signs and the presence of cognitive disability in almost all the probands in the CAUSES-ID series suggest that hypotonia is centrally mediated for these individuals.<sup>16</sup>

The examination of cerebellar hypoplasia provides further evidence of the cerebellum's role in controlling eye movements and tone. Cerebellar hypoplasia is an uncommon report in children presenting to a pediatric neurologist (0.5%).<sup>17</sup> The rates of visual signs (strabismus, abnormal eye movements, or nystagmus) and hypotonia are both statistically higher in patients with cerebellar hypoplasia than controls (40% versus 7% and 49% versus 13% respectively), who underwent magnetic resonance imaging for

similar clinical features but turned out not to have cerebellar hypoplasia.<sup>17</sup>

The examination of the genes in diagnosed CAUSES-ID-strabismus probands underscores the association between strabismus and motor control defects: 74% of these genes have been associated with both strabismus and motor control defects. Owing to the small size of the gene set, only high-level biological processes could be linked, indicating a tentative link with chromosomal organization and transcription processes. Higher resolution in reported phenotypes could allow a more accurate estimation of the co-occurrence between different phenotypes and the identification of a larger and more robust set of genes corresponding to ID-strabismus-motor-defect probands. In combination with functional assays, future studies might illustrate how this group of genes affects cerebellar development and if it affects different biological processes compared with ID without strabismus.

Our replicated observation of an association between strabismus and hypotonia in ID across different data sources could suggest a common underlying mechanism or pathway contributing to both strabismus and hypotonia. We propose a role for the cerebellum in both strabismus and hypotonia. As global developmental delay often precedes ID, ophthalmologic screening should be undertaken for all children with global developmental delay, as recommended by the American Academy of Neurology, which may prevent visual deterioration due to untreated strabismus.<sup>18</sup> The clinical presentations and management may not be distinguishable, whereas the investigation of possible cerebellar involvement in strabismus may help clinicians and researchers better understand the etiology and prognosis, particularly within subgroups of patients affected by ID.

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### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pediatrneurol.2019.04.002>.

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