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Clinical Letters

CHD2 mutations: Only epilepsy? Description of cognitive and behavioral profile in a case with a new mutation

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1. Introduction

The chromodomain helicase DNA binding domain 2 (*CHD2*) gene (OMIM: 602119) was originally characterized by Woodage et al. [1] and has been repeatedly reported to play a pivotal role in cerebrocortical development. *CHD2* gene mutations was recently described in patients with photosensitive epilepsies [2], with myoclonic-atonic epilepsy (MAE), Lennox–Gastaut syndrome (LGS), Dravet syndrome (DS) and other forms of epileptic encephalopathies featuring generalized epilepsy with intellectual disability (ID) [3,4]. Furthermore there is emerging evidence suggesting that *CHD2* might contribute to a broad spectrum of neurodevelopmental disorders (NDDs) including developmental delay, ID, autism spectrum disorders (ASD), with phenotypic variability among individuals. Here we describe a patient with an unreported [5]*de novo CHD2* frameshift mutation presenting with mild facial dysmorphism, infantile epilepsy, ID and severe behavioral disorder. This case expands the clinical spectrum of manifestations associated with *CHD2* mutations and supports a multidisciplinary approach for a detailed and careful description of the epilepsy-cognition-behavior complex.

1.1. Case report

The proband is a 27-years old woman, first daughter of healthy unrelated parents. Her family history was unremarkable. She was born at term after a normal pregnancy. Her psychomotor development was referred as normal until the age of 2,5 years when seizures and behavioral problems appeared. She graduated from high school with special education program.

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1.1.1. Epilepsy and EEG findings

at age 2,5 years she presented with repeated episodes of myoclonic jerks mainly involving the upper limbs, mostly upon awakening. A sleep electroencephalogram (EEG) showed multiple and diffuse polyspikes and spike-waves complexes. Valproate (VPA) failed to control the episodes; add on with ethosuximide induced seizure control for a few years. At the age of 11 years seizures reappeared with short lasting absences, myoclonic seizures and generalized tonic clonic seizures (GTCS) occurring upon awakening, followed by prolonged post-ictal confusion. At that time her awake EEG showed a background activity of 8 Hz and interictal generalized multiple spike and waves complexes prevalent over the frontal area (Fig. 1a,b). Lamotrigine (LTG) was added-on and she continued having 1–2 seizures/year. At the age of 25 years the EEG showed epileptiform abnormalities characterized by spike and waves complexes (Fig. 1c). She is now seizure free since one year. Her last EEG is negative for epileptic abnormalities. Of note she never showed photosensitivity (Fig. 1d).

1.1.2. Neuropsychological profile

The Wechsler Adult Intelligence Scale-Revised (WAIS-R) showed moderate intellectual disability (total IQ: 45), with homogeneous verbal and performance IQ scores, and a non-pathologic deterioration index. The patient showed substantial impairments in all cognitive areas investigated by the test (Supplementary Table1). At the neuropsychological assessments, the most relevant alterations were found in immediate and delayed verbal learning, verbal fluency, and executive functions (Supplementary Table 2).

1.1.3. Psychiatric profile

Examinations of the psychiatric features of the patient have been carried out at her age of 27. Mental state examination showed impairments in several domains of behavior. Appearance was disheveled; demeanor was partly hostile and partly mistrustful, leading to withdrawn. Speech was slow and confuse. Thought content was characterized by several and serious ideas of reference, although a frank delusional content cannot be revealed, partly because of the patient was non-cooperative and possibly reticent and partly as a consequence of poor mental capacity due to intellectual disability. However, thought was clearly oriented toward psychotic contents, with many false beliefs and unrealistic, idiosyncratic, dereistic ideas. Perceptual alterations, such as illusions or hearing odd sounds, were reported, however no frank hallucinations or hallucinatory behavior was found. Thought processes were in great part circumstantial and concrete, with loose associations of ideas and incoherent construct interpolation. Mood was apparently elated, with labile and inappropriate affect. Attentive dysfunctions and low ability to abstract were observed in terms of cognitive functioning. Insight was poor, while judgment is considered defective. We supported these clinical observations with a series of rating scale. SCL-90R was carried out with the aid of trained raters, in agreement with guidance for the administration in patients suffering from intellectual disability. SCL-90R showed the highest altered scores in the Phobic Anxiety and Psychoticism items, with intermediate-high scores also in the Obsession-Compulsion and Anxiety items. Overall, the Global Severity Index of 1.6 and the Positive Symptoms Distress Index of 2.2 indicated an intermediate level of psychiatric symptoms and global distress (Supplementary Table 3). The rater-administered 24-item Brief Psychiatric Rating Scale (BPRS) resulted in an intermediate-high global score of 65 (Supplementary Table 3), with the highest scores in the Emotional Withdrawal, Uncooperativeness, Hostility, Self-Neglect, and Unusual Thought Content items.

The patient showed low scores on all social cognition tests that were administered, consistently with a lack of social and emotional reciprocity (Supplementary Table 2). However, clinical evaluation tended to exclude a diagnosis of Autism Spectrum Disorder. Indeed, the patient maintained some efficient social interactions, although she showed defective social communications, mostly non-verbal ones. Patterns of interest were restricted but not stereotyped or inflexible. However, she was described to hyper-react to meaningless environmental stimuli. More importantly, these symptoms do not appear to cause clinically significant impairment in areas of functioning *per se*. To support these evaluations we administered the Ritvo Autism and Asperger's Diagnostic Scale (RAADS), whose score was 55 (i.e. below the diagnostic threshold, although approximating it, Supplementary Table 3), although results of this test should be taken into account very cautiously given the patient's intellectual disability. Taken together, these results exclude a frank diagnosis of Autism Spectrum Disorder, although the patient exhibits subthreshold autistic traits.

The Mini-International Neuropsychiatric Interview was used for diagnosis categorization (Supplementary Table 3). No primary psychiatric diagnosis was found, while the patient was best categorized, also according to clinical judgment and neuropsychological evaluations, as suffering from both Intellectual disability and Psychotic Disorder due to Another Medical Condition.

1.1.4. Physical evaluation

the patient shows dysmorphisms including squared-shaped face, high arched eyebrows, hyperthelorism, full cheeks, short philtrum, (Fig. 2a) and overweight (Body Mass Index: 26). Blood test and neuroimaging study were negative.

1.1.5. Cytogenetics

High resolution G-Banded karyotype and array-CGH analysis did not detect genomic rearrangements. Sanger sequencing and Multiplex Ligation-dependent Probe Amplification (MLPA) of *SCLC2A1* did not disclose mutations. A next generation sequencing panel exploring 23 genes associated with epileptic encephalopathy (for more details see the "Supplementary material") showed a heterozygous deletion c.4164del in exon 33. of *CHD2* (NM_001271.3) (Fig. 2b). This deletion creates a frameshift starting at codon Met1388. The new reading frame ends in a stop codon 17 positions downstream (p.Met1388Ilefs*18). The mRNA produced might be targeted for nonsense mediated decay. Segregation analysis showed a *de novo* origin of the mutation.

2. Discussion

CHD2 codes for a member of the chromodomain helicase DNA-binding family of proteins and 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 [1].

Some *CHD2* variants have been described as a risk factor for photosensitivity in epilepsy [2], that is present in about two-thirds of the cases. The *CHD2*- related epileptic phenotype can include different seizures types such as absences, myoclonic jerks, atonic, tonic, myoclonic–atonic, atonic–myoclonic, and GTCS, and convulsive and nonconvulsive status epilepticus. The seizures onset ranges from 6 months to 5 years and seizures are reported as drug-resistant [3,4].

In the majority of the cases a developmental delay was reported before seizure onset, mostly affecting the language. Moderate to severe ID, short-term memory problem, visual perceptual disability and short attention span have been reported. Behavioral disorders such as aggressive and impulsive, behaviour, repetitive behaviours, limited social skills were reported, more rarely ADHD or ASD.