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**CHD2 haploinsufficiency is associated with developmental delay, intellectual disability, epilepsy and neurobehavioural problems**

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**Abstract**

**Background:** The chromodomain helicase DNA binding domain (CHD) proteins modulate gene expression via their ability to remodel chromatin structure and influence histone acetylation. Recent studies have shown that CHD2 protein plays a critical role in embryonic development, tumor suppression and survival. Like other genes encoding members of the CHD family, pathogenic mutations in the CHD2 gene are expected to be implicated in human disease. In fact, there is emerging evidence suggesting that CHD2 might contribute to a broad spectrum of neurodevelopmental disorders. Despite growing evidence, a description of the full phenotypic spectrum of this condition is lacking.

**Methods:** We conducted a multicentre study to identify and characterise the clinical features associated with haploinsufficiency of CHD2. Patients with deletions of this gene were identified from among broadly ascertainment clinical cohorts undergoing genomic microarray analysis for developmental delay, congenital anomalies and/or autism spectrum disorder.

**Results:** Detailed clinical assessments by clinical geneticists showed recurrent clinical symptoms, including developmental delay, intellectual disability, epilepsy, behavioural problems and autism-like features without characteristic facial gestalt or brain malformations observed on magnetic resonance imaging scans. Parental analysis showed that the deletions affecting CHD2 were de novo in all four patients, and analysis of high-resolution microarray data derived from 26,826 unaffected controls showed no deletions of this gene.

**Conclusions:** The results of this study, in addition to our review of the literature, support a causative role of CHD2 haploinsufficiency in developmental delay, intellectual disability, epilepsy and behavioural problems, with phenotypic variability between individuals.

**Keywords:** Autism spectrum disorder, CHD2, Developmental delay, Epilepsy, Learning disability

**Background**

Chromatin remodeling is the dynamic modification of chromatin architecture essential to many biological processes, including cell division, gene expression, and DNA replication, packaging and repair [1-3]. The chromodomain helicase DNA binding (CHD) proteins belong to the SNF2-related superfamily of ATPases, which use the energy from ATP hydrolysis to change nucleosome positioning, composition and chromatin structure. The CHD family is defined by the presence of tandem chromatin organisation modifier domains in the N-terminal region and a central SNF2-related helicase/ATPase domain [4]. The latter is the catalytic core mediating chromatin alteration. Members of the CHD family are divided into three subfamilies according to their additional structural motifs. (1) CHD1 and CHD2 possess a C-terminal DNA binding domain recognizing AT-rich DNA motifs.

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(2) CHD3 and CHD4 contain a pair of plant homeo-
domain zinc finger domains in their N-terminal regions and
lack a DNA binding domain. (3) CHD5 to CHD9, which
contain diverse additional functional domains such as the
BRK (Brahma and Kismet) domain, SANT-like (switch-
ing-defective protein 3, adaptor 2, nuclear receptor core-
pressor, transcription factor IIIB) domain, CR domain and
DNA binding domain [1,5].

As CHD proteins play pivotal roles in modulating
chromatin structure and are involved in processes such as
gene activation and repression, DNA recombination
and repair, cell-cycle regulation, development and cell
differentiation, dysregulation of these proteins may have
adverse effects on human development. Heterozygous
mutations of the CHD7 gene are known to cause the
multisystem abnormalities associated with autosomal
dominant CHARGE syndrome (coloboma, heart anom-
aly, choanal atresia, retardation, genital and ear anomal-
ies) [OMIM:214800]. Characteristic anomalies include
ocular coloboma, choanal atresia, cranial nerve defects,
distinctive external and inner ear abnormalities, hearing
loss, cardiovascular malformations, intellectual disability
(ID), urogenital anomalies and growth retardation. More
recently, exon sequencing studies have shown loss of
function mutations affecting one allele of CHD8 to be
associated with autism spectrum disorder (ASD) [6-8].

There is emerging evidence showing CHD2 haplo-
sufficiency is associated with neurodevelopmental abnor-
malities. Deletions affecting this gene are very rare, and,
so far, there is only one case report of a child with global
developmental delay, epilepsy and ASD who was found
to have a de novo deletion encompassing the RGMA and
CHD2 genes [9]. However, because of the importance of
RGMA in central nervous system axonal growth, hap-
loinsufficiency of this gene was thought to be a good
candidate to explain the patient’s developmental delay
and seizures. A deletion affecting CHD2 was also re-
ported in the supplemental data derived from genomic
microarray analysis of 996 patients ascertained to have
ASD [10]. This deletion involves CHD2, but not RGMA,
and the patient was reported to have ASD and mild ID
with no history of seizures or language delay. Recent
studies have implicated de novo intragenic sequence mu-
tations in CHD2 in individuals with ID and a range of
epileptic encephalopathies [11-13]. Although there is in-
creasing evidence suggesting that mutations in CHD2
contribute to a broad spectrum of neurodevelopmental
disorders, a description of the full phenotypic spectrum
is lacking.

In order to investigate the role of CHD2 haploinsuf-
ciency in neurodevelopmental disorders, we describe the
first series of patients with deletions affecting CHD2 from
among a cohort of 42,313 patients broadly ascertained by
clinical genetics laboratories to have developmental delay,
intellectual disability, multiple congenital anomalies and/
or ASD. We also present a review of the literature to cor-
relate our patients’ phenotypes with those previously re-
ported with deletions and loss-of-function sequence
mutations affecting this gene.

Methods
We conducted a multicentre study of retrospective gen-
omic copy number variation (CNV) data from six genetic
diagnostics laboratories (see Additional file 1: Table S1), to
collect phenotypic information from patients with dele-
tions affecting CHD2. For all patients, phenotypic infor-
mation was collected from genetics clinic assessments and
medical chart reviews. This study is compliant with the re-
search ethics boards of each participating institution.
Signed informed consent was obtained from all study par-
ticipants or their legal representatives. DNA extracted
from uncultured cells, typically from peripheral blood
lymphocytes, was used to perform genomic CNV analysis
in all participating laboratories. Microarray experiments
were performed according to the manufacturer’s instruc-
tions. As described in Table S1, the microarray platforms
used at each of the six diagnostic centres were oligo-
nucleotide array-based. Deletions were confirmed, and
parental follow-up studies were performed with multiplex
ligation-dependent probe amplification (MLPA), array
comparative genomics hybridization (aCGH) or fluores-
cence in situ hybridization (FISH) analysis. FISH analysis
was performed using fosmid G248P83477D10 or CTD-
2314 N10 bacterial artificial chromosome. We investigated
the frequency of deletions affecting CHD2 in high-
resolution CNV data from among 13 control cohorts
comprising a total of 26,826 individuals [10,14-26].

Results
We reviewed genomic CNV data from six genetic diag-
nostics laboratories that perform microarray analysis for
patients broadly ascertained to have delayed develop-
mental milestones in motor, speech and/or cognition
skills (developmental delay); diagnosis of global develop-
mental delay or ID, multiple congenital anomalies; and/
or ASD. We identified four deletions affecting CHD2 ex-
onic sequences from a total of 42,313 patients analyzed.
The deletions ranged in size from approximately 78 kb
to 237 kb, with only one case also involving the RGMA
gene, and all were found to be de novo (Figure 1). No
other clinically significant CNVs were found in these pa-
tients. The clinical findings in these patients included
developmental delay, learning difficulties or ID in all
four patients, as well as seizures in three patients
(Table 1). The dysmorphic features observed in each of
these patients are described in turn in the subsections
below. However, no characteristic facial gestalt was
found. Brain magnetic resonance imaging (MRI) did not
reveal any malformations in our patients. Analysis of
data derived from 26,826 individuals from population-
based control cohorts evaluated by high-resolution CNV
analysis did not show deletions affecting exonic se-
quences of CHD2, confirming the extreme rarity of this
deletion in the general population (see Additional file 1:
Table S2).

Patient 1
Patient 1 has a 191-kb de novo deletion involving CHD2,
the ASB9P1 noncoding pseudogene, the uncharacterised
LOC100507217 noncoding gene and microRNA MIR3175
(Figure 1). This 11-year-old girl was referred for medical
genetics evaluation because she had fine and gross motor
delays as well as seizures. She was born by Caesarean sec-
tion at 38 weeks gestation with a birth weight of 2,977 g
(25th percentile) to healthy nonconsanguineous Caucasian
parents. She sat upright at age 1 year, walked at 22 months
and spoke her first words at 3 years. She had learning dis-
abilities with specific deficits in language and mathemat-
ics, and she repeated grade 3. She also had short-term
memory problems, a short attention span, poor social
skills and aggressive behaviour. She developed seizures at
6 years of age, which were characterised by absence sei-
zures with eyelid myoclonia (Jeavons syndrome) and
confirmed by video electroencephalogram (EEG). Her
medications included lamotrigine and ethosuximide. She
also had auditory neuropathy consistent with bilateral
mild loss of peripheral auditory function at higher fre-
quencies. Her physical examination revealed that she had
subtle dysmorphic features, with a square-shaped face,
high forehead, short philtrum, thin upper vermillion
border of the lip and prominent columella. She had mild
thoracic scoliosis, fusion of the proximal interphalangeal
joint in both thumbs, bilateral fifth-finger brachydactyly,
tapered fingers and cutaneous 2-3 syndactyly of the toes.

Her neurological examination was normal, with the excep-
tion of frequent episodes of eyelid fluttering bilaterally. An
MRI scan taken when she was 9 years of age was normal,
as was a skeletal survey; however, an abdominal ultra-
sound showed a duplex right kidney. She had a normal
acylcarnitine profile and normal plasma amino acids, elec-
trolytes, lactate, urinary organic acids and FRAXA and
FRAXE fragile X syndrome tests.

Patient 2
Patient 2 is a 9-year-old girl who has a 210-kb deletion
affecting CHD2, the ASB9P1 noncoding pseudogene, the uncharacterised LOC100507217 noncoding gene and microRNA MIR3175 (Figure 1), similar to patient 1. She
was referred to medical genetics for mild delays in
motor and language development as well as seizures.
She was born at term (41 weeks gestation) after an un-
eventful pregnancy to nonconsanguineous parents. Her
birth weight was 3,610 g (50th percentile). She was
found to have mild axial hypotonia as an infant. She first
walked at age 15 months. She had feeding problems in
infancy. She was diagnosed with attention-deficit/hyper-
activity disorder and was being treated with dextroam-
phetamine and amphetamine. She showed limited social
skills without any other features associated with ASD.
She had visual perceptual disabilities, a communication
disorder characterised by mixed receptive and expressive
language difficulties and short-term memory problems.
She repeated grade 1, and her performance on the
Wechsler Intelligence Scale for Children—Fourth Edition
was classified in the Low Average range for her age
group. Absence seizures that began at 3 years of age
were being treated with levetiracetam and valproic acid.
Her physical examination showed that she had reduced
body fat mass, a prominent forehead, a triangular face,
full lips, widely spaced maxillary central incisors and

Figure 1 Summary of deletions observed in our patients and reported in the literature.
| Characteristics          | Patient 1                  | Patient 2                  | Patient 3                  | Patient 4                  | Pinto et al. [10] | Capelli et al. [9] |
|-------------------------|---------------------------|---------------------------|---------------------------|---------------------------|-------------------|-------------------|
| Gender                  | F                         | F                         | F                         | M                         | Not specified     | F                 |
| Age (yr)                | 11                        | 9                         | 6                         | 16                        | Not specified     | 6                 |
| Chr15 deletion [hg19]   | 93,324,047 to 93,515,100   | 93,286,333 to 93,496,391  | 93,456,168 to 93,534,338  | 93,563,564 to 93,800,894  | 93,390,003 to 93,482,000 | 93,412,860 to 93,923,856 |
| Size                    | 191 kb                     | 210 kb                    | 78 kb                     | 237 kb                    | 83 kb             | 511 kb            |
| RefSeq genes            | CHD2, ASBP1, LOC100507297, MIR317S | CHD2, ASBP1, LOC100507297, MIR317S | CHD2, RGMA             | CHD2, LOC100507217, MIR317S | CHD2, RGMA, LOC100507217, MIR317S | CHD2, MIR317S |
| Inheritance             | De novo                   | De novo                   | De novo                   | De novo                   | De novo           | De novo           |
| Development             | Motor delay                | Communication disorder (receptive and expressive language difficulties) | Globally delayed         | Globally delayed with more significant speech delay | Unknown           | Globally delayed |
|                         |                           |                           |                           |                            |                   | Speech impairment |
| Cognition               | Learning disability       | Learning disability       | ID                        | ID                        | ID                | Unknown           |
|                         | Short-term memory problems| Short-term memory problems| Visual perceptual disability |                           |                   |                   |
| Behaviour               | Short attention span      | ADHD                      | Aggressive, impulsive, repetitive behaviours | ASD | ASD | Autistic behaviour |
|                         |                           | Limited social skills     | Aggressive behaviour      | ASD                        | Short attention span |
| Seizure type (age of onset) | Jeavons syndrome         | Absence seizures (3 yr)   | No epilepsy               | Complex partial and generalised seizures | No epilepsy       | Unspecified seizures (2 yr) |
|                         |                           | Absence seizures          |                           |                            |                   |                   |
|                         | Eyelid myoclonia (6 yr)   |                           |                           |                            |                   |                   |
| Brain MRI               | Normal                    | Not done                  | Normal                    | Normal                    | Altered angular gyrus | No severe abnormalities |
| Other                   | Mild hypotonia            | Mild hypotonia            | Mild hypotonia            | Tourette's syndrome       | Gait ataxia       | Slight hypotonia  |
|                         | Feeding difficulties      | Feeding difficulties      | Feeding difficulties      |                           |                   |                   |
| Dysmorphic features     | Square-shaped face        | Triangular face           | Brachycephaly             | Protruding ears           | Facial gestalt suggestive of Angelman syndrome |
|                         | High forehead             | Prominent forehead       | Broad forehead            | Micrognathia              |                   |                   |
|                         | Prominent columella       | Full lips                 | Short nose, upturned tip  |                           |                   |                   |
|                         | Short philtrum            |                          |                           |                            |                   |                   |
|                         | Fifth-finger brachydacty  |                          |                           |                            |                   |                   |
|                         | Syndactyly of toes 2 and 3|                          |                           |                            |                   |                   |
|                         | Other features            | Reduced body fat mass     | Strabismus                | Mild thoracic scoliosis   | Strabismus        |                   |
|                         | Mild thoracic scoliosis   |                           |                           |                            |                   |                   |
|                         | PIP joint fusion of thumbs|                           |                           |                            |                   |                   |
|                         | Mild peripheral hearing loss (higher frequencies) | |                           |                            |                   |                   |
|                         | Duplex kidney             |                           |                           |                            |                   |                   |

*ADHD, Attention-deficit hyperactivity disorder; ASD, Autism spectrum disorder; Chr, Chromosome; ID, Intellectual disability; MRI, Magnetic resonance imaging; PIP, Proximal interphalangeal; RefSeq, National Center for Biotechnology Information (NCBI) Reference Sequence Database (http://www.ncbi.nlm.nih.gov/refseq/).
micognathia. Her neurological examination was normal. Investigations performed for the assessment of her seizures and developmental delays included G-banding karyotype, a metabolic screen including carnitine level and acylcarnitine profile, plasma amino acids, and urinary organic acids, all of which were normal. An EEG showed generalised epileptogenic dysfunction and photosensitivity. No brain imaging was performed.

**Patient 3**
Patient 3 has a *de novo* 78-kb intragenic deletion affecting several 5′ exons of CHD2. No other gene was deleted in this patient. This 6-year-old girl was referred to the clinical genetics clinic for assessment of her profound delay in motor development and hypotonia. Her mother’s pregnancy was unremarkable, and she was born by Caesarean section at term with a birth weight of 2,920 g (25th percentile) to healthy nonconsanguineous parents. She had feeding difficulties as an infant and had ongoing issues with chewing and swallowing food properly in early childhood. She was found to have mild hypotonia in infancy, but she had normal tone at age 6 years. She sat upright at 9 months of age and walked at 26 months. At 6 years of age, she was not able to climb stairs with alternating feet and had difficulty pedaling a tricycle. She had mild delays in her fine motor skills, and, although she had normal speech, her language comprehension skills were delayed. She scored below the first percentile on the Wechsler Preschool and Primary Scale of Intelligence—Third Edition full-scale IQ test at 4 years of age. She displayed repetitive behaviours, such as walking in circles, mouthing objects and head-banging, but she did not meet the criteria for ASD. She had a history of aggressive behaviour towards others, which has mostly resolved. She was described as having lack of insight and judgment, as well as impulsive behaviour. She had never had seizures, and her EEG and brain MRI were normal. Her medical history is significant for developmental delay and hypotonia. Her neurological examination was otherwise unremarkable. Molecular genetic testing showed normal results for methylation-specific MLPA analysis for Prader-Willi and Angleman syndromes, MECP2 sequencing and FRAXA fragile X syndrome testing.

**Patient 4**
Patient 4 was found to have a 237-kb *de novo* deletion involving CHD2 and RGMA. Analysis by aCGH in this 16-year-old girl was performed because of poorly controlled epilepsy as well as ASD. She is known to have very challenging behavioural issues and Tourette’s syndrome. She presented in childhood with delays in motor, speech and cognition, with a more significant delay in language. At school, she exhibited difficulties in spelling and reading skills and had difficulty with mathematics. Her IQ ranged between 35 and 49. Complex partial and generalised seizures were noted between 3 and 24 months of age. Her physical examination showed that she had normal growth parameters with mild thoracic scoliosis. No striking dysmorphic features were reported. Her brain MRI was normal.

**Discussion**
We present the clinical features of four individuals with heterozygous *de novo* deletions affecting CHD2 who were identified from among a phenotypically heterogeneous cohort of 42,313 patients with developmental delays or ID, multiple congenital anomalies and/or ASD. The clinical symptoms of our patients are consistent with and include delays in speech and/or motor development, seizures, ID and/or learning difficulties, and neurobehavioural abnormalities, which may include autistic features, ADHD and/or aggressive behaviour. Our examination of 26,826 individuals from 13 control cohorts did not show any deletion affecting exonic sequences of this gene, indicating that deletions affecting CHD2 are extremely rare.

Our review of the literature on CHD2 deletions turned up one case report describing a *de novo* deletion affecting CHD2 and RGMA in a patient with speech and motor delays, including ID, gait ataxia, dysmorphic features, autistic features with attention deficit, and seizures beginning at 24 months of age [9]. These features were attributed to haploinsufficiency of RGMA and/or CHD2. In our cohort, only one patient had a heterozygous deletion affecting CHD2 and RGMA. Nevertheless, all of our patients had similar clinical findings, suggesting that CHD2 contributes significantly to the broad spectrum of neurodevelopmental disorders and mild dysmorphic features seen in patients with CHD2 deletions (Table 1). In addition, in an examination of the supplemental data from genomic CNV analysis of an ASD cohort, Pinto et al. [10] reported a *de novo* deletion of CHD2 in one patient with mild ID and ASD but no seizures [10]. This suggests that epilepsy may not always be present in patients with CDH2 haploinsufficiency, as we observed in one of our four patients. In another report in the literature, Kulkarni et al. [27] described a *de novo* translocation t(X;15)(p22.2;q26.1)dn disrupting CHD2 in a child with developmental delay, scoliosis and hirsutism. It is possible, however, that the clinical presentation of their patient may have been affected by disrupted expression of other genes near the translocation breakpoints. Interestingly, two of our patients with CHD2 deletions had mild thoracic scoliosis, suggesting that CHD2 disruption...
| Characteristics                  | Rauch et al. [12] | Carvill et al. [11] | Allen et al. [13] | Suls et al. [28] |
|---------------------------------|-------------------|---------------------|------------------|------------------|
| **Gender**                      | F, M              | F                   | M                | M                |
| **Age (yr)**                    | 5.75              | 17                  | 12               | Unknown          |
| **Protein change**              | p.Thr604 Leufs*19 (frame shift) | p.Glu412 Glyfs*64 (frame shift) | p.Arg121* (frame shift) | c.1502+1 G>A (splice donor) |
| **Inheritance**                 | De novo           | De novo             | De novo          | De novo          |
| **Development**                 | Globally delayed | Mild delay          | Normal prior to epilepsy | Normal prior to epilepsy |
| **Cognition**                   | Mild ID           | Moderate ID         | Severe ID        | Severe ID        |
| **Behaviour**                   | Uncontrolled behavioural anomalies | ASDBehavioural problems | Unknown         | Unknown          |
| **Seizure type**                | AS (5 yr)         | AtS (1 yr), AS, FS, MI, MJ-AS, TC | AtS (2 yr), MJ, SE, TC | FS (14 mo), Atypical AS, FDS, MS |
| **Brain MRI**                   | Unknown           | Unknown             | Unknown          | Normal           |
| **Other**                       | Unknown           | Unknown             | Unspecified delay | Unspecified delay |
| **Other features**              | Duane anomaly     |                     | Language regression after corpus callosotomy | Mild ataxia |

*AS, Absence seizure; ASD, Autism spectrum disorder; ATs, Atonic seizure; FDS, Focal dyscognitive seizure; FS, Febrile seizure; H, Hemiclonic; ID, Intellectual disability; LGS, Lennox-Gastaut syndrome; MA, Myoclonic absence; MJ, Myoclonic jerk; MRI, Magnetic resonance imaging; MS, Myoclonic seizure; NCS, Nonconvulsive status; SE, Status epilepticus; TC, Tonic-clonic; TS, Tonic seizure.*
may predispose individuals to vertebral anomaly, as reported by Kulkarni et al. [27] and as described in the Chd2-mutant mouse model [5,27]. Together, the consistent clinical features among patients diagnosed by routine clinical microarray and the de novo occurrence of all deletions affecting CHD2 reported thus far support a causative role of CHD2 haploinsufficiency for developmental delay, intellectual disability, epilepsy and behavioural problems, with phenotypic variability among individuals (Table 1). The results of recent studies in which researchers used massively parallel sequencing in patient cohorts investigated for epilepsy, ASD or ID provide supporting evidence for a role of CHD2 haploinsufficiency in manifestation of the characteristics observed in our patients (Table 2). Carvill et al. [11] performed sequence analysis of 66 candidate genes in 500 patients clinically diagnosed with epileptic encephalopathy. They found mutations predicted to be pathogenic in four patients with heterozygous de novo nonsense mutations and in two patients with de novo missense mutations disrupting the highly conserved residues in the SNF2-related helicase/ATPase domain. They described all six of their patients as having moderate to severe ID in addition to the onset of myoclonic seizures by 3 years of age. A role for CHD2 in ID is further substantiated by a report of a de novo frameshift mutation identified by exome sequencing in one patient [12]. In another report, an exome sequencing screen carried out for de novo mutations in patients with infantile spasms and Lennox-Gastaut syndrome revealed one patient with a CHD2 missense mutation [13]. More recently, Suls et al. [28] found three patients carrying de novo CHD2 sequence mutations who had febrile seizures followed by therapy-resistant generalised seizures (Table 2). In addition, they showed that a knockdown of chd2 in zebrafish resulted in clinical and electrographic seizures [28]. Interestingly, none of our four patients with a deletion of CHD2 had febrile seizures. These previous studies, together with our present case series, provide strong evidence that haploinsufficiency of CHD2 is associated with neurodevelopmental disabilities. Despite the presence of mild dysmorphic features in most patients described thus far, no specific facial gestalt has yet been reported. In addition, no brain malformation has been visualised by MRI. Although massively parallel sequencing studies suggest a strong association between CHD2 haploinsufficiency and seizures or ID, our study, which is based on broadly ascertained clinical cohorts, shows that such associations are not always observed. Some phenotypic variability between individuals seems to be present. Future studies will reveal whether other genetic factors influence the phenotype of this disorder or if CHD2 haploinsufficiency is associated with other phenotypes.

Conclusions
Herein we describe the first series of patients with deletions affecting CHD2. We provide additional evidence that deletions and pathogenic point mutations affecting CHD2 are associated with neurodevelopmental problems, which include delays in speech and/or motor development, seizures, ID or learning difficulties, minor dysmorphic features and behaviour problems involving social difficulties and maladaptive behaviours. Although haploinsufficiency of CHD2 is associated with a broad spectrum of neurodevelopmental disorders, we show that variability in the clinical expression of the phenotype can be observed. The overview of all currently reported mutations and their associated phenotypic features provided in this study provides a valuable resource for health-care providers caring for individuals with CHD2 mutations.

Additional file

Additional file 1: Table S1. Number of patients tested and microarray platform used by genetic diagnostics laboratories. Table S2. Control cohorts examined for exonic deletions at CHD2.

Abbreviations
aCGH: Array comparative genomics hybridization; ADHD: Attention-deficit/hyperactivity disorder; ASD: Autism spectrum disorder; CHD: Chromodomain helicase DNA binding domain; CNV: Copy number variation; EEC: Electroencephalogram; FISH: Fluorescence in situ hybridization; ID: Intellectual disability; MLPA: Multiplex ligation-dependent probe amplification.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SC, BL and DJS conceived of this study and participated in its design. SC, GY, BA, JL, ACL, CRM, IWA, AKV, SWS, CM0 and DI5 performed data accumulation and interpretation and participated in manuscript preparation. RL, AKV, KB, GM, FT and JS participated in data accumulation. SC, DJS, GY, ACL, CRM, AKV, BH, JS and SWS participated in critically revising the manuscript. All authors read and approved the final manuscript.

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References

1. Hall JA, Georgel PT. CHD proteins: a diverse family with strong ties. Biochem Cell Biol 2007, 85:463–476.
2. Tsukiyama T. The in vivo functions of ATP-dependent chromatin-remodelling factors. Nat Rev Mol Cell Biol 2002, 3:422–429.
3. Smith CL, Peterson CL. ATP-dependent chromatin remodeling. Curr Top Dev Biol 2005, 65:115–148.
4. Tajul-Arifin K, Teadale R, Rawas T, Hurne DA, Mattick JS, RIKEN GER Group, G3E. Identification and analysis of chromodomain-containing proteins encoded in the mouse transcriptome. Genome Res 2003, 13:1416–1429.
5. Marfella CGA, Imbalzano AN. The Chd family of chromatin remodelers. Mutat Res 2007, 618:30–40.
6. Neale BM, Kou Y, Liu L, Malayan A, Samocha KE, Sabo A, Lin CP, Stevens C, Wang LS, Makarov V, Poliski P, Voon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Vallodares O, Schaefer C, Liu H, Zhao T, Cai G, Lihm J, Dennenfelder R, Jadoba Q, Peralta Z, Nagasawamy U, Mumzy D, Reid JG, Newsham L, Wu Y, et al. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature 2012, 485:242–245.
7. O’Roak BJ, Vives L, Fu W, Egertson JD, Stanaway B, Phelps IG, Carvill G, Kumar A, Lee C, Arkenas K, Munson J, Hatt J, Turner EH, Levy R, O’Day DR, Krumm N, Coe BP, Martin BK, Borenstein E, Nickerson DA, Mefford HC, Deykin D, Akey JM, Bernier R, Eichler EE. Shendure J: Multiplex targeted sequencing identifies recurrently mutated genes in autism spectrum disorders. Science 2012, 338:1619–1622.
8. O’Roak BJ, Vives L, Girirajan S, Karakoc E, Krumm N, Coe BP, Levy R, Ko A, Lee C, Smith JD, Turner EH, Stanaway B, Vernot B, Malig M, Baker C, Reily B, Akey JM, Borenstein E, Rieder MJ, Nickerson DA, Bernier R, Shendure J, Eichler EE. Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations. Nature 2012, 485:246–250.
9. Capelli LP, Krepschil AOV, Gurgel-Giannetti J, Mendes MF, Rodrigues T, Varela MC, Koffmann CP, Rosenberg C. Deletion of the RMGA and CHD2 genes in a child with epilepsy and mental deficiency. Eur J Med Genet 2012, 55:132–134.
10. Pinto D, Pagnaninata AT, Lee K, Arney R, Merico D, Regan C, Royon J, Magalhaes TR, Coreia C, Abrahams BS, Almeida J, Baccelli E, Bader GD, Bailey AJ, Baird G, Battaglia A, Berney T, Bolshakova N, Boïte S, Bolton PF, Bourgeron T, Brennan S, Brian J, Byson SE, Caron AR, Casaloo G, Casey J, Chung BH, Cochrane L, Corsello C, et al. Functional impact of global rare copy number variation in autism spectrum disorders. Nature 2010, 466:368–372.
11. Carvill GL, Heavin SB, Wendle SC, McMahon JM, O’Roak BJ, Cook J, Khan A, Dorschner MO, Weaver M, Calvert S, Malone C, Wallace G, Stenton T, Bay AM, Beasal E, Howell KB, Kivity S, Mackay MT, Rodriguez-Casero V, Webster R, Korczyn A, Avfai Z, Zelrick N, Lerman-Sagie T, Levin D, Maller RS, Gill D, Andrade DM, Freeman JL, Sadler LG, et al. Targeted resequencing in epileptic encephalopathies identifies new de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013, 45:825–830.
12. Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, Schwarzmaier T, Albrecht B, Bartholdi D, Beggo J, Di Donato N, Dufke A, Cremer K, Hempel M, Horn D, Hoyer J, Joset P, Röpke A, Moog O, Riess A, Thiel CT, Tschach A, Wiesener A, Wohlfahr E, Zweier C, Ebci AB, Zink AM, Rump A, Meisinger C, Graillart H, Sticht H, et al. Range of genetic mutations associated with severe nonsyndromic sporadic intellectual disability: an exome sequencing study. Lancet 2012, 380:1674–1682.
13. Ep4K Consortium and Epilepsy Phenome/Genome Project, Allen AS, O’Roak BJ, Cook J, Khan A, Dorschner MO, Weaver M, Calvert S, Malone C, Wallace G, Stenton T, Bay AM, Beasal E, Howell KB, Kivity S, Mackay MT, Rodriguez-Casero V, Webster R, Korczyn A, Avfai Z, Zelrick N, Lerman-Sagie T, Levin D, Maller RS, Gill D, Andrade DM, Freeman JL, Sadler LG, et al. Targeted resequencing in epileptic encephalopathies identifies new de novo mutations in CHD2 and SYNGAP1. Nat Genet 2013, 45:825–830.
14. Stewart AFR, Dandona S, Chen L, Assogba O, Belanger M, Ewart G, LaRose R, Hill RM, Parkin M, Whittaker P, Yu F, Chang K, Hawes A, Lewis LR, Ren Y, Wheeler D, Rose J, Day PM, Burt N, Beaulieu C, Laroche C, et al. Defining cardiovascular disease in the Ottawa Heart Genomics Study. J Am Coll Cardiol 2009, 53:1471–1472.
15. The International HapMap 3 Consortium, Altschuler DM, Gibbs RA, Peltonen L, Altschuler DM, Gibbs RA, Peltonen L, Dermitzakis E, Schaffner SF, Yu F, Peltonen L, Dermitzakis E, Bonnen PE, Altschuler DM, Gibbs RA, de Bakker PW, Deloukas P, Gabriel SB, Gwinn M, Hunt S, Insuory M, Jia X, Patole A, Parkin M, Whittaker P, Yu F, Chang K, Hawes A, Lewis LR, Ren Y, Wheeler D, et al. Integrating common and rare genetic variation in diverse human populations. Nature 2010, 467:562–570.
16. The Wellcome Trust Case Control Consortium, Cudkowick N, Hurles ME, Cardin L, Pearson RD, Plagnol V, Robinson S, Vukcevic D, Barnes C, Conrad...
18. Itsara A, Cooper GM, Baker C, Girirajan S, Li J, Absher D, Krauss RM, Myers RM, Rieder PM, Chapman DI, Mefford H, Ying P, Nickerson DA, Eichler EE: Population analysis of large copy number variants and hotspots of human genetic disease. *Am J Hum Genet* 2009, 84:148–161.

19. Silversides CK, Lionel AC, Costain G, Merico D, Migita O, Liu B, Yuen T, Rickaby K, Thivolet-Blanchard A, Marshall CR, Scherer SW, Bassett AS: Rare copy number variations in adults with tetralogy of Fallot implicate novel risk gene pathways. *PLoS Genet* 2012, 8:e1002843.

20. Bierut LJ, Agravat A, Bucholz KK, Doherty KF, Laurie C, Pugh E, Fisher S, Fox L, Howells W, Bertelsen S, Hinrichs AL, Almasy L, Brosseau A, Kulzer-Vehe R, Dick DM, Edenberg HJ, Folstad T, Grucza RA, Hatsukami D, Hesselbrock V, Johnson EO, Kramer J, Krueger RF, Kuperman S, Lynskey M, Mann K, Neuman RJ, Nöthen MM, Numberger JT, Poirier P, the Gene Environment Association Studies (GENEVA) Consortium, et al: A genome-wide association study of alcohol dependence. *Proc Natl Acad Sci U S A* 2010, 107:5082–5087.

21. Verhoeven VJ, Hysi PG, Wojciechowski R, Fan Q, Guggenheim JA, Höhn R, Johnson EO, Kramer J, Krueger RF, Kuperman S, Lynskey M, Mann K, McNeur RJ, Nöthen MM, Nurnberger JI Jr, Poirier P, the Gene Environment Association Studies (GENEVA) Consortium, et al: A genome-wide meta-analysis of multiancestry cohorts identifies multiple new susceptibility loci for refractive error and myopia. *Nat Genet* 2013, 45:314–318.

22. Coviello AD, Haring R, Wells M, Vaidya D, Lehtimäki T, Kelison S, Lunetta KL, Le C, Fornage M, Lagou V, Mangino M, Onland-Moret NC, Chen B, Eriksson J, Garcia M, Liu YM, Koster A, Lohman K, Lyttkaiinen LP, Petersen AK, Prescott J, Stolk L, Vanderput L, Wood AR, Zhuang JW, Kuokas A, Hartikainen AL, Pouta A, Bandinelli S, Bisser P, et al: A genome-wide association meta-analysis of circulating sex hormone-binding globulin reveals multiple loci implicated in sex steroid hormone regulation. *PLoS Genet* 2012, 8:e1002805.

23. Costain G, Lionel AC, Merico D, Foryshe P, Russell K, Lovther C, Yuen T, Husted J, Stavropoulos-Di, Speevak M, Chow EW, Marshall CR, Scherer SW, Bassett AS: Pathogenic rare copy number variants in community-based schizophrenia suggest a potential role for clinical microarrays. *Hum Mol Genet* 2013, 22:4485–4501.

24. Qi L, Cornells MC, Kraft P, Stanya KJ, Kao WHK, Pankow JS, Dupuis J, Floresz JC, Fox CS, Paré G, Sun Q, Girman CJ, Laurie CC, Mirel DB, Manolio TA, Chapman DI, Boerwinkle E, Rieder PM, Hunter DJ, Meigs JB, Lee CH, Hu FB, van Dam RM, Meta-Analysis of Glucose and Insulin-Related traits Consortium (MAGIC), Diabetes Genetics Replication and Meta-analysis (DIAGRAM) Consortium: Genetic variants at 2q24 are associated with susceptibility to type 2 diabetes. *Hum Mol Genet* 2010, 19:2706–2715.

25. Below JE, Garnazon ER, Morrison J, Konokshaev A, Pluhnowik A, McGirg PA, Para DJ, Ebelin SC, Hallman DM, Nicola J, Bell GI, Cruz M, Cox NJ, Hanis CL: Genome-wide association and take full advantage of: *Submit your next manuscript to BioMed Central and take full advantage of:*

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