These selected examples of the COs highlight the need for greater allocation of resources to areas of disproportionately low levels of evidence in child psychiatry research. The aim of our study was to shed light on research gaps within the current AACAP PPs as the organization moves toward development of CPGs. Increasing the knowledge base surrounding these lower quality recommendations will provide valuable insight for health care professionals to optimally serve their patients, but will require extensive resources. We suggest that the AACAP provide more feedback in their CPGs that is directed toward investigators and funding agencies, such as the National Institute of Mental Health. We believe that feedback will help to guide and encourage the gold standards of evidence-based medicine.

Although we used both ClinicalTrials.gov and ICTRP, which is regarded as a comprehensive method of locating ongoing research, a possible limitation of our research is that our searches did not locate studies that may have been relevant to this investigation.[5]

Kia Golmoradi, BS
Jake X. Checketts, BS
Gretchan Moore, BS
Matt Vassar, PhD
Tara R. Buck, MD

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Ms. Golmoradi, Mr. Checketts, Ms. Moore, and Dr. Vassar are with Oklahoma State University Center for Health Sciences. Dr. Buck is with the University of Oklahoma School of Community Medicine.

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Correspondence to Jake X. Checketts, BS: jake.checketts@okstate.edu

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Catatonia in Children and Adolescents: A High Rate of Genetic Conditions

To the Editor:

Pediatric catatonia is a rare and severe neuropsychiatric syndrome. We previously reported, in 58 children and adolescents with catatonia, a high prevalence (up to 20%) of medical conditions, some of which have specific treatments.[1] Here we extend the cohort inclusion and report the first systematic molecular genetic data for this syndrome. Among the 89 patients consecutively admitted for catatonia (according to the pediatric catatonia rating scale)[2] between 1993 and 2014, we identify 51 patients (57.3%) who had genetic laboratory testing, of whom 37 had single nucleotide polymorphism (SNP) microarray tests for Copy Number Variants (CNVs) and 14 had routine genetic explorations (karyotyping and searches for specific chromosomal abnormalities by fluorescence in situ hybridization [FISH]) or a specific diagnosis test based on clinical history. To assess the causality of observed genetic findings in each patient, we used a causality assessment score (CAUS)[3] including 5 causality-support criteria on a 3-point scale (0 = absent; 1 = moderate; 2 = high): the existence of similar cases in the literature; the presence of a clinical contributing factor; the presence of a biological contributing factor; the presence of other paraclinical symptoms; and response to a specific treatment related to the suspected genetic or medical condition.

In total, 19 patients (21.3%) had a genetic condition. Table 1[4-80] shows the rating for each CAUS item. Fifteen patients (16.9%) had a genetic condition judged likely to have contributed to the catatonia syndrome (CAUS $\geq$5): 5 single-gene conditions (Huntington disease, fatal familial insomnia (FFI), *PRODH* mutations, Kleefstra syndrome, and Sanfilippo syndrome); 4 metabolic conditions of unknown origin (low serotonin level in the cerebrospinal fluid [n = 2], creatine deficit, storage disease); one cytogenetic abnormality (Down syndrome); and 5 CNVs with a plausible mechanistic relationship to the presentation (22q13.3 deletion including the SHANK3 gene, 16p13 duplication, 8p23.3 deletion of the end of DLGAP2, and all of CLN8, 2q22.1 deletion, and

TABLE 1 Genetic Risk Factors (N = 19) in a Prospective Series of Children and Adolescents With Catatonia (N = 89): Clinical, Paraclinical, and Therapeutic Arguments for Causal Assessment Score (CAUS)

				CAUS Item Scores					
Diagnosis	**Sex**	**Age (y)**	**Psychiatric Diagnosis**	**References[a]**	**Clinical**	**Biological**	**Other Laboratory Evaluations**	**Therapeutic**	**To CAUS**
Single Genetic Conditions									
Huntington disease	M	16	SCZ	2 (4–9) Dystonia, behavioral disorder motor, cognitive, psychiatric symptoms	2 Family history, motor, cognitive, psychiatric symptoms	2 Affected mother elongated CAG repeat in huntingtin gene	2 MRI	0	8
Fatal familial insomnia	M	18	MDE	1 (10–14) Insomnia, dysautonomia, dysarthria, ataxia, myoclonus, extrapyramidal, pyramidal, ID bulbar symptoms, MDE, psychiatric symptoms: hallucination, aggression	2 Insomnia, dysautonomia, dysarthria, ataxia, myoclonus, MDE	2 PNRP D178N/129 mutation	2 Polysomnography, EEG	1 Worse with BZD and ECT	8
ProDH mutation	M	14	SCZ	1 (15–20) SCZ, ASD, ID, seizure; behavioral disorder	2 Behavioral disorder, SCZ, parental history of SCZ	2 ProDH mutation: 4 missense mutations (P406L, R431H, Q19P, R185W)	2 Hyperprolinemia	0	7
Sanfilippo	F	18	ASD, ID	2 (21–25) ASD, language delay, behavioral disorder, hyperactivity, aggressiveness, ID, dementia, disintegrative disorder, dysmorphia, bone and joint damage	2 ASD, behavioral disorder, hyperactivity, aggressiveness, ID, dementia,disintegrative disorder, dysmorphia, bone and joint damage	2 Molecular diagnosis	2 MRI, X-ray	0	8

(*continued*)

TABLE 1 Continued

Diagnosis	Sex	Age (y)	Psychiatric Diagnosis	CAUS Item Scores: References[a]	Clinical	Biological	Other Laboratory Evaluations	Therapeutic	To CAUS
Kleefstra syndrome	F	17	ASD, ID	2 (26) ID, dysmorphia, seizure, hypotonia, catatonia	2 ID, dysmorphia seizure, hypotonia	2 Exome sequencing: EHMT13b insertion in exon 24 Val1140 duplication CGH micro-array: balanced translocation 2–4	0	0	6
Metabolic Conditions of Unknown Origin									
Low serotonin level in CSF	M	17	SCZ, MDE	1 (27–31) MDE, ASD Impulsiveness, neurological disorders	1 MDE, Impulsiveness, tremor frontal and extrapyramidal syndrome, headache, facial paralysis, cerebellum syndrome,	2 5-HT deficit in the CSF	1 EEG	0	5
Low serotonin level in CSF	F	16	ASD, MDE	1 (27–31) ASD, MDE , impulsiveness, neurological disorders	1 ASD, MDE, impulsiveness, seizure	2 5-HT deficit in the CSF	1 EEG	0	5
Intracerebral creatine deficit	F	15	ASD, OCD	2 (32–35) ASD, language delay behavioral disorder, seizure, ID, motor dysfunction, extrapyramidal syndrome	1 ASD, seizure	2 In vitro diagnosis on fibroblast; increased urinary creatine	2 Spectro-MRI, EEG	2 Clinical improvement and Magnetic resonance spectroscopy normalization with creatine	9

(*continued*)

TABLE 1 Continued

Diagnosis	Sex	Age (y)	Psychiatric Diagnosis	CAUS Item Scores: References[a]	Clinical	Biological	Other Laboratory Evaluations	Therapeutic	To CAUS
Storage disease	M	16	SCZ	1 (36) Psychiatric symptoms	2 Splenomegaly, confusion, frontal signs, supranuclear paralysis, dysarthria	0 Molecular explorations refused by parents	2 Abdominal ultrasound	0	5
CNV and Chromosomal Abnormalities									
Down syndrome	M	19	ASD, ID, MDE	2 (37–41) ASD, ID, MDE, catatonia, dysmorphia	2 ASD, ID, MDE, dysmorphia	2 21 trisomy on karyotype	0	0	6
22q13.3 deletion	F	16	ID, BD	2 (42–48) ID, language impairment, periodic catatonia, minor dysmorphia	2 ID, periodic catatonia Minor dysmorphia	1 CGH-array Agilant 60Kb FISH: 55.9 Kb deletion *de novo* 22q13.3	0	0	5
16p13.1 duplication	M	16	ASD, SCZ, ADHD	2 (49–56) ASD, ID, SCZ, learning disability language impairment, ADHD, seizure	2 ASD, SCZ learning disability, ADHD	2 Human 610 Quad V1 /Illumina 1.16 Mb duplication 16p13.11 696 Kb duplication 2p22.3	0	0	6
8p23.3 deletion	M	17	SCZ	2 (57–63) ASD, SCZ, ID behavioral disorder; catatonia features described	2 SCZ, borderline intelligence; brother: ID carried same deletion	1 Human 610 quad V1 /Illumina 196 Kb deletion 8p23.3 (deletion of the 3′ end of DLGAP2 and all of CNL8)	0	0	5

(*continued*)

TABLE 1 Continued

Diagnosis	Sex	Age (y)	Psychiatric Diagnosis	CAUS Item Scores: References[a]	Clinical	Biological	Other Laboratory Evaluations	Therapeutic	To CAUS
2q22.1 deletion	M	19	ASD, ID	1 (64,65) ASD, ID, Dysmorphia	2 ASD, ID, dysmorphia, seizure, hyperlaxity	1 Illumina HumanCytoSNP-12 v2.1 132 Kb deletion 2q22.1, paternal transmission	1 EEG	0	5
13q33.1-34 deletion	F	14	ASD, ID, MDE	1 (66–75) ID, coagulation factor VII and X deficit, central nervous system anomalies, dysmorphia, dystonia	1 ID, coagulation factor VII and X deficit, dysmorphia, seizure	2 Illumina HumanCytoSNP-12 v2.1 4.7 Mb deletion 13q31–34 hemostatic Disorders	1 MRI	0	5
2q36 deletion	M	15	ASD, ID, SCZ	1 (76–79) ASD, ID, seizure	1 ASD, ID, seizure	2 Human 610 quad V1 /Illumina 1.9 Mb deletion 2q36, maternal transmission	0	0	4
Deletion exon 6 of PARKIN 2 + anti-NMDA receptor encephalitis	F	17	Mania	0	1 Malignant catatonia worsened by APA	2 DNA chips Human 610 Quad V1 /Illumina 106 kb deletion in the PARKIN 2 gene deleting exon 6	0	0	3
Xp22.33 duplication	M	19	ASD, ID	0 (80)	1 Seizure	1 Illumina HumanOmniExpress-24 v1 150 Kb duplication Xp22.33	0	0	2

(*continued*)

TABLE 1 Continued

Diagnosis	Sex	Age (y)	Psychiatric Diagnosis	CAUS Item Scores: References[a]	Clinical	Biological	Other Laboratory Evaluations	Therapeutic	To CAUS
21q21.1duplication 6q14 duplication Xq25 deletion	F	14	ID, BD	0	2 Family history: one sister with ASD + one sister with acute delirium	1 Illumina HumanCytoSNP-12 v2.1 134.9 Kb duplication 21q21.1 203.9 Kb duplication 6q14 180.3 Kb deletion Xq25	0	0	3

Note: ADHD = attention-deficit/hyperactivity disorder; APA = atypical antipsychotic; ASD = autism spectrum disorder; BD = bipolar disorder; BZD = benzodiazepines; CGH = comparative genomic hybridization; CSF = cerebrospinal fluid; ECT = electroconvulsive therapy; EEG = electroencephalography; F = female; FISH = fluorescence in situ hybridization; ID = intellectual disability; M = male; MDD = major depressive disorder; MDE = major depressive episode; MRI = magnetic resonance imaging; OCD = obsessive-compulsive disorder; SCZ = schizophrenia; 5-HT = 5-hydroxytryptamine (serotonin).

[a]*Numbers in parentheses in this column are references.*

13q33.1q34 deletion). Four patients had a CNV judged to have a questionable causal link with catatonia: maternally transmitted 2q36 deletion; deletion of exon 6 of PARK2 in a context of an anti-NMDA receptor encephalitis; Xp22.33 duplication; and three CNVs in one patient, namely Xq25 deletion, 2q21.1 deletion, and 6q14 duplication. We have reported these four additional CNVs with uncertain causal relationships to encourage further observations on possible neuropsychiatric clinical features (see Table S1, available online).

Clinicians who see patients with catatonia should be aware of the frequency of medical and particularly genetic disorders that are contributing to catatonia vulnerability. Some of these disorders are treatable (eg, creatine deficit),[32] resulting in better outcomes than from psychiatric treatment alone. On the other hand, clinicians who treat patients with genetically based neurodevelopmental syndromes should be aware that it can be difficult to diagnose catatonia in these patients because of the overlapping symptoms. Correct diagnosis of catatonia permits the clinician to offer patients-specific treatments (high-dose benzodiazepine; electroconvulsive therapy if benzodiazepines are ineffective)[1] that can reverse the severe acute deterioration that is typical of catatonia syndrome.

Marie Raffin, MD
Angele Consoli, MD, PhD
Marianna Giannitelli, MD, PhD
Anne Philippe, MD, PhD
Boris Keren, MD, PhD
Nicolas Bodeau, MS
Douglas F. Levinson, MD
David Cohen, MD, PhD
Claudine Laurent-Levinson, MD, PhD

Accepted May 9, 2018.

Drs. Raffin, Consoli, Giannitelli, Cohen, Laurent-Levinson, and Mr. Bodeau are with the Université Pierre et Marie Curie, Hôpital Pitié-Salpêtrière, Paris, France. Dr. Cohen is also with Institut des Systèmes Intelligents et Robotiques, Université Pierre et Marie Curie, Paris, France. Dr. Laurent-Levinson is also with Stanford University, CA. Dr. Philippe is with INSERM U1163, Institut Imagine, Université René Descartes, Paris, France. Dr. Keren is with La Pitié-Salpêtrière Hospital, Paris, France. Dr. Levinson is with Stanford University, CA.

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Correspondence to Marie Raffin, MD: marie.raffin@aphp.fr

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TABLE S1 Details About Nine Copy Number Variants

	Chromosome	Locus	Size (bp)	Location (GRCh37/hg19)
Deletion	22	22q13.3	55,933	51,122,392-51,178,324
Duplication	16	16p13.1	1,155,714	15,125,441-16,281,154
Deletion	8	8p23.23	187,299	1,578,073-1,765,371
Deletion	2	2q22.1	132,553	137,854,860-137,987,412
Duplication	13	13q33.1q34	6,349,922	104,220,115-110,570,036
Deletion	2	2q36	1,877,246	225,478,730-227,355,975
Deletion	6	6q25.2-q27	106,009	162,368,885-162,474,893
Duplication	X	Xp22.33	150,280	1,519,874-1,670,153
Duplication	21	21q21.1	134,914	22,142,748-22,277,661
Duplication	6	6q14.1	203,856	78,848,097-79,051,952
Deletion	X	Xq25	180,260	125,104,917-125,285,176