CONTROL ID: 2326292

PRESENTATION TYPE: 1. Standard Poster

TITLE: MUTATIONS IN *HUWE1* CAUSE INTELLECTUAL DISABILITY, SPEECH DIFFICULTIES AND EPILEPTIC ENCEPHALOPATHIES

AUTHORS (LAST NAME, FIRST NAME): Johannesen, K.[1]; Fenger, C.[2]; Schweiger, S.[6]; Helbig, K. L.[3]; Abrahamsen, R.[2, 4]; Schubert, R.[5]; Striano, P.[7]; Uldall, P.[1]; Eysturoy, A.[2]; Larsen, L.[2]; Baranano, K.[8]; Cohen, J.[8]; Tommerup, N.[9]; Gardella, E.[1]; Dahl, H.[2]; Zechner , U.[6]; Rubboli, G.[1]; Møller, R. S.[1]

INSTITUTIONS (ALL):

1. Research, The Danish Epilepsy Centre Filadelfia, Dianalund, Denmark.
2. Amplexa Genetics, Odense, Denmark.
3. Division of Clinical Genomics, Ambry Genetics, Aliso Viejo, CA, United States.
4. Faculty of Medicine, University of Copenhagen, Copenhagen, Denmark.
5. Division of Pediatric Neurology, NY Methodist Hospital, New York, NY, United States.
6. Institut für humangenetik, Universitätsmedizin der Johannes Gutenberg-Universität, Mainz, Germany.
7. Pediatric Neurology and Muscular Diseases Unit, DINOGMI-Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, "G. Gaslini" Institute, Genova, Italy.
8. Kennedy Krieger Institute and Johns Hopkins, Maryland, MD, United States.
9. Willhelm Johannsen Centre for Functional Genome Research, Department of Cellular and Molecular Medicine, ICMM, The Faculty of Health Sciences, The University of Copenhagen, Copenhagen, Denmark.

CURRENT TOPIC: 11. Genetics

CURRENT SUB-TOPIC: 11A. Human Studies

ABSTRACT BODY:

Rationale: Many genes for X-linked Intellectual Disability (XLID) have been published recently, however in more than 50 % of XLID families the genetic causes still remain unclear. The same can be said about epilepsy syndromes, even though Next Generation Sequencing has revealed multiple novel genetic causes. The *HUWE1* gene is located on chromosome Xp11.22 and encodes an E3 ubiquitin ligase. Mutations in *HUWE1* have been described in several families with intellectual disability (ID). Typically males are affected, while females are asymptomatic carriers, or have a milder phenotype. Only a few patients with a *HUWE1* mutation and epilepsy have been described. In this paper we describe the phenotypic spectrum of seven patients with a *HUWE1* mutation and severe epilepsy.

Methods: We reviewed phenotypic data of patients with *HUWE1* mutations. The probands underwent detailed clinical examinations, review of the patients' medical records, neuroimaging and EEG investigations. Seizures were diagnosed according to the International League Against Epilepsy classification.

Results: We identified seven unrelated patients with a mutation in *HUWE1*. Three of the patients were girls. All mutations occurred *de novo*. The phenotypic spectrum included mild to severe intellectual disability, severe speech delay/speech difficulties and early onset epilepsy in all patients. The observed epilepsy phenotypes were broad and included focal epilepsy, Lennox-Gastaut syndrome, unspecified epileptic encephalopathy and Landau-Kleffner Syndrome. In one patient it was associated with progressive microcephaly and growth retardation. Seizures were intractable to a broad range of antiepileptic medications in the majority of the patients. The three girls all had epileptic encephalopathies, absent speech and moderate to severe ID. X-inactivation data was available for one of the females, showing a skewed X-inactivation.

Conclusions: The present study shows that mutations in *HUWE1* can cause severe epileptic encephalopathies, absent speech and moderate-severe ID in females. Furthermore, the study expands the phenotypic spectrum in males with *HUWE1* mutations from X-linked ID with or without treatable epilepsy to include severe epileptic encephalopathies. This study defines a novel gene for epileptic encephalopathies affecting both males and females.

(no table selected)

(No Image Selected)