European Journal of Medical Genetics 59 (2016) 436–443

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Copy number variation analysis in adults with catatonia confirms haploinsufficiency of *SHANK3* as a predisposing factor

Jeroen Breckpot [a, 1], Marieke Vercruyssen [b, 1], Eddy Weyts [c], Sean Vandevoort [c], Greet D'Haenens [c], Griet Van Buggenhout [a], Lore Leempoels [b], Elise Brischoux-Boucher [d], Lionel Van Maldergem [d], Alessandra Renieri [e, f], Maria Antonietta Mencarelli [f], Carla D'Angelo [g], Veronica Mericq [h], Mariette J. Hoffer [i], Maithé Tauber [j], Catherine Molinas [j], Claudia Castiglioni [k], Nathalie Brison [a], Joris R. Vermeesch [a], Marina Danckaerts [b], Pascal Sienaert [b], Koenraad Devriendt [a], Annick Vogels [a, *]

[a] *Center for Human Genetics, Catholic University Leuven, Leuven, Belgium*
[b] *University Psychiatric Center KU Leuven, Catholic University of Leuven, Belgium*
[c] *St-Camillus Psychiatric Hospital, Bierbeek, Belgium*
[d] *Center for Human Genetics, Franche-Comté University, Besançon, France*
[e] *Medical Genetics, University of Siena, Policlinico Le Scotte, Siena, Italy*
[f] *Medical Genetics, Azienda University Hospital, Siena, Italy*
[g] *Human Genome and Stem Cell Center, University of Sao Paulo, Sao Paulo, Brazil*
[h] *Institute of Maternal and Child Research, Faculty of Medicine, University of Chile, Santiago, Chile*
[i] *Department of Clinical Genetics, Leiden University Medical Center, Leiden, The Netherlands*
[j] *Endocrinology Unit, Children's Hospital, CHU Toulouse, Reference Center for Prader-Willi Syndrome, INSERM UMR 1043, Paul Sabatier University, Toulouse, France*
[k] *Unit of Neurology, Department of Pediatric Neurology, Clínica las Condes, Santiago, Chile*

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
22 July 2016
Accepted 8 August 2016
Available online 9 August 2016

Keywords:
Catatonia
Psychiatric disorder
SHANK3
14q11.2 duplication
SUPT16H

ABSTRACT

Background: Catatonia is a motor dysregulation syndrome co-occurring with a variety of psychiatric and medical disorders. Response to treatment with benzodiazepines and electroconvulsive therapy suggests a neurobiological background. The genetic etiology however remains largely unexplored. Copy Number Variants (CNV), known to predispose to neurodevelopmental disorders, may play a role in the etiology of catatonia.

Methods: This study is exploring the genetic field of catatonia through CNV analysis in a cohort of psychiatric patients featuring intellectual disability and catatonia. Fifteen adults admitted to a psychiatric inpatient unit and diagnosed with catatonia were selected for array Comparative Genomic Hybridization analysis at 200 kb resolution. We introduced a CNV interpretation algorithm to define detected CNVs as benign, unclassified, likely pathogenic or causal with regard to catatonia.

Results: Co-morbid psychiatric diagnoses in these patients were autism, psychotic or mood disorders. Eight patients were found to carry rare CNVs, which could not be classified as benign, comprising 6 duplications and 2 deletions. Microdeletions on 22q13.3, considered causal for catatonia, were detected in 2 patients. Duplications on 16p11.2 and 22q11.2 were previously implicated in psychiatric disorders, but not in catatonia, and were therefore considered likely pathogenic. Driven by the identification of a rare 14q11.2 duplication in one catatonic patient, additional patients with overlapping duplications were gathered to delineate a novel susceptibility locus for intellectual disability and psychiatric disorders on 14q11.2, harboring the gene *SUPT16H*. Three remaining variants respectively on 2q36.1, 16p13.13 and 17p13.3 were considered variants of unknown significance.

Conclusion: The identification of catatonia-related copy number changes in this study, underscores the importance of genetic research in patients with catatonia. We confirmed that 22q13.3 deletions, affecting

* Corresponding author. Center for Human Genetics, Catholic University Leuven, Herestraat 49, B-3000, Leuven, Belgium.
E-mail addresses: molinas.c@chu-toulouse.fr (C. Molinas), annick.vogels@uzleuven.be (A. Vogels).
[1] Joint first authors.

http://dx.doi.org/10.1016/j.ejmg.2016.08.003

the gene *SHANK3*, predispose to catatonia, and we uncover 14q11.2 duplications as a novel susceptibility factor for intellectual and psychiatric disorders.

1. Introduction

Catatonia is a motor dysregulation syndrome characterized by alternation of excessive and reduced mobility, often in association with speech abnormalities. It should be considered in any patient with marked deterioration in psychomotor function and overall responsiveness (movement, speech, self-care, skills). Prevalence estimates of catatonia among psychiatric patients range from 7.6 to 38% (Fink, 2009; Taylor and Fink, 2003). Although common and severe, catatonia remains poorly recognized. There have been efforts to enhance early diagnosis, as reflected by changes in catatonia classification in DSM-5, where it appears as a distinct clinical-diagnostic entity (Tandon et al., 2013). A clinical diagnosis of catatonia is based on the presence of at least 3 of the following DSM-5 criteria: catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypy, grimacing, echolalia or echopraxia. Symptoms may present in different combinations and co-occur with a variety of other psychiatric or medical conditions (Daniels, 2009). This clinical heterogeneity hampers early recognition and treatment, which are important as catatonia is sometimes associated with autonomic symptoms, that can be life threatening.

Regardless of the comorbid pathology, there is a unique response to treatment with benzodiazepines, zolpidem and electroconvulsive therapy (ECT), suggesting a biological etiology separate from other psychiatric disorders (Dhossche et al., 2010; Javelot et al., 2015). Benzodiazepines and ECT are agonists of the inhibitory function of the GABA-A receptor complex. Their therapeutic effect on catatonia suggests a dysfunctional neurotransmission as the underlying neurobiological mechanism. A possible genetic etiology underlying disrupted synaptic transmission in the development of catatonia, is supported by the occurrence of catatonic symptoms in patients with Prader-Willi Syndrome (PWS) (Dhossche and Bouman, 1997; Poser and Trutia, 2015). PWS is caused by the lack of expression of genes on the paternally derived 15q11q13 chromosomal segment, including a set of genes coding for particular subunits of the $GABA_A$ receptor, namely *GABRB3, GABRA5* and *GABRG3*, which encode the β3, α5, and γ3 subunits, respectively (Coghlan et al., 2012). This has led to the assumption that altered inhibitory GABAergic neurotransmission may underlay catatonia in PWS (Dhossche et al., 2005). In addition to this GABAergic hypothesis, excess glutamate or hyperactivity of glutamate receptors such as the N-Methyl-D-Aspartate receptor (NMDAR), seem to be involved as well, as catatonic symptoms in selected cases resolve by treatment with the NMDA antagonist Amantadine (Northoff et al., 1999). The beneficial effects of NMDA antagonists on catatonia are ascribed to recovery of GABA-A function in brain regions that were previously GABA-A deficient due to NMDA hyperactivity (Carroll et al., 2007).

Despite the evidence of a role of disturbed neurotransmission involving different synaptic receptors, studies on the genetic etiology of catatonia are scarce. Three studies reported familial transmission with anticipation and parent-of-origin effect in periodic catatonia (Beckmann et al., 1996; Stober et al., 1995, 1998). The same research group reported linkage of periodic catatonia to 15q15 and 22q13 (Stober et al., 2000). Whereas the causative gene for catatonia on 15q15 remains obscure, catatonia related to 22q13 has been attributed to loss of one functional copy of the *SHANK3* gene, as loss-of-function mutations and deletions affecting this gene were found in catatonic patients with intellectual disability and comorbid psychiatric disease (Serret et al., 2015). In addition, catatonia has been recurrently found in association with Down syndrome (Ghaziuddin et al., 2015) and the 22q11 deletion syndrome (Faedda et al., 2015).

More recent genomic technologies such as chromosomal microarray and massive parallel sequencing may help to identify other chromosomal regions and genes playing a role in the etiology of this motor dysregulation disorder. In this study, we performed copy number analysis in 15 adults with intellectual disability and catatonia to identify chromosomal deletions and duplications predisposing to this psychiatric disorder.

2. Materials and methods

2.1. Patients

From January 2005 until January 2015, 283 adult psychiatric patients with intellectual disability were recruited from an inpatient unit in the St-Camillus Psychiatric Hospital in Bierbeek, Belgium, for clinical and psychiatric evaluation. During psychiatric hospitalization, 15 out of these 283 adults were clinically diagnosed with catatonia. Diagnosis was made by a psychiatrist and an educational psychologist with expertise in intellectual disability. Medical files were analyzed retrospectively to collect data on their medical history, cognitive functioning and psychiatric comorbid diagnosis, and to score catatonia based on DSM-5 criteria. Because of the unique response of catatonia to treatment with benzodiazepines, such as lorazepam, benzodiazepine-like products such as zolpidem, and/or electroconvulsive therapy, response to such treatment was added as an additional criterion, favoring the diagnosis of catatonia. For all patients, a genome-wide screen for copy number alterations was performed by array comparative genomic hybridization.

The study was approved by the ethical committee at the University Hospitals Leuven. Appropriate informed consent was obtained from all participating patients or their legal representatives.

2.2. Array comparative genomic hybridization (array CGH)

Genomic DNA was extracted from peripheral leukocytes of EDTA-treated blood according to standard procedure guidelines. Array CGH was carried out using the Oxford Gene Technology (OGT) CytoSure™ ISCA oligoarray set (Oxford Gene Technology, Oxford, UK) containing 180k DNA oligonucleotides with a minimum resolution of 200 kb. Microarray hybridization and copy number variant (CNV) analysis were performed according the manufacturer's instructions. All genome coordinates were according to NCBI human genome build 37 (hg19, February 2009).

2.3. Copy number variant (CNV) interpretation algorithm

We introduced an algorithm to classify detected CNVs as benign, unclassified, likely pathogenic or causal for catatonia (Supplementary Fig. 1). (1) A CNV was considered causal, either

Table 1
Molecular and clinical data from patients 1 to 8. A rare CNV, which was not classified as benign, was identified in these patients. Abbreviations: del: deletion, dup: duplication, ECT: electroconvulsive therapy; F: female, M: male, IQ: intelligence quotient (FSIQ, PIQ and VIQ: full scale, performance and verbal IQ).

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender	F	F	M	**F**	M	M	M	M
Region	22q13.33del	22q13.33del	2q36.1dup	16p11.2dup	22q11.21dup	14q11.2dup	16p13.13dup	17p13.3dup
Range (hg19)	51,123,497	51,123,497	223,297,323	29,592,791	18,661,699	21,567,757	12,254,805	1,492,408
	–51,220,923	–51,220,923	–223,565,371	–30,193,606	–21,661,435	–21,856,165	–12,892,529	–1,576,184
Size	97 kb	97 kb	268 kb	600 kb	3 Mb	289 kb	638 kb	84 kb
Inheritance	de novo	unknown	unknown	unknown	unknown	unknown	unknown	unknown
Classification	pathogenic	pathogenic	unknown	likely pathogenic	likely pathogenic	likely pathogenic	unknown	unknown
Clinical diagnosis	no	no	**trisomy 21**	no	no	no	no	no
Dysmorphic features	low anterior hairline, long fingers	micrognathia, mild facial asymmetry	facial stigmata of Down syndrome	brachycephaly, relative macrocrania, hypertelorism, broad face, wide mouth, double hair whorl	/	long, hypotonic face, ptosis, relative macrocrania	long face, protruding ears, pointed chin, pectus excavatum	long and small face, big ears, hypotonic face, drooling
Other disease	no	no	Graves' disease	dolichocolon	sarcoidosis	scoliosis	neonatal hypoxia	no
Neurology	cerebral and cerebellar atrophy, postoperative seizure	post-ECT seizures	normal	neuro-syphilis, epilepsy, parkinsonism, acoustic neuroma left	epilepsy, unilateral facial palsy	epilepsy	normal	post-ECT seizures
Comorbid psychiatric diagnosis (ICD-10)	unspecified nonorganic psychosis, autistic behavior	unspecified nonorganic psychosis, pervasive developmental disorder	unspecified nonorganic psychosis, unspecified mood disorder	schizophrenia	schizophrenia	schizophrenia	unspecified nonorganic psychosis	unspecified nonorganic psychosis
Intellectual disability	profound FSIQ: 19 PIQ: 15 VIQ: 23	severe FSIQ: 39	severe IQ 30-40	moderate IQ 55	mild	moderate FSIQ: 41 PIQ: 45 VIQ: 36	moderate	mild FSIQ: 72 PIQ: 66 VIQ: 82

when this CNV was completely overlapping with chromosomal syndromes known to cause catatonia, or when this CNV was harboring catatonia-related genes known to be dosage sensitive. (2) CNVs were considered likely pathogenic, when the CNV affects genes or the critical region of a chromosomal syndrome known to be implicated in intellectual disability or psychiatric disease, but not in catatonia. A list of known chromosomal syndromes and genes, related to intellectual disability and psychiatric disease is based on an internal database, and is available upon request. (3) CNVs affecting regions smaller than 200 kb and not fulfilling the criteria under (1) or (2) were discarded from further analysis. (4) CNVs known to be prevalent in more than 1% of the normal population (based on a local database with over 7000 individuals), were considered benign. (5) All remaining rare CNVs were considered variants of unknown significance, and were further evaluated, based on gene content (OMIM, literature), inheritance and phenotype correlations with similar chromosomal variants, reported in literature or in publicly available databases, such as DECIPHER or the database of genomic variants. Parents were tested when available to determine the inheritance of causal chromosomal imbalances and rare CNVs of unknown significance.

3. Results

Fifteen patients (12 males, 3 females) clinically diagnosed with catatonia were selected among 283 intellectually disabled psychiatric adults from a single inpatient psychiatric unit. Array CGH results and clinical descriptions, including response to treatment, are presented in Table 1, Table 2 and Supplementary Table 1. Intellectual disability ranged from mild to severe. The age of the patients ranged from 29 to 63 years. Ten patients responded to lorazepam, zolpidem or ECT. Three adults with predominant psychotic symptoms (patient 6, 12 and 13) were treated with clozapine, which is known to be incompatible with concomitant use of lorazepam. Two patients (patients 9 and 14) did not receive any of these treatments.

No clinical genetic diagnosis could be established in any of these patients, except for patient 3, who was diagnosed with Down syndrome, confirmed by fluorescence *in situ* hybridization. Array CGH analysis in this male was performed, to ensure that no additional CNVs, causing or aggravating catatonia, were present. CNVs were classified in accordance with our CNV interpretation algorithm discussed above. Seven patients (47%) were found to carry only benign CNVs (Supplementary Table 1). In the remaining 8 patients (53%), one trisomy 21 and 8 rare submicroscopic imbalances, which could not be classified as benign, were detected. Three of these variants were established predisposing factors for catatonia: 22q13.3 deletions including the *SHANK3* gene in patients 1 and 2, and trisomy 21 in patient 3 were considered causal (Ghaziuddin et al., 2015; Serret et al., 2015). In patients 4 and 5, duplications on 16p11.2 and 22q11.2 were identified. These are known susceptibility loci for psychiatric pathologies and intellectual disability (Fernandez et al., 2010; Lo-Castro et al., 2009; Shinawi et al., 2010; Szatkiewicz et al., 2014; Wentzel et al., 2008), but they have not previously been linked to catatonia. We therefore considered them as likely pathogenic. The remaining 4 CNVs detected were rare duplications of unknown significance, affecting regions on 2q36.1, 14q11.2, 16p13.13 and 17p13.3. These duplications have hitherto not been described as predisposing factors for intellectual disability nor for psychiatric

Table 2
DSM-5 criteria for the diagnosis of catatonia in the included patients and response to treatment (RTT). Catatonia was diagnosed, based on at least 3 of the following symptoms: catalepsy, waxy flexibility, stupor, agitation, mutism, negativism, posturing, mannerisms, stereotypy, grimacing, echolalia or echopraxia. Response to treatment (RTT): benzodiazepine (lorazepam (LZP)), zolpidem (ZPD), or electroconvulsive therapy (ECT). Three adults with predominant psychotic symptoms (patient 6, 12 and 13) were treated with clozapine.

	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15
Catalepsy			x				x		x						x	
Waxy flexibility	x				x											
Stupor	x		x	x		x	x	x	x						x	x
Agitation	x		x	x		x		x		x		x	x	x		x
Mutism				x		x	x		x	x		x	x	x	x	x
Negativism				x			x	x	x	x		x				x
Posturing	x				x		x	x		x						x
Mannerisms	x				x						x					
Sterotypies					x	x	x			x	x		x		x	
Grimacing						x		x	x	x						x
Echolalia					x					x						
Echopraxia	x							x								
Other	staring rigidity		staring	rigidity ambitendence perseveration resistance tremor		ambidentence perseveration automatic obedience mitgehen autonomous symptoms	perseve-ration, pillow sign		rigidity, perseve-ration automatic obedience, mitgehen, autonomous symptoms		perseve-ration	perseveration, mitgehen, tics		ambi-tendence	rigidity	pillow sign
RTT	LZP	ECT[a]	LZP	ECT	LZP	ECT	CZP	LZP	ECT	/	LZP	ZPD	CZP	CZP	/	LZP

[a] treatment with LZP was applied during the first catatonic episode in patient 1, ECT during the second catatonic event.

disorders, and were subjected to a literature search. The 22q13.3 deletion in patient 1 occurred *de novo*. For the remaining patients, no parental samples to define inheritance were available.

Patient 3, who was clinically diagnosed with Down syndrome, carried a 268 kb duplication on 2q36.1 in addition to trisomy 21. This region was not reported as polymorphic in our locally curated CNV database, nor in the Database of Genomic Variants. An overlapping duplication was detected in one DECIPHER patient (DECIPHER 287451), who presented psychiatric problems, motor delay and seizures, and who was found to carry 2 additional duplications of unknown significance on 19q13. None of the duplicated genes within this 2q36.1 region have been linked to psychiatric pathology previously. Therefore, it is currently unclear if this variant may have caused or aggravated the psychiatric pathology or catatonia in this patient. A similar observation was made for patient 7, who carries a 289 kb duplication on 16p13.13p13.12. Although an identical duplication was found in our local database in a patient (DECIPHER 288002) with autism, learning disabilities and short stature, this region has not been linked to psychiatric or developmental disorders in any other patient. The duplication on 17p13.3, which was detected in patient 8, encompassed *SLC43A2, SCARF1, RILP* and *PRPF8*. Duplications on 17p13 affecting *YWHAE, CRK* and/or *LIS1* (*PAFAH1B1*), are known susceptibility factors for intellectual disability, hypotonia, autism, behavioral problems, brain malformations, facial dysmorphic features, and hand or feet anomalies (Bruno et al., 2010; Curry et al., 2013). The current duplication did however not affect these genes. Moreover, this duplication partially overlapped with copy number gains in the normal population (Coe et al., 2014; Cooper et al., 2011). Therefore, this variant was considered unclassified, rather than likely pathogenic.

Finally, patient 6 was found to carry a 288 kb duplication on 14q11.2. This duplicated region (chr14: 21,567,757–21,856,165) has hitherto not been reported in normal controls in the Database of Genomic Variants, nor in our locally curated database. Excluding CNVs larger than 5 Mb in size, thirteen additional patients with overlapping duplications were retrieved from literature and DECIPHER. Parental analysis of the duplication could not be established for the index patient, neither for five additional patients with 14q11.2 duplications. The duplication occurred *de novo* in five and was maternally inherited in three patients. Clinical details were obtained from 8 patients, including three previously reported patients (D'Angelo et al., 2013; Smyk et al., 2016; Vuillaume et al., 2014) and 5 patients reported in DECIPHER (DECIPHER 289620, 289709, 277175, 27947 and 256272). A clinical and molecular overview is depicted in Table 3 and Fig. 1. Supplementary Table 2 features the remaining five DECIPHER patients, from whom limited (DECIPHER 284790, 287656 and 258497) or no clinical data (DECIPHER 322324 and 292187) could be retrieved. Excluding the latter two, all patients presented with either intellectual disability or behavioral/psychiatric disorders. Therefore, as per our CNV interpretation algorithm, this 14q11.2 duplication was considered causal for the delayed development, and likely pathogenic for the catatonic episode in patient 6.

4. Discussion

Rare CNVs which could not be classified as benign according the CNV interpretation algorithm for catatonia, were detected in 8 out of 15 intellectually disabled patients with catatonia and comorbid psychiatric disease (53%). In 3 out of 15 patients (20%), the genetic etiology of catatonia was established: patients 1 and 2 were diagnosed with a 22q13.3 deletion, causing Phelan-McDermid syndrome, and patient 3 with trisomy 21.

SHANK3 has been identified as the critical gene in neurological and behavioral aspects of Phelan-McDermid syndrome (Phelan and

Table 3
Molecular and clinical overview of 14q11.2 duplications. L: length, ID: intellectual disability, NA: not available, OCD: obsessive compulsive disorder, OFC: occipital-frontal circumference, W: weight. α: father with aggressive behavior, mother with mild ID: one brother with mild ID, psychopathic behavior and paranoid schizophrenia, one brother died neonatally from seizures, and one brother with psychopathic behavior. Segregation analysis refused. B: foster child – no parental data available: one brother with mild ID, one sister with psychiatric disorder, one healthy sister with normal IQ.

Decipher ID	Patient 6	D'Angelo et al. Decipher 258583	Vuillaume et al.	Decipher 289709	Smyk et al.	Decipher 277175	Decipher 279249	Decipher 289620	Decipher 256272
Gender	M	M	M	M	M	F	F	M	M
Age	50 y	4.3 y	13y 8mo	22 y	8 y	9 y	4 y	53 y	6 y
14q11.2 dup (hg19)	21,567,757 −21,856,165	21,244,696 −22,250,879	21,424,185 −22,299,149	21,469,875 −21,952,439	21,507,092 −21,952,439	21,530,059 −22,022,116	21,762,802 −21,927,271	21,819,565 −22,003,106	21,697,792 −21,771,482
Size (kb)	288 kb	1.01 Mb	874 kb	482 kb	445 kb	492 kb	165 kb	183 kb	74 kb
Inheritance	unknown[α]	**de novo**	mat	**de novo**	**de novo**	unknown	**de novo**	unknown[β]	mat
Array platform	OGT 180k	Affymetrix 100k	Agilent 44k	OGT 180k	8 × 60k OGT	Affymetrix 250k	Agilent 180k	OGT 180k	Agilent 44k
Facial dysmorphism	long, hypotonic face, ptosis, relative macrocrania	brachycephaly, narrow forehead, low anterior hairline, strabismus, arched eyebrows, synophrys, thin upper lip, low-set ears, microdontia, extra nipples	NA	deep-set eyes, synophrys, short palpebral fissures, short philtrum, small dysplastic ears	flat face, micrognathia, epicanthic folds, short nose, broad nasal bridge, low set ears, wide mouth, tented upper lip, extra nipple	narrow forehead, inverted mouth, small teeth, small, posteriorly rotated ears, short neck	thin upper lip	straight eyebrows	brachycephaly, prognatism, facial asymmetry
Behavioral or psychiatric problems	schizophrenia catatonia	aggression, mild hyperphagia	hyperphagia, behavioral problems	hyperphagia, aggression, sexual disinhibition	behavioral problems, ADHD	ADHD, impulsivity, aggression, still tantrums, OCD	normal	autism, aggression	aggression, hyperactivity
Development	moderate ID	severe ID	ID	mild ID	ID	severe ID	moderate ID	moderate ID	ID
Neurology	normal	neonatal hypotonia	NA	normal	normal	epilepsy	normal	epilepsy	normal
Other anomalies	scoliosis	hypogonadism, small penis, cryptorchidism, small feet	NA	hypogonadism, morbid obesity	feeding difficulties hypothyroidism	hyperphagia, hypothyroidism, strabism, pectus excavatum	brachydactyly, feet in varus position, stiff left ankle, myopia	short toes IV-V	Dent disease (X-linked recessive, OMIM 300009); genu varum
Growth parameters	W: 10th centile L: 10–25th centile OFC: 90th centile	W: >95th centile L: <3rd centile OFC: <3rd centile	obesity	W: >95th centile L: 10th centile OFC: 10th centile	L: 25th centile OFC: 75th centile	W: 97th centile L: 10th centile OFC: 5th centile	W: 25th centile L: <3rd centile OFC: <3rd centile	W: 10th centile L: 3rd centile OFC: 3rd centile	W: <3rd centile L: <3rd centile OFC: <3rd centile
Genes	SUPT16H	SUPT16H, CHD8	SUPT16H, CHD8	SUPT16H, CHD8	SUPT16H, CHD8	SUPT16H, CHD8	SUPT16H, CHD8	SUPT16H, CHD8	HNRNPC

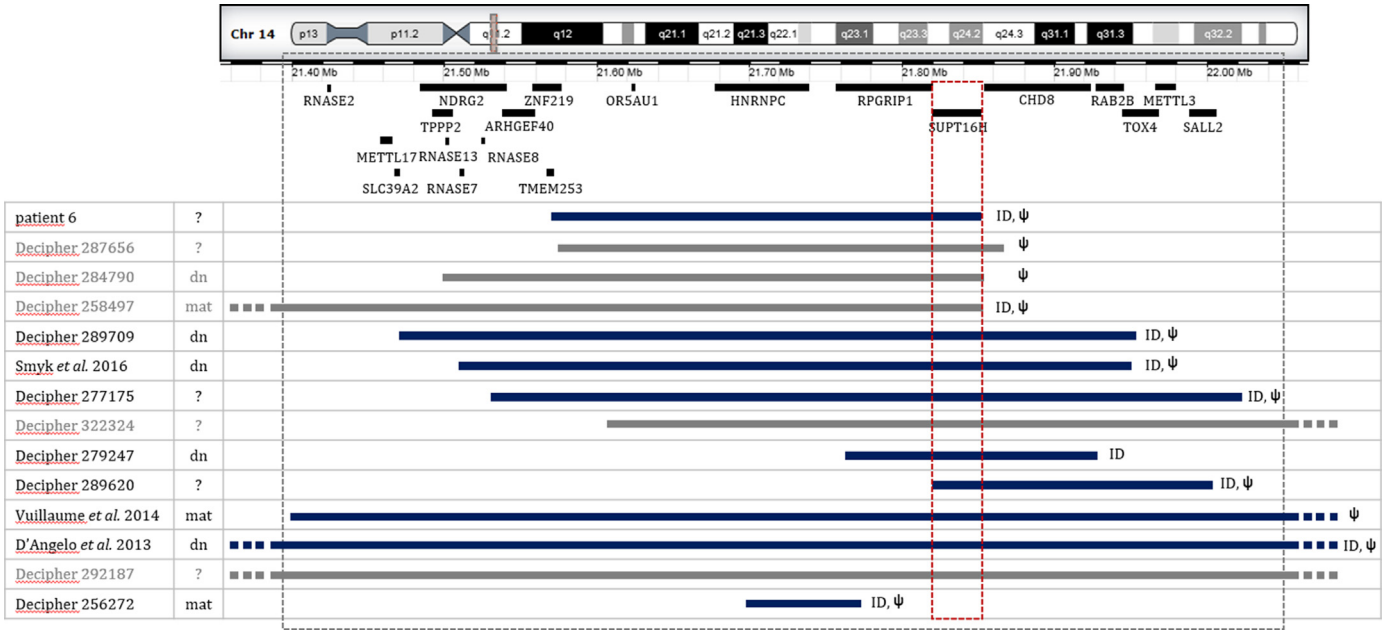

Fig. 1. Molecular overview of 14q11.2 duplications, identified in patient 6 and in additional patients retrieved from literature or DECIPHER. Blue bars depict the duplicated regions in well-phenotyped patients. Grey bars present duplications in patients from whom limited (DECIPHER 284790, 287656 and 258497) or no clinical data (DECIPHER 322324 and 292187) could be retrieved. The red box delineates the minimal region of overlap, excluding the duplication in DECIPHER patient 256272. Abbreviations: dn: *de novo*, mat: maternally inherited, ?: unknown inheritance, ID: intellectual disability, φ: psychiatric or behavioral disorder.

McDermid, 2012). Loss of SHANK3 function can be caused either by chromosomal loss on 22q13.3 or by smaller intragenic deletions or point mutations (Durand et al., 2007). Patients 1 and 2 both carry an identical 97 kb deletion, partially affecting *SHANK3*. Similar deletions have been reported in DECIPHER patients with Phelan-McDermid syndrome. SHANK3 is a scaffolding protein, enriched in the postsynaptic glutamatergic excitatory synapses and interacting with various synaptic molecules. A major interaction partner of SHANK3 is the NMDAR complex (Duffney et al., 2013), well known for its role in anti-NMDAR-encephalitis. Interestingly, this non-infectious encephalitis has specific clinical features compatible with catatonia like catalepsy, stupor, mutism, posturing and stereotypical movements (Dhossche et al., 2011; Kramina et al., 2015). This suggests dysfunction of the postsynaptic NMDAR-SHANK3 unit in at least some of the catatonic patients. The NMDAR is widely expressed both in excitatory glutamatergic and inhibitory GABAergic neurons throughout the brain. GABA-A agonists quickly alleviate catatonic symptoms in most patients, indicating that dysregulation of this neurotransmitter system is involved in catatonia as well. It was hypothesized that catatonic symptoms in anti-NMDAR-encephalitis may arise from NMDAR hyperfunction causing dysregulation of the GABA-A function (Daniels, 2009; Inta et al., 2015). Besides its role in postsynaptic density, it was found that SHANK3 may function to enrich hyperpolarization-activated cyclic nucleotide-gated (HCN) channels at the postsynaptic sites. The current produced by HCN channels is known as I(h) and plays a key role in controlling rhythmic activity of spontaneously firing neurons (Azene et al., 2003; Biel et al., 2009). Loss of SHANK3 function selectively and severely impairs I(h) currents during neuronal development (Yi et al., 2016). External lithium has a positive effect on HCN gating by producing depolarizing activation shift of these channels (Azene et al., 2003). This may be an explanation for the positive effect of lithium on catatonia-like deterioration previously described in two patients with *SHANK3* deletions (Serret et al., 2015).

Trisomy 21 was diagnosed in one catatonic male, patient 3. This chromosomal disorder has been described in association with catatonia in 7 patients (Ghaziuddin et al., 2015; Jap and Ghaziuddin, 2011; Torr and D'Abrera, 2014). The neurobiological mechanism underlying catatonia in Down syndrome is yet unknown and no candidate genes have been described until now.

The duplications on 16p11.2 and 22q11.2, detected in patient 4 and 5 respectively, are known susceptibility loci for psychiatric pathologies and intellectual disability, but not for catatonia. Although catatonia commonly co-occurs with psychiatric conditions, we cannot deduce unequivocally that CNVs that predispose to psychiatric or intellectual disorders, can also provoke catatonia. Therefore, these duplications were considered likely pathogenic, rather than causal for catatonia in these patients. Awareness of catatonic events in patients carrying similar duplications, as well as systematic CNV studies in other catatonia cohorts, are required to confirm that duplications on 22q11.2 and 16p11.2 can indeed cause catatonia.

The duplications on 2q36.1, 16p13.13 and 17p13.3 were considered variants of unknown significance, since no sufficient data could be retrieved to link these CNVs or the duplicated genes within these regions, to either catatonia or to psychiatric disorders or intellectual disability. Unfortunately, as for most of the patients included in this study, no parental samples could be retrieved to test inheritance. The absence of parental DNA is a common constraint for genetic studies in institutionalized adult patients, and obviously complicates CNV interpretation.

The 14q11.2 duplication in patient 6 has not been linked to catatonia previously. A literature search revealed thirteen additional patients with partially overlapping duplications, sized less than 5 Mb. Intellectual disability or psychiatric/behavioral disorders were present in all patients for which clinical details could be retrieved. The frequent *de novo* occurrence of 14q11.2 duplications (5 out of 8 probands) alludes to a reduced reproductive fitness associated with this genotype. This is in line with the finding that such duplications have not been described in CNV studies in normal controls. All duplication breakpoints were unique, advocating non-homologous end-joining as the underlying mutagenic mechanism. Disregarding the 74 kb duplication in DECIPHER patient 256272,

the smallest region of overlap comprises only the gene *SUPT16H,* which encodes a subunit of the 'facilitates chromatin transcription complex'. This complex acts as a histone chaperone to mediate mRNA elongation, DNA replication and DNA repair (Belotserkovskaya et al., 2003). 14q11.2 deletions, affecting *SUPT16H* and its neighboring gene *CHD8*, are recurrently associated with intellectual disability, autism and macrocephaly (Drabova et al., 2015; Prontera et al., 2014; Terrone et al., 2014; Zahir et al., 2007). Pathogenic variants within *SUPT16H* have not been described, whereas patients with disruptive *CHD8* mutations constitute a subgroup of autism, associated with macrocephaly (80%), gastrointestinal complaints and facial dysmorphism, characterized by pronounced supraorbital ridges, hypertelorism, downslanting palpebral fissures, a broad nose and pointed chin (Bernier et al., 2014; Neale et al., 2012; O'Roak et al., 2012). Recently, Smyk et al. reported similar facial features and relative macrocephaly in a patient with a *de novo* duplication on 14q11.2, comprising both *SUPT16H* and *CHD8* (Smyk et al., 2016). This phenotypic overlap between deletions and duplications on 14q11.2 was not reproduced in this study. Although patients with 14q11.2 duplications presented both a genetic and phenotypic heterogeneity, microcephaly is clearly more common than macrocephaly in this cohort. Other recurrent features included intellectual disability, ranging from mild to severe, epilepsy, hypogonadism, psychiatric disorders (autism) and behavioral problems (hyperactivity, aggression, hyperphagia). The question remains whether these features can all be attributed to the gene *SUPT16H,* or whether copy number gain of other genes within 14q11.2 can modify *SUPT16H* expression or independently cause psychiatric disorders or intellectual disability. A phenotypic effect due to gain of the neighboring gene *CHD8* should be considered, although this gene is only affected in a subset of 14q11.2 duplication patients. *HNRNPC,* proximal to *SUPT16H*, encodes a nuclear ribonucleoprotein involved in (pre-)mRNA processing, and is the only duplicated gene in DECIPHER patient 256272. This 74 kb duplication was inherited from a healthy mother. Further genomic studies in psychiatric patients will be required to determine whether gain-of-function mutations in either *SUPT16H*, *CHD8* or *HNRNPC* provoke psychiatric disorders. We conclude that duplications on 14q11.2 predispose to intellectual disability and a broad spectrum of behavioral and psychiatric problems. Apart from patient 6, no other 14q11.2 duplication patients were diagnosed or reported with catatonia. Therefore, in accordance with our CNV interpretation algorithm, this 14q11.2 duplication was considered causal for intellectual disability and likely pathogenic for catatonia in this patient.

The identification of catatonia-related copy number changes in this study, underscores the importance of genetic research in patients with catatonia, in order to untangle the neurobiological background, and to uncover novel therapeutic targets for this disorder.

Studying psychiatric disorders in intellectually disabled adults is challenging, since an accurate psychiatric diagnosis becomes difficult as the level of intellectual functioning declines. The applicability of existing standardized classification systems such as DMS for persons with intellectual disability is debatable (Fletcher et al., 2009). Although most catatonic signs are non-verbal and can be clinically detected, the severity of some symptoms like agitation, mutism and grimacing may be different from catatonic patients without intellectual disability. Future studies are required to validate clinical criteria for catatonia in patients with intellectual disability.

Acknowledgments

We would like to thank the patients and their families for their cooperation in this study. We thank Dr. Jan M Wit, Dr. Hermine van Duyvenvoorde and Dr. Claudia Ruivenkamp for their assistance in retrieving the data. K.D. is a clinical investigator of FWO Vlaanderen. J.B. is supported by a clinical research fund (KOF) from the University Hospitals Leuven. The authors declare to have no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmg.2016.08.003.

References

Azene, E.M., Xue, T., Li, R.A., 2003. Molecular basis of the effect of potassium on heterologously expressed pacemaker (HCN) channels. J. Physiol. 547 (Pt 2), 349–356.

Beckmann, H., Franzek, E., Stober, G., 1996. Genetic heterogeneity in catatonic schizophrenia: a family study. Am. J. Med. Genet. 67 (3), 289–300.

Belotserkovskaya, R., Oh, S., Bondarenko, V.A., Orphanides, G., Studitsky, V.M., Reinberg, D., 2003. FACT facilitates transcription-dependent nucleosome alteration. Science 301 (5636), 1090–1093.

Bernier, R., Golzio, C., Xiong, B., Stessman, H.A., Coe, B.P., Penn, O., Witherspoon, K., Gerdts, J., Baker, C., Vulto-van Silfhout, A.T., Schuurs-Hoeijmakers, J.H., Fichera, M., Bosco, P., Buono, S., Alberti, A., Failla, P., Peeters, H., Steyaert, J., Vissers, L.E., Francescatto, L., Mefford, H.C., Rosenfeld, J.A., Bakken, T., O'Roak, B.J., Pawlus, M., Moon, R., Shendure, J., Amaral, D.G., Lein, E., Rankin, J., Romano, C., de Vries, B.B., Katsanis, N., Eichler, E.E., 2014. Disruptive CHD8 mutations define a subtype of autism early in development. Cell 158 (2), 263–276.

Biel, M., Wahl-Schott, C., Michalakis, S., Zong, X., 2009. Hyperpolarization-activated cation channels: from genes to function. Physiol. Rev. 89 (3), 847–885.

Bruno, D.L., Anderlid, B.M., Lindstrand, A., van Ravenswaaij-Arts, C., Ganesamoorthy, D., Lundin, J., Martin, C.L., Douglas, J., Nowak, C., Adam, M.P., Kooy, R.F., Van der Aa, N., Reyniers, E., Vandeweyer, G., Stolte-Dijkstra, I., Dijkhuizen, T., Yeung, A., Delatycki, M., Borgstrom, B., Thelin, L., Cardoso, C., van Bon, B., Pfundt, R., de Vries, B.B., Wallin, A., Amor, D.J., James, P.A., Slater, H.R., Schoumans, J., 2010. Further molecular and clinical delineation of co-locating 17p13.3 microdeletions and microduplications that show distinctive phenotypes. J. Med. Genet. 47 (5), 299–311.

Carroll, B.T., Goforth, H.W., Thomas, C., Ahuja, N., McDaniel, W.W., Kraus, M.F., Spiegel, D.R., Franco, K.N., Pozuelo, L., Munoz, C., 2007. Review of adjunctive glutamate antagonist therapy in the treatment of catatonic syndromes. J. Neuropsychiatry Clin. Neurosci. 19 (4), 406–412.

Coe, B.P., Witherspoon, K., Rosenfeld, J.A., van Bon, B.W., Vulto-van Silfhout, A.T., Bosco, P., Friend, K.L., Baker, C., Buono, S., Vissers, L.E., Schuurs-Hoeijmakers, J.H., Hoischen, A., Pfundt, R., Krumm, N., Carvill, G.L., Li, D., Amaral, D., Brown, N., Lockhart, P.J., Scheffer, I.E., Alberti, A., Shaw, M., Pettinato, R., Tervo, R., de Leeuw, N., Reijnders, M.R., Torchia, B.S., Peeters, H., O'Roak, B.J., Fichera, M., Hehir-Kwa, J.Y., Shendure, J., Mefford, H.C., Haan, E., Gecz, J., de Vries, B.B., Romano, C., Eichler, E.E., 2014. Refining analyses of copy number variation identifies specific genes associated with developmental delay. Nat. Genet. 46 (10), 1063–1071.

Coghlan, S., Horder, J., Inkster, B., Mendez, M.A., Murphy, D.G., Nutt, D.J., 2012. GABA system dysfunction in autism and related disorders: from synapse to symptoms. Neurosci. Biobehav Rev. 36 (9), 2044–2055.

Cooper, G.M., Coe, B.P., Girirajan, S., Rosenfeld, J.A., Vu, T.H., Baker, C., Williams, C., Stalker, H., Hamid, R., Hannig, V., Abdel-Hamid, H., Bader, P., McCracken, E., Niyazov, D., Leppig, K., Thiese, H., Hummel, M., Alexander, N., Gorski, J., Kussmann, J., Shashi, V., Johnson, K., Rehder, C., Ballif, B.C., Shaffer, L.G., Eichler, E.E., 2011. A copy number variation morbidity map of developmental delay. Nat. Genet. 43 (9), 838–846.

Curry, C.J., Rosenfeld, J.A., Grant, E., Gripp, K.W., Anderson, C., Aylsworth, A.S., Saad, T.B., Chizhikov, V.V., Dybose, G., Fagerberg, C., Falco, M., Fels, C., Fichera, M., Graakjaer, J., Greco, D., Hair, J., Hopkins, E., Huggins, M., Ladda, R., Li, C., Moeschler, J., Nowaczyk, M.J., Ozmore, J.R., Reitano, S., Romano, C., Roos, L., Schnur, R.E., Sell, S., Suwannarat, P., Svaneby, D., Szybowska, M., Tarnopolsky, M., Tervo, R., Tsai, A.C., Tucker, M., Vallee, S., Wheeler, F.C., Zand, D.J., Barkovich, A.J., Aradhya, S., Shaffer, L.G., Dobyns, W.B., 2013. The duplication 17p13.3 phenotype: analysis of 21 families delineates developmental, behavioral and brain abnormalities, and rare variant phenotypes. Am. J. Med. Genet. A 161A (8), 1833–1852.

D'Angelo, C.S., Kohl, I., Varela, M.C., de Castro, C.I., Kim, C.A., Bertola, D.R., Lourenco, C.M., Perez, A.B., Koiffmann, C.P., 2013. Obesity with associated developmental delay and/or learning disability in patients exhibiting additional features: report of novel pathogenic copy number variants. Am. J. Med. Genet. A 161A (3), 479–486.

Daniels, J., 2009. Catatonia: clinical aspects and neurobiological correlates. J. Neuropsychiatry Clin. Neurosci. 21 (4), 371–380.

Dhossche, D., Fink, M., Shorter, E., Wachtel, L.E., 2011. Anti-NMDA receptor

encephalitis versus pediatric catatonia. Am. J. Psychiatry 168 (7), 749–750 author reply 750.
Dhossche, D.M., Bouman, N.H., 1997. Catatonia in an adolescent with prader-willi syndrome. Ann. Clin. Psychiatry 9 (4), 247–253.
Dhossche, D.M., Song, Y., Liu, Y., 2005. Is there a connection between autism, Prader-Willi syndrome, catatonia, and GABA? Int. Rev. Neurobiol. 71, 189–216.
Dhossche, D.M., Stoppelbein, L., Rout, U.K., 2010. Etiopathogenesis of catatonia: generalizations and working hypotheses. J. ECT 26 (4), 253–258.
Drabova, J., Seemanova, E., Hancarova, M., Pourova, R., Horacek, M., Jancuskova, T., Pekova, S., Novotna, D., Sedlacek, Z., 2015. Long term follow-up in a patient with a de novo microdeletion of 14q11.2 involving CHD8. Am. J. Med. Genet. A 167A (4), 837–841.
Duffney, L.J., Wei, J., Cheng, J., Liu, W., Smith, K.R., Kittler, J.T., Yan, Z., 2013. Shank3 deficiency induces NMDA receptor hypofunction via an actin-dependent mechanism. J. Neurosci. 33 (40), 15767–15778.
Durand, C.M., Betancur, C., Boeckers, T.M., Bockmann, J., Chaste, P., Fauchereau, F., Nygren, G., Rastam, M., Gillberg, I.C., Anckarsater, H., Sponheim, E., Goubran-Botros, H., Delorme, R., Chabane, N., Mouren-Simeoni, M.C., de Mas, P., Bieth, E., Roge, B., Heron, D., Burglen, L., Gillberg, C., Leboyer, M., Bourgeron, T., 2007. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat. Genet. 39 (1), 25–27.
Faedda, G.L., Wachtel, L.E., Higgins, A.M., Shprintzen, R.J., 2015. Catatonia in an adolescent with velo-cardio-facial syndrome. Am. J. Med. Genet. A 167A (9), 2150–2153.
Fernandez, B.A., Roberts, W., Chung, B., Weksberg, R., Meyn, S., Szatmari, P., Joseph-George, A.M., Mackay, S., Whitten, K., Noble, B., Vardy, C., Crosbie, V., Luscombe, S., Tucker, E., Turner, L., Marshall, C.R., Scherer, S.W., 2010. Phenotypic spectrum associated with de novo and inherited deletions and duplications at 16p11.2 in individuals ascertained for diagnosis of autism spectrum disorder. J. Med. Genet. 47 (3), 195–203.
Fink, M., 2009. Catatonia: a syndrome appears, disappears, and is rediscovered. Can. J. Psychiatry 54 (7), 437–445.
Fletcher, R.J., Havercamp, S.M., Ruedrich, S.L., Benson, B.A., Barnhill, L.J., Cooper, S.A., Stavrakaki, C., 2009. Clinical usefulness of the diagnostic manual-intellectual disability for mental disorders in persons with intellectual disability: results from a brief field survey. J. Clin. Psychiatry 70 (7), 967–974.
Ghaziuddin, N., Nassiri, A., Miles, J.H., 2015. Catatonia in Down syndrome; a treatable cause of regression. Neuropsychiatr. Dis. Treat. 11, 941–949.
Inta, D., Sartorius, A., Gass, P., 2015. NMDA receptor blockade and catatonia: a complex relationship. Schizophr. Res. 168 (1–2), 581–582.
Jap, S.N., Ghaziuddin, N., 2011. Catatonia among adolescents with down syndrome: a review and 2 case reports. J. ECT 27 (4), 334–337.
Javelot, H., Michel, B., Steiner, R., Javelot, T., Cottencin, O., 2015. Zolpidem test and catatonia. J. Clin. Pharm. Ther. 40 (6), 699–701.
Kramina, S., Kevere, L., Bezborodovs, N., Purvina, S., Rozentals, G., Strautmanis, J., Viksna, Z., 2015. Acute psychosis due to non-paraneoplastic anti-NMDA-receptor encephalitis in a teenage girl: case report. Psych. J. 4 (4), 226–230.
Lo-Castro, A., Galasso, C., Cerminara, C., El-Malhany, N., Benedetti, S., Nardone, A.M., Curatolo, P., 2009. Association of syndromic mental retardation and autism with 22q11.2 duplication. Neuropediatrics 40 (3), 137–140.
Neale, B.M., Kou, Y., Liu, L., Ma'ayan, A., Samocha, K.E., Sabo, A., Lin, C.F., Stevens, C., Wang, L.S., Makarov, V., Polak, P., Yoon, S., Maguire, J., Crawford, E.L., Campbell, N.G., Geller, E.T., Valladares, O., Schafer, C., Liu, H., Zhao, T., Cai, G., Lihm, J., Dannenfelser, R., Jabado, O., Peralta, Z., Nagaswamy, U., Muzny, D., Reid, J.G., Newsham, I., Wu, Y., Lewis, L., Han, Y., Voight, B.F., Lim, E., Rossin, E., Kirby, A., Flannick, J., Fromer, M., Shakir, K., Fennell, T., Garimella, K., Banks, E., Poplin, R., Gabriel, S., DePristo, M., Wimbish, J.R., Boone, B.E., Levy, S.E., Betancur, C., Sunyaev, S., Boerwinkle, E., Buxbaum, J.D., Cook Jr., E.H., Devlin, B., Gibbs, R.A., Roeder, K., Schellenberg, G.D., Sutcliffe, J.S., Daly, M.J., 2012. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature 485 (7397), 242–245.
Northoff, G., Lins, H., Boker, H., Danos, P., Bogerts, B., 1999. Therapeutic efficacy of N-methyl D-aspartate antagonist amantadine in febrile catatonia. J. Clin. Psychopharmacol. 19 (5), 484–486.
O'Roak, B.J., Vives, L., Fu, W., Egertson, J.D., Stanaway, I.B., Phelps, I.G., Carvill, G., Kumar, A., Lee, C., Ankenman, K., Munson, J., Hiatt, J.B., Turner, E.H., Levy, R., O'Day, D.R., Krumm, N., Coe, B.P., Martin, B.K., Borenstein, E., Nickerson, D.A., Mefford, H.C., Doherty, D., Akey, J.M., Bernier, R., Eichler, E.E., Shendure, J., 2012. Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 338 (6114), 1619–1622.
Phelan, K., McDermid, H.E., 2012. The 22q13.3 deletion syndrome (Phelan-McDermid syndrome). Mol. Syndromol. 2 (3–5), 186–201.
Poser, H.M., Trutia, A.E., 2015. Treatment of a prader-willi patient with recurrent catatonia. Case Rep. Psychiatry 2015, 697428.
Prontera, P., Ottaviani, V., Toccaceli, D., Rogaia, D., Ardisia, C., Romani, R., Stangoni, G., Pierini, A., Donti, E., 2014. Recurrent approximately 100 Kb microdeletion in the chromosomal region 14q11.2, involving CHD8 gene, is associated with autism and macrocephaly. Am. J. Med. Genet. A 164A (12), 3137–3141.
Serret, S., Thummler, S., Dor, E., Vesperini, S., Santos, A., Askenazy, F., 2015. Lithium as a rescue therapy for regression and catatonia features in two SHANK3 patients with autism spectrum disorder: case reports. BMC Psychiatry 15, 107.
Shinawi, M., Liu, P., Kang, S.H., Shen, J., Belmont, J.W., Scott, D.A., Probst, F.J., Craigen, W.J., Graham, B.H., Pursley, A., Clark, G., Lee, J., Proud, M., Stocco, A., Rodriguez, D.L., Kozel, B.A., Sparagana, S., Roeder, E.R., McGrew, S.G., Kurczynski, T.W., Allison, L.J., Amato, S., Savage, S., Patel, A., Stankiewicz, P., Beaudet, A.L., Cheung, S.W., Lupski, J.R., 2010. Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. J. Med. Genet. 47 (5), 332–341.
Smyk, M., Poluha, A., Jaszczuk, I., Bartnik, M., Bernaciak, J., Nowakowska, B., 2016. Novel 14q11.2 microduplication including the CHD8 and SUPT16H genes associated with developmental delay. Am. J. Med. Genet. A. 170 (5), 1325–1329.
Stober, G., Franzek, E., Lesch, K.P., Beckmann, H., 1995. Periodic catatonia: a schizophrenic subtype with major gene effect and anticipation. Eur. Arch. Psychiatry Clin. Neurosci. 245 (3), 135–141.
Stober, G., Haubitz, I., Franzek, E., Beckmann, H., 1998. Parent-of-origin effect and evidence for differential transmission in periodic catatonia. Psychiatr. Genet. 8 (4), 213–219.
Stober, G., Saar, K., Ruschendorf, F., Meyer, J., Nurnberg, G., Jatzke, S., Franzek, E., Reis, A., Lesch, K.P., Wienker, T.F., Beckmann, H., 2000. Splitting schizophrenia: periodic catatonia-susceptibility locus on chromosome 15q15. Am. J. Hum. Genet. 67 (5), 1201–1207.
Szatkiewicz, J.P., O'Dushlaine, C., Chen, G., Chambert, K., Moran, J.L., Neale, B.M., Fromer, M., Ruderfer, D., Akterin, S., Bergen, S.E., Kahler, A., Magnusson, P.K., Kim, Y., Crowley, J.J., Rees, E., Kirov, G., O'Donovan, M.C., Owen, M.J., Walters, J., Scolnick, E., Sklar, P., Purcell, S., Hultman, C.M., McCarroll, S.A., Sullivan, P.F., 2014. Copy number variation in schizophrenia in Sweden. Mol. Psychiatry 19 (7), 762–773.
Tandon, R., Heckers, S., Bustillo, J., Barch, D.M., Gaebel, W., Gur, R.E., Malaspina, D., Owen, M.J., Schultz, S., Tsuang, M., van Os, J., Carpenter, W., 2013. Catatonia in DSM-5. Schizophr. Res. 150 (1), 26–30.
Taylor, M.A., Fink, M., 2003. Catatonia in psychiatric classification: a home of its own. Am. J. Psychiatry 160 (7), 1233–1241.
Terrone, G., Cappuccio, G., Genesio, R., Esposito, A., Fiorentino, V., Riccitelli, M., Nitsch, L., Brunetti-Pierri, N., Del Giudice, E., 2014. A case of 14q11.2 microdeletion with autistic features, severe obesity and facial dysmorphisms suggestive of Wolf-Hirschhorn syndrome. Am. J. Med. Genet. A 164A (1), 190–193.
Torr, J., D'Abrera, J.C., 2014. Maintenance electroconvulsive therapy for depression with catatonia in a young woman with Down syndrome. J. ECT 30 (4), 332–336.
Vuillaume, M.L., Naudion, S., Banneau, G., Diene, G., Cartault, A., Cailley, D., Bouron, J., Toutain, J., Bourrouillou, G., Vigouroux, A., Bouneau, L., Nacka, F., Kieffer, I., Arveiler, B., Knoll-Gellida, A., Babin, P.J., Bieth, E., Jouret, B., Julia, S., Sarda, P., Genevieve, D., Faivre, L., Lacombe, D., Barat, P., Tauber, M., Delrue, M.A., Rooryck, C., 2014. New candidate loci identified by array-CGH in a cohort of 100 children presenting with syndromic obesity. Am. J. Med. Genet. A 164A (8), 1965–1975.
Wentzel, C., Fernstrom, M., Ohrner, Y., Anneren, G., Thuresson, A.C., 2008. Clinical variability of the 22q11.2 duplication syndrome. Eur. J. Med. Genet. 51 (6), 501–510.
Yi, F., Danko, T., Botelho, S.C., Patzke, C., Pak, C., Wernig, M., Sudhof, T.C., 2016. Autism-associated SHANK3 haploinsufficiency causes Ih channelopathy in human neurons. Science 352 (6286) aaf2669.
Zahir, F., Firth, H.V., Baross, A., Delaney, A.D., Eydoux, P., Gibson, W.T., Langlois, S., Martin, H., Willatt, L., Marra, M.A., Friedman, J.M., 2007. Novel deletions of 14q11.2 associated with developmental delay, cognitive impairment and similar minor anomalies in three children. J. Med. Genet. 44 (9), 556–561.

Web resources

DECIPHER – https://decipher.sanger.ac.uk/.
The database of genomic variants – http://dgv.tcag.ca/dgv/app/home.