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

S. Troisi[1], P. Bernardo[2], D. Galletta[3], F. Iasevoli[3], L. D'Ambrosio[3], E. Gennaro[4], F. Zara[5], S. Striano[1], A. de Bartolomeis[3], A. Coppola[1]

[1]*Department of Neuroscience, Reproductive and Odontostomatological Sciences, Epilepsy Centre, Federico II University, Naples, Italy*
[2]*Department of Mental Health, Physical and Preventive Medicine, Clinic of Child and Adolescent Neuropsychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy*
[3]*Section of Psychiatry Unit on Treatment Resistant Psychosis, and Laboratory of Molecular and Translational Psychiatry, Department of Neuroscience, University School of Medicine Federico II, Naples, Italy*
[4]*Genetic Laboratory, E.O. Ospedali Galliera, Genova, Italy*
[5]*Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, "G. Gaslini" Institute, Genoa, Italy*

Introduction

The gene *CHD2* (15q26.1) encodes chromodomain helicase DNA-binding protein 2, a protein that modifies gene expression, acting on chromatin structure.
CHD2 mutations were described in patients with photosensitive epilepsies, with myoclonic-atonic epilepsy, Lennox-Gastaut syndrome, Dravet syndrome and other forms of epileptic encephalopathies (EE). Furthermore *CHD2* mutations can contribute to a broad spectrum of neurodevelopmental disorders including intellectual disability (ID), autism spectrum disorders, developmental delay. Here we describe a patient bearing an unreported *de novo CHD2* frameshift mutation presenting with mild facial dysmorphism, infantile epilepsy, ID and severe behavioral disorder.

Case report

The proband is a 27-years old woman, first daughter of healthy unrelated parents.
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.

Physical evaluation. The patient shows mild facial dysmorphism (Fig 2a) and overweight. Her neurological examination, blood tests and neuroimaging study are negative.

Epilepsy and EEG findings. At the 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 reapperead with short lasting absences, myoclonic seizures and generalized tonic clonic seizures (GTCS). Lamotrigine was added on and she continued having 1-2 seizures/year. Her EEG showed interictal diffuse epileptic abnormalities (Fig1a,b). She is now seizure free since one year. Her last EEG is negative for epileptic abnormalities. Of note she never showed photosensitivity.

Neuropsycological and psychiatric profile. Examination of the cognitive and psychiatric features of the patient have been carried out at the age of 27. The patient showed a moderate intellectual disability and substantial impairments in all cognitive areas investigated by the tests. Mental state examination showed impairments in several behavioral domains, too. The patient reached low scores in all social cognition tests, consistently with a lack of social and emotional reciprocity. Clinical evaluation and the Ritvo Autism and Asperger's Diagnostic Scale (RAADS-R) excluded a frank diagnosis of Autism Spectrum Disorder, although the patient exhibited subthreshold autistic traits. The Mini-International Neuropsychiatric Interview (M.I.N.I) was used for diagnosis caterigorization: no primary psychiatric diagnosis was found, while the patient was best categorized as suffering from both Intellectual disability and Psychotic Disorder due to Another Medical Condition. All the tests and their results are synthesized in Table 1.

Citogenetics. Karyotype and array-CGH analysis resulted negative. Sanger Sequencing of *SLC2A1* didn't disclose mutations. The Next Generation Sequencing panel exploring 23 genes associated with EE revealed a heterozygous deletion c.4164del in exon 33 of *CHD2* (Fig 2b). This deletion creates a frameshift starting at codon Met1388: the new reading frame ends in a stop codon and the mRNA produced might be targeted for nonsense mediated decay. Segregation analysis showed a *de novo* origin of the mutation.

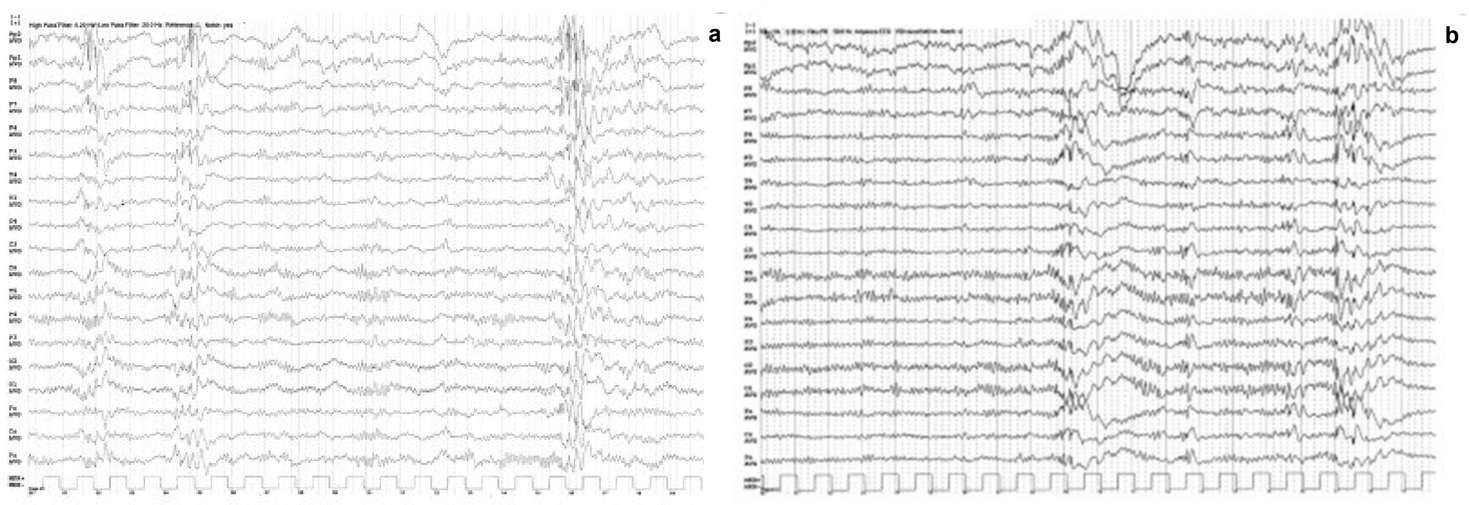

Fig 1. a) awake EEG performed at the age of 11 years showing a background activity of 8 Hz and **diffuse spontaneous multiple spike and spike-wave discharges** prevalent over the frontal area; b) awake EEG performed at the age of 25years showing epileptiform abnormalities characterized by diffuse spike and wave complexes.

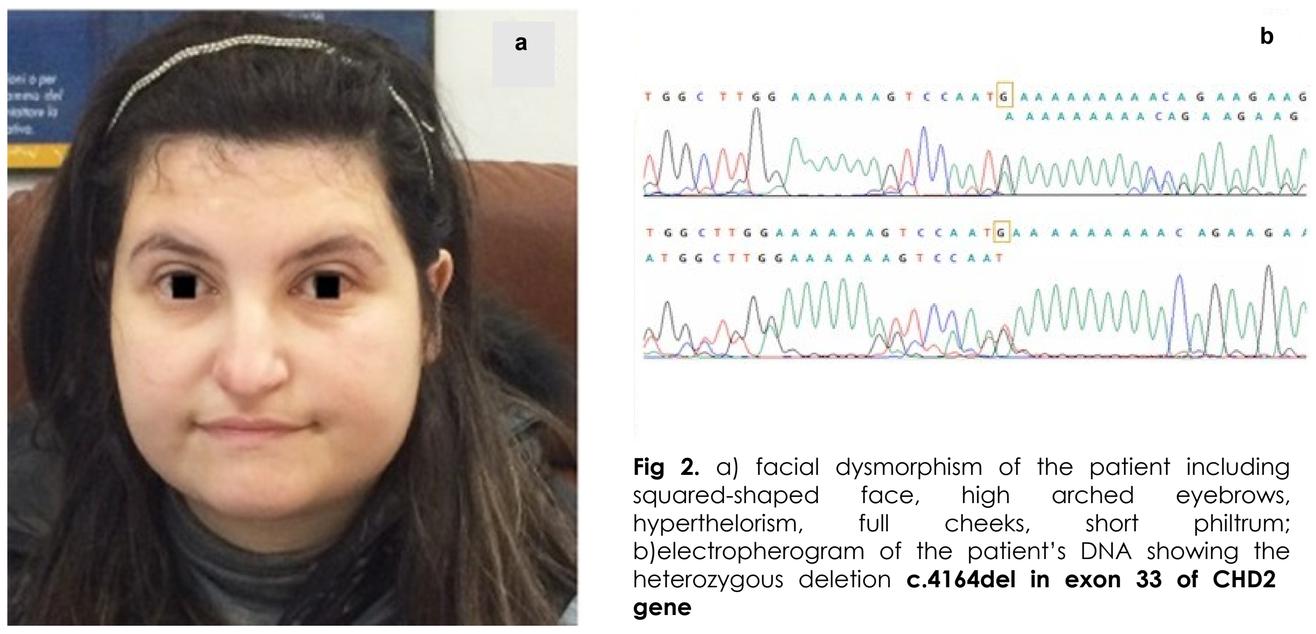

Fig 2. a) facial dysmorphism of the patient including squared-shaped face, high arched eyebrows, hyperthelorism, full cheeks, short philtrum; b)electropherogram of the patient's DNA showing the heterozygous deletion **c.4164del in exon 33 of CHD2 gene**

WAIS-R	**IQ 45** (homogenous verbal and performance IQ scores) **Moderate intellectual disability**
Neuropsychological Assessment	Impairment in immediate and delayed verbal learning, verbal fluency, executive functions, social cognitive ability
Brief Psychiatric Rating Scale Emotional	**Intermediate-high global score** (65): highest scores in the Withdrawal, Uncooperativeness, Hostility, Self-Neglect, Unusual Thought Content items
SCL-90R	**Intermediate level of psychiatric symptoms** (highest altered scores in Obsession-Compulsion, Phobic Anxiety, Psychoticism)
RAADS-R	Score 55 below the diagnostic threshold (>65)
M.I.N.I Plus 5.0.0	***Psychotic Disorder due to a General Medical Condition***

Table 1. Neuropsychological Assessment and evaluations carried out to provide a behavioral profile of the patient

Conclusions

Our patient showed a phenotipe affecting both neurological and psychiatric areas and characterized by: drug responsive childhood onset generalized epilepsy including myoclonic seizures, absences and GTCSs, moderate ID, severe behavioral problems and aberrant emotional and affective complex aspects disrupting social functioning.
We suggest that a multidisciplinary neurological and psychiatric evaluation should be advised for individual bearing *CHD2* mutations.

References

1. Woodage T, Basrai MA, Baxevanis AD, Hieter P, Collins FS. Characterization of the CDH family of proteins. Proc Natl Acad Sci USA 1997; 94:11472-7.
2. Galizia EC, Myers CT, Leu C, de Kovel CG, Afrikanova T, Cordero-Maldonado ML, et al. CHD2 variants are a risk factor for photosensitivity in epilepsy. Brain 2015; 138:1198-207.
3. Trivisano M, Striano P, Sartorelli J, Giordano L, Traverso M, Accorsi P, et al. CHD2 mutations are a rare cause of generalized epilepsy with myoclonic-atonic seizures. Epilepsy Behav 2015; 51:53-6.
4. Chénier S, Yoon G, Argiropoulos B, Lauzon J, Laframboise R, Ahn JW, et al. CHD2 haploinsufficiency is associated with developmental delay, intellectual disability, epilepsy and neurobehavioural problems. J Neurodev Disord 2014; 6:9.