Focal epilepsy in a patient with a *de novo* Xq25 duplication

Giulia Turchi[1], Anna Catone[1], Elvira Nicolella[1], Salvatore Striano[1], Antonietta Coppola[1]

[1]Centro Epilessia, Dipartimento di Scienze Neurologiche, Università Federico II, Napoli

Case report:

The proband is a 4-years-old man. He was born at term by panned cesarean section, after complicated pregnacy for an growth delay during the ninth month of pregnancy. At birth, the boy's weight was 2.1 Kg, and length was 48 cm. **Urogenital** (hypospadias and caliceal dilation) **and cardiac** (IVD left-right shunt; IAD with left-right stable shunt) malformations were diagnosed in neonatal period. A history of severe psycomotor delay was reported: he started walking at three years old and he never learn to speak fluently being able only to utter few words. At first medical examination, the proband showed **dysmorphic features**, (bitemporal constriction, turricephalia, small hands and tapered extremity **Fig 1 e 2**), and strabismus in the left eye. At the age of 15 months he experienced a generalized febrile seizures (38,5°). At the age of 3 years, he presented with afebrile tonic clonic seizure, during the awakening, with fecal incontinence. Valproate therapy was started. Seizures stopped after Levetiracetam treatment was added.

Methods:

We report the clinical, instrumental, cytogenetic and molecular investigations of a boy admitted to Epilepsy Center for epilepsy and intellectual disability.

Results:

The interictal EEG (fig. 5) showed right temporal focus, worsened by sleep. The parossistic activity is characterized by sharp-wave complex or sharp wave- slow wave complex. Awake EEG recorded showing background activity theta rhythm (6Hz), symmetric and monomorphic. The parossistic abnormalities are showed also during the awake EEG recorded but less evident.

The brain TC (fig. 3 e 3 a) showed a temporal arachnoid cyst. The cyst showed slow growth, so it was removed by surgical operation.

A high resolution chromosal analysis was performed, that resulted normal. A further screening for genomic rearrangements was performed by **array-CGH (Fig.5)**. This analysis revealed a chromosomic duplication on **Xq25,** encompassing 13 kb (122,673,975,123,546,561) 0,87 MB with negative maternal segregation, then *de novo* mutation

Fig. 1 e 2-Dysmorphisms (turricephalia, bitemporal costriction, tapered extremity)

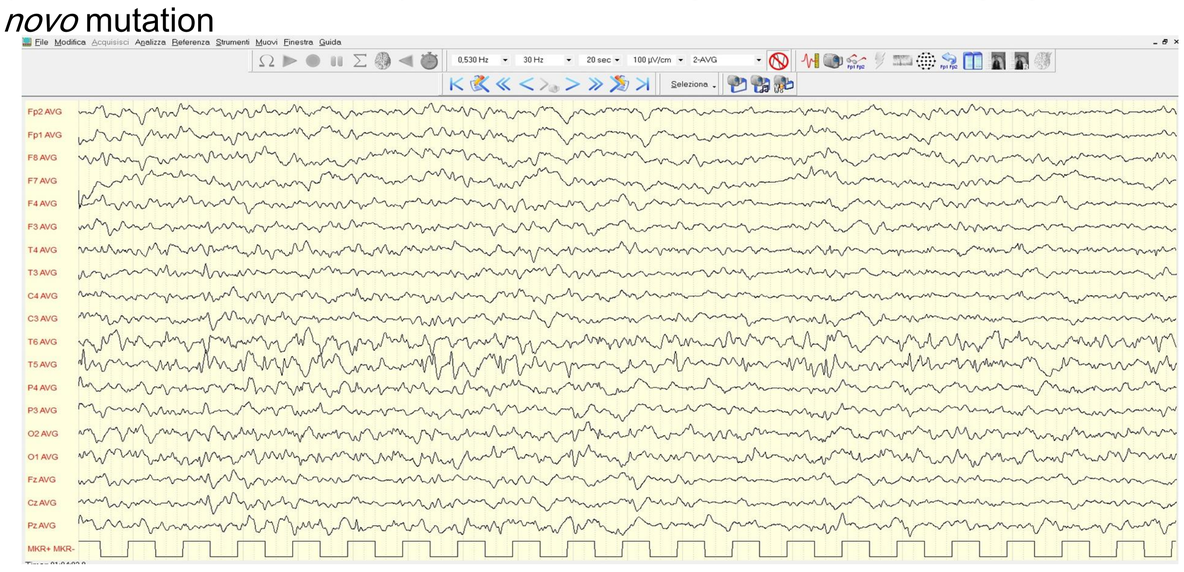

Fig. 4 – Interictal EEG during sleep:

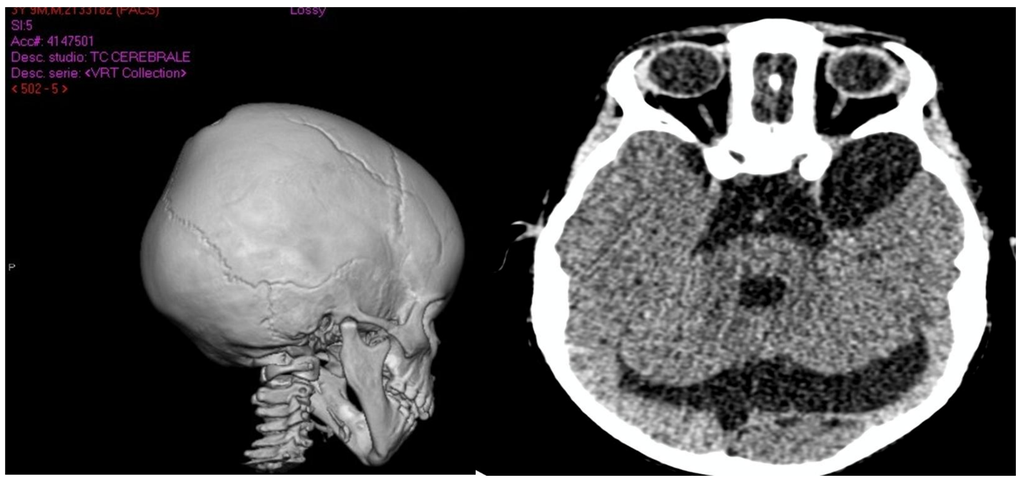

Fig 3 - Brain CT 3D reconstruction shows turricephalia

Fig 4- Brain TC show temporal arachonid cyst

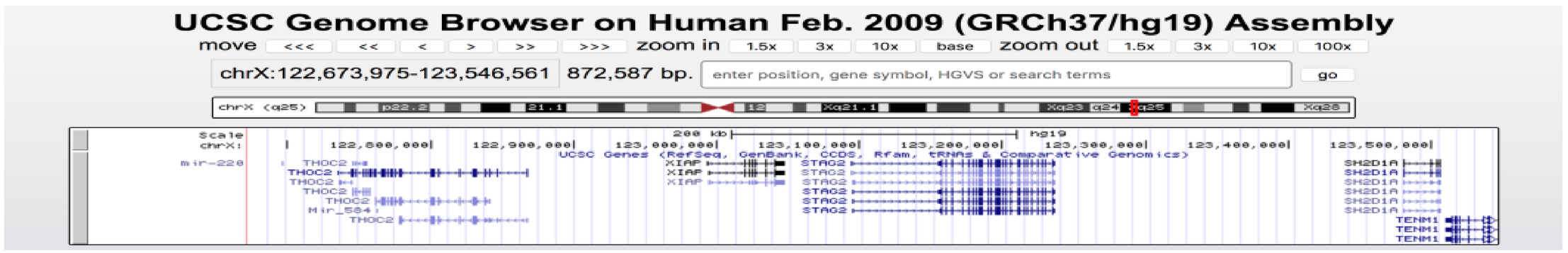

Fig. 5- Graphic presentation of array-CGH results. The analysis shows 0,87 MB duplication and the genes envolved in the duplication

Discussion:

The Xq25 duplication syndrome is a genomic disorder caused by submicroscopic duplication along the long arm of the X-chromosome. Here we reported the clinical case of a patient presenting with many of the common features of the syndrome (**delayed milestones, speech disturbances, intellectual disability**) and with seizures too. **Epilepsy in this syndrome is rare**. It has been described in less than 20% of the cases reported in literature, and there is not description of the characteristic and of the follow up. In our patient the onset of the seizures is in childhood and we achieved good control of the seizures with VPA and Lev.

In our patient the duplication involve three genes: *STAG2, THOC2 and XIAP*. Recent data refine the candidate region, identifying a minimal duplicated region, encompassing ***STAG2*** gene, which encodes a component of the cohesin complex. It was suggested that increased ***STAG2*** gene copy number and dysregulation of its downstream target genes may be **responsible** for the specific clinical findings of this syndrome.

References:

1.Xq25 duplication: the crucial role of STAG2 gene in this novel human cohesinopathy Leroy C. et al. Clin Genet. 2016 Jan;89(1):68-73. doi: 10.1111/cge.12567

2. Definition of minimal duplicated region encompassing the XIAP and STAG2 genes in the Xq25 microduplication syndrome. Di Benedetto D, et al. Am J Med Genet A. 2014 Aug;164A(8):1923-30. doi: 10.1002/ajmg.a.36570. Epub 2014 Apr 14

3Microduplication of chromosome Xq25 encompassing STAG2 gene in a boy with intellectual disability. Yingjun X, et al. Eur J Med Genet. 2015 Feb;58(2):116-21. doi: 10.1016/j.ejmg.2014.10.002. Epub 2014 Oct 24