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A Novel Genetic Syndrome Caused by Haploinsufficiency of *CHD2*, a Regulator of Chromatin Structure

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Introduction

Dynamic regulation of gene transcription, achieved through epigenetic modification of DNA/histones and chromatin remodeling, is essential for cell differentiation and development [1]. An emerging theme in the pathogenesis of genetic disease, including intellectual disability (ID), autism spectrum disorder (ASD) and congenital multisystem disorders, is the identification of mutations in genes involved in epigenetic modification or chromatin remodeling.

Deletion of *CHD2* is linked to Neurodevelopmental Disease

There is accumulating evidence linking loss-of-function mutations in *Chromodomain helicase DNA-binding domain containing protein 2* (*CHD2*) to neurodevelopmental disease. Recently, we described chromosome 15q26.1 microdeletions encompassing *CHD2* in a series of patients ascertained from six genetic diagnostic laboratories that perform chromosomal microarray analysis for patients broadly ascertained to have motor, speech and/or cognition delay (developmental delay), global developmental delay or ID, multiple congenital anomalies, and/or ASD [2]. Four from a total of 42,313 patients analyzed were identified with *de novo CHD2* deletions, ranging in size from 78 kb to 237 kb (Table 1). The clinical findings in these four patients included developmental delays, learning difficulties or ID, and seizures were documented in 3 of the 4 patients. Although dysmorphic features were common, there was no characteristic facial gestalt identified. Brain magnetic resonance imaging (MRI) was normal when performed. Analysis of 26,826 individuals from a population-based control cohort evaluated by chromosomal microarray analysis did not reveal *CHD2* deletions, suggesting that haploinsufficiency of *CHD2* directly contributes to the clinical phenotype of the patients studied.

Prior to our publication, two individuals with microdeletions involving the *CHD2* locus had previously been described. Capelli et al. reported a *de novo* deletion affecting *CHD2* and the adjacent locus *RGMA* in a patient with speech and motor delays, ID, autistic features with attention deficit disorder, gait ataxia, and seizures which began at 24 months of age [3]. Pinto et al. reported one *de novo* deletion of *CHD2* in a patient with mild ID and no documented seizures at the time of publication [4]. The phenotypic similarities in these unrelated patients underscore the hypothesis that *CHD2* haploinsufficiency is the underlying cause of the documented clinical features.

Since our publication, two additional patients with chromosome 15q26.1 microdeletions involving *CHD2* and *RGMA* have been reported [5]. These two adult individuals had a similar phenotype to the patients previously published, including moderate ID, behavioural problems and generalized epilepsy (Table 1). Both patients also presented with differing degrees of scoliosis, which was noted in two of our microdeletion patients [2], in addition to adolescent-onset truncal obesity. The authors speculate that haploinsufficiency of *RGMA*, encoding a member of the repulsive guidance molecule family that functions as an axon guidance protein in the developing and adult central nervous system, may contribute to the truncal obesity phenotype, while *CHD2* haploinsufficiency is responsible for the neurodevelopmental phenotype and scoliosis [5]. Given that obesity was not noted in the other two patients with deletions overlapping both *CHD2* and *RGMA* (Table 1 and Figure 1; Patients 4 and 6), there are clearly too few cases at this point to associate deletion of *RGMA* with obesity or whether it is a coincidental finding.

A review of the literature also uncovered a single case describing a *de novo* chromosome 15q26.1 microdeletion encompassing *CHD2* in a child with developmental delay, growth delay, mild dysmorphic features, and primary generalized epilepsy [6], providing additional evidence to support the requirement of *CHD2* in proper neurodevelopment.

In total, 9 patients with chromosome 15q26.1 microdeletions (<1 Mb) encompassing *CHD2* have been described in the literature (see Figure 1 and Table 1). Developmental delay and ID were reported in 9/9 (100%), behavioural problems were reported in 9/9 (100%), scoliosis was reported in 4/9 (44%) and seizures were reported in 7/9 (78%). Alignment of all patients' deletions reveals that *CHD2* deletions, with or without deletion of *RGMA*, may produce seizures indicating that deletion of *RGMA* is not required for manifestation of this phenotype. Larger and more complex deletions involving *CHD2* have also been identified (reported deletions sizes were 3.3 Mb and 5 Mb, in addition to one patient with 6 copy number changes, including a 2 Mb chromosome 15q26.1 deletion) [7-9]. Although the clinical phenotypes are likely modified by the greater number of genes deleted in these patients, developmental delay, facial dysmorphia, and seizures were common features shared by these larger *CHD2* deletion carriers. These data strongly suggest that haploinsufficiency of *CHD2* contributes to the spectrum of neurodevelopmental disorders identified in these patients.

Segregating Sequence Changes within CHD2 are Associated with Neurodevelopmental Disorder

In addition to the 9 patients that have been described with *CHD2* microdeletions, patients with predicted pathogenic loss-of-function mutations in *CHD2* have been reported in the literature. Although it is not clear whether the reported mutations are equivalent to haplo-

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Details	Patient 1 [2]	Patient 2 [2]	Patient 3 [2]	Patient 4 [2]	Patient 5 [4]	Patient 6 [3]	Patient 7 [5]	Patient 8 [5]	Patient 9 [6]
Gender	F	F	F	F	M	F	M	M	F
Age	11	9	6	16		6	25	21	
chr15 deletion coordinates [hg19]	93,324,047-93,515,100	93,286,333-93,496,391	93,456,168-93,534,338	93,563,564-93,800,894	93,399,003-93,482,000	93,412,860-93,923,856	93,203,932-93,619,522	93,545,581-93,651,582	92,832,405-93,563,624
Size	191 kb	210 kb	78 kb	237 kb	83 kb	511 kb	415 kb	106 kb	731 kb
RefSeq Genes	*CHD2, ASB9P1, LOC100507217, MIR3175*	*CHD2, ASB9P1, LOC100507217, MIR3175*	*CHD2*	*CHD2, RGMA*	*CHD2, LOC100507217, MIR3175*	*CHD2, RGMA, LOC100507217, MIR3175*	*CHD2, RGMA*	*CHD2, RGMA*	*CHD2, ST8IA2, c15orf32, FAM174B*
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Development	Motor delay, Speech delay, learning disability, Short-term memory problems	Communication disorder, learning disability, Short-term memory problems, Visual perceptual disability	Globally delayed, ID	Globally delayed, ID	Unknown, ID	Globally delayed, Speech impairment	Globally delayed, ID	Globally delayed with limited language, ID, Unable to read or write	Globally delayed, ID
Behaviour	Short attention span, Aggression, Limited social skills	ADHD, Limited social skills	Aggressive, impulsive, repetitive behaviours	ASD, Aggression	ASD	ASD, Short attention span	Aggression	Aggression, Temper tantrums	Behavioural problems
Seizure type (age of onset in years)	Jeavons syndrome (6), Absence, Eyelid myoclonia	Absence (3)	None	Complex partial and generalized	None	Unspecified (2)	Generalized (2)	Absence (2), General tonic-clonic	Absence (3.5), Tonic, Myoclonic, Tonic-clonic (induced by touch)
Brain MRI	Normal	Not done	Normal	Normal	Altered angular gyrus	No severe abnormalities	Normal	Not done	Normal
Dysmorphic Features	Square-shaped face, High forehead, Prominent columella, Short philtrum, Fifth-finger brachydactyly, Syndactyly of toes 2 and 3	Triangular face, Prominent forehead, Full lips, Widely spaced central maxillary incisors, Micrognathia	Brachycephaly, Broad forehead, Short nose, upturned tip		Protruding ears, Micrognathia	Suggestive of Angelman syndrome, Wide mouth, Widely spaced teeth, Prognathia	Upslanting palpebral fissures, Long eyelashes, Short philtrum, Hypoplastic alae nasi, Narrow hands and feet, Tapering fingers	Slight upslanting palpebral fissures, Large ear lobes, Low posterior hairline, Bulbous nasal tip, with upturned nares, High palate, Small hands with tapering fingers	Widely set eyes, Deep pits on helix of ears bilaterally, Crowded teeth, prominent incisors, Microcephaly
Other features	Mild thoracic scoliosis, PIP joint fusion of thumbs, Mild peripheral hearing loss, Duplex kidney	Reduced body fat mass, Mild hypotonia, Feeding difficulties	Strabismus, Mild hypotonia, Feeding difficulties	Mild thoracic scoliosis, Tourette's syndrome		Strabismus	Severe kyphoscoliosis, Truncal obesity, Psychiatric disorder, Neonatal hypotonia	Mild scoliosis, Micropenis, testes in inguinal canal, Truncal obesity, Hypotonia, Fetal hydrops, Feeding difficulties	Decreased fetal heart rate, IUGR

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; Chr, Chromosome; ID, Intellectual Disability; IUGR, Intrauterine Growth Restriction; MRI, Magnetic Resonance Imaging; PIP, Proximal Interphalangeal; RefSeq, National Center for Biotechnology Information (NCBI) Reference Sequence Database (http://www.ncbi.nlm.nih.gov/refseq/).

Table 1: Clinical characteristics of patients with *CHD2* microdeletions.

insufficiency, in our review of the literature, at least 21 individuals with unique *de novo* heterozygous *CHD2* mutations have thus far been described (Table 2). These individuals were ascertained from a cohort of patients with epileptic encephalopathies, ID, and ASD [10-18]. The phenotype of *CHD2* mutation carriers is comparable to chromosome 15q26.1 microdeletion carriers, and includes mild-to-profound developmental delay with instances of regression, ID, ASD, behavioural problems and seizures. The presence of dysmorphic features was generally not reported. Interestingly, the seizures associated with *CHD2* mutation were generally more complex than the microdeletion carriers, and were reported in over 90% of the patients identified. Furthermore, sequence variants in *CHD2* were found to be over-represented in

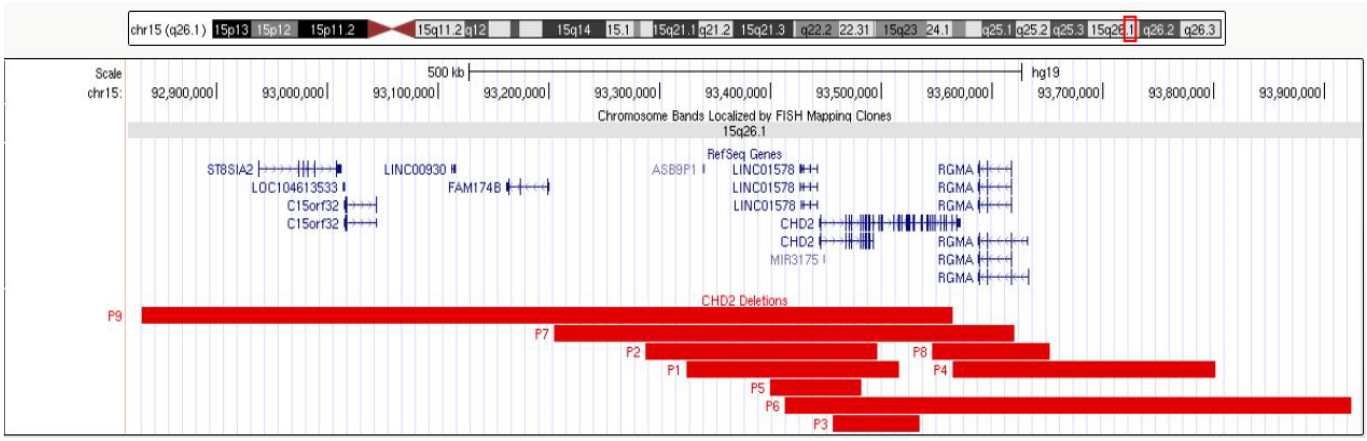

Figure 1: Snapshot of the UCSC Genome browser (Human Feb. 2009 (GRCh37/hg19) Assembly) displaying all of the published chromosome 15q26.1 microdeletions involving *CHD2* to date. The P# designation adjacent to each deletion (red bar) corresponds to the patient designation in Table 1.

Details	Patient 1 [11]	Patient 2 [13]	Patient 3 [13]	Patient 4 [13]	Patient 5 [16]	Patient 6 [10]	Patient 7 [10]	Patient 8 [10]	Patient 9 [10]	Patient 10 [10]	Patient 11 [10]	Patient 12 [18]	Patient 13 [22]
Gender	M	M	F	M	F	M	F	F	M	M	M	M	F
Age	26	6	24	6	5	6	12	29	12	15	6	Teenager	
Mutation	c.417dupA p.Gln1392Thrfs*17	c.1810-2A>C p.?	c.4971G>A p.Trp1657*	c.1396C>T p.Arg466*	c.1809 del p.Thr604Leufs*19	p.Glu1412Glyfs*64	p.Arg121*	p.Gly491Valfs*13	p.Arg1644Lysfs*22	p.Trp548Arg	p.Leu823Pro	c.1502+1G>A	c.335C>G p.Ser112*
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Development	Motor delay Speech delay Severe learning disability	Mild ID	Normal development Mild ID	Subtle speech and motor delay Mild ID	Global delay ID	Mild delay Moderate ID	Global delay with regression Severe ID	Profound global delay Limited language Severe ID	Global delay with regression Severe ID	Global delay Poor verbal understanding Regression Mild ID	Global delay Regression Severe ID	Global delay Language regression ID	ID
Behaviour	ASD Hyperactivity	Not reported	Not reported	ASD ADHD	Not reported	Severe ASD Aggression	Aggression	None	Obsessive behaviour	Childhood aggression	ASD Aggression	Not reported	None
Seizure type (age of onset in years)	Atypical absence (2.5) Myoclonic Generalized tonic-clonic Nocturnal tonic	Generalized tonic-clonic (1) Myoclonic Atypical absence	Myoclonic (2) Myoclonic absence Generalized tonic-clonic	Generalized tonic-clonic (3) Hemiclonic and atonic Myoclonic Atypical absence	Absence (5)	Febrile (1) Absence Atonic Myoclonic Tonic-clonic Photic stimulation	Myoclonic (1) Tonic Tonic-clonic Typical absence Photic stimulation	Myoclonic (1) Tonic Tonic-clonic Atypical tonic Photic stimulation	Atonic (2) Myoclonic Tonic-clonic Absence	Focal dyscognitive seizures (3) Hemiclonic Generalized tonic-clonic Myoclonic Photic stimulation	Focal dyscognitive (2.5) Myoclonic Myoclonic absence Atonic	Myoclonic (0.5) Focal dyscognitive Tonic-clonic Absence Atonic	None
Brain MRI	Normal	Normal	Normal	Non-specific atrophy	Not reported	No increase in corpus callosum	Normal	Normal	Decreased occipital lobe volume Deep sulci Marked atrophy Decreased corpus callosum, white matter volume	Normal	Limited sequences Mild volume loss Increase in ventricular size	Normal	Not reported
Other features	Large mouth Small for age (childhood)	Ataxia Dysarthria	Not reported	Not reported	Duane anomaly	Crouch gait Transient ataxia	Short stature Stooped gait Poor coordination Poor balance	Needs help to walk	Short stature Crouch gait Transient ataxia	Mild crouch gait	Crouch gait	Not reported	Not reported

Details	Patient 14 [14]	Patient 15 [14]	Patient 16 [14]	Patient 17 [14]	Patient 18 [12]	Patient 19 [12]	Patient 20 [12]	Patient 21 [17]
Gender	M	F	M	M	F	M	M	M
Age	9	13	9	6	13	12	14	17
Mutation	p.Arg1637Ter	p.Glu966SerfsTer2	p.Gly1651TrpfsTer16	p.Gln1641Ter	p.Gly1575Valfs*	p.Leu1591fsX	p.Gln909*	c.4256del19 p.Lys1419fsX1241
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Development	None	Limited phrases, Limited speech, ID	Word loss, ID	Limited phrases, Limited speech, ID	Global delay, Limited speech, Moderate-to-severe ID	Global delay, Regression, Moderate-to-severe ID	Motor delay, Late regression, Mild ID	Motor delay Late regression ID
Behaviour	Severe ASD	Severe ASD	Severe ASD	Severe ASD	ASD ADHD Aggression	ADHD Aggression	ADHD Aggression	Hyperactivity

Seizure type (age of onset in years)	None	Unspecified	Unspecified	Unspecified	Absence (2.5) Myoclonic Typical absence Tonic Generalized tonic-clonic Photic stimulation	Generalized tonic-clonic (3.5) Atypical absence Myoclonic Myoclonic Absence	Atypical tonic (2.5) Generalized tonic-clonic Myoclonic Photic stimulation	Myoclonic (3.5) Absence Myoclonic-atonic Tonic-clonic Photic stimulation
Brain MRI	Not reported	Not reported	Not reported	Not reported	Generalized cerebellar atrophy, Foreshortened posterior corpus callosum	Normal	Cerebellar atrophy, Hypoplastic corpus callosum	Not reported
Other features	Not reported	GI issues (constipation), Sleep disturbances	GI issues (constipation), Colour blindness	Not reported	Short stature	Mild ataxia	Short stature Crouch gait Ataxia	Not reported

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; ID, Intellectual Disability; GI, Gastrointestinal; MRI, Magnetic Resonance Imaging.

Table 2: Clinical characteristics of patients with *CHD2* mutations.

patients with photosensitive epilepsy syndrome and associated with photosensitivity in common epilepsies suggesting that *CHD2* may influence this particular trait [19]. Interestingly, partial loss of *chd2* function in the zebrafish model leads to a similar phenotype of seizures [13] and photosensitivity [19].

CHD2 is Essential for Normal Neurodevelopment

While the genetic pathways regulated by CHD2 are currently not well elucidated, there is irrefutable evidence that *CHD2* is required for proper development. Mice homozygous for a C-terminal truncating mutation of *CHD2* are not viable, with general growth delay in late embryogenesis and perinatal death [20]. Heterozygous *Chd2* mutants exhibit decreased survival rates, especially in the neonatal period, and have increased incidence of non-neoplastic lesions affecting a number of primary organs, most notably the kidneys.

A recent study has shown that CHD2 plays a role in embryonic neurogenesis [21]. CHD2, primarily expressed in Pax6 positive radial glial cells, was found to maintain the self-renewal capacity of this cell population, increasing the generation of intermediate progenitors through direct binding to the *repressor element 1-silencing transcription factor* (*REST*) genomic region. *CHD2* knockdown led to a decrease in radial glial cells and an increase in intermediate progenitors, suggesting that loss of *Chd2* expression during neurogenesis contributes to abnormal development of the central nervous system.

The Biochemical Function of CHD2

CHD2 is one member of a distinct family of nine evolutionarily conserved genes encoding proteins involved in chromatin remodeling. The protein domains characterizing CHD2 and this family include, but not limited to, the chromodomain (chromatin organization modifier), SNF2-related ATP-dependent helicase domain, and specific DNA-binding domains [22]. CHD2 was recently shown to function as an ATP-dependent chromatin assembly factor that has the ability to assemble periodic nucleosome arrays on a naked DNA template *in vitro* [23]. *In vivo*, more specifically in a human myoblast cell line, CHD2 was found to mediate the deposition of the H3.3 histone variant within the promoters of myogenic-specific loci, which serves as a functional epigenetic mark demarcating transcriptionally competent genes [24]. The absence of a skeletal muscle phenotype in patients with *CHD2* deletions or mutations suggests that the role of CHD2 in this cell type may not be dosage-sensitive or its partial loss may be compensated for by the functional redundancy of the CHD proteins. Indeed, Siggens et al. have recently shown in K562 cells (a human erythromyeloblastoid leukemia cell line) that CHD1 and CHD2 cooperate via transcription-coupled recruitment to regulate the chromatin structure at transcriptionally active genes [25].

CHD Family and Genetic Disease

CHD proteins function in a variety of cellular processes through their ability to remodel chromatin and facilitate gene activation or repression of a multitude of gene targets. Therefore, it is not surprising that mutations in several *CHD* genes are directly linked to human disease. Most notably, haploinsufficiency of *CHD7* via microdeletions or heterozygous mutations in *CHD7* causes CHARGE syndrome, an acronym summarizing the six cardinal features of the multisystem disorder (Coloboma, Heart defects, choanal Atresia, mental Retardation, Genital and Ear anomalies) [26] (extensively reviewed in [27] and [28]). It is interesting to note that *Chd7* mRNA is expressed in organs affected in CHARGE syndrome. As *Chd7* mutations in mice block neuronal differentiation, it has been proposed that a similar mechanism exists in humans [29].

Microdeletions encompassing *CHD8* were identified in patients presenting with ID and/or ASD and/or macrocephaly [30]. While the minimal deleted region contains *CHD8* and the adjacent *SUPT16H* locus, the importance of abrogated CHD8 function in the phenotype of these patients is underscored by the identification of disruptive *CHD8* mutations in individuals with DD or ASD [31] and recapitulation of a subset of features of the human phenotype in the zebrafish model [32]. Although other CHD proteins have yet to be linked to human genetic disease, it has been demonstrated that CHD4 and CHD5 carry out important functions in neurogenesis [33,34]. Although beyond the scope of this communication, the contribution of CHD dysfunction in the etiology of cancer has been long recognized [35].

Conclusion

Haploinsufficiency of the chromatin remodeler CHD2 causes neurodevelopmental disease in humans. Determining the tissue-specific transcriptional targets of CHD2 and deciphering the regulatory role it plays on chromatin will provide further insight on its functions in development and may help to predict the impact of disease mutations on that function. With the significant increase in the use of chromosomal microarrays and exome sequencing technologies in genetic diagnosis, it is conceivable that, given their pivotal role in chromatin remodeling, all CHD family members will be eventually linked to human disease.

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