GENOTYPE AND PHENOTYPE CHARACTERIZATION IN TWO PATIENTS WITH MEHMO SYNDROME

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INTRODUCTION

MEHMO sy. (Mental retardation, Epileptic seizures, Hypogonadism and –genitalism, Microcephaly, Obesity) is an X-linked disease previously described in three families only:

-*DeLozier-Blanchet et al, 1989, 1999* – 1 family with 2 affected members

-*Steinműller et al, 1998* - 1 family with 5 affected members, assigns the disease to locus Xp11.3-p22.13

-*Leshinsky-Silver et al, 2002* – 1 affected member, suggested mitochondrial involvement

The aim was to identify the genetic etiology in two unrelated Slovak male probands (4.5 and 1.5 years old, respectively) with the clinical diagnosis of MEHMO and describe the genotype-phenotype correlation.

PATIENT PHENOTYPE

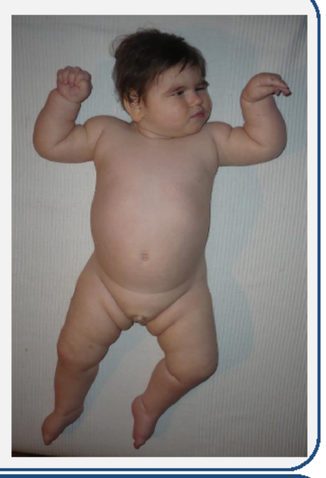
The first patient 4.5 years old boy suffering from:

- **severe psychomotor delay** (corresponding to 2nd-3rd month), **microcephaly** with facial stigmatization (full cheeks, downturned mouth corners, almond-shape eyes , long eye lashes, hypotelorism, large thick ears), **axial hypotonus**, edematous hands and feet, tapered fingers, **epilepsy** (several seizures a day despite combination of antiepileptic drugs)
- **kryptorchism, micropenis, panhypopituitarism** (low levels of growth hormone, TSH, ACTH), **diabetes** (hypoglycemias in the first 6 months of life, later hyperglycemia requiring insulin treatment, no positivity of islet autoantibodies)

Family history - non-consanguinous parents, no other boys from the side of the mother - mother s mother had 1 miscarriage (gendre unknown) and a brother who died in the first months of life – **X-linked recessive inheritance**.

The second patient 1.5 years old boy – similar features

The clinical picture and family history indicated towards the MEHMO syndrome.



METHODS

the library was prepared from whole blood DNA using **Agilent V4+UTR** and sequenced using **HiSeq2500** (TheragenEtex, South Korea).
All variants on X chromosome without rs or without MAF in dbSNP were analysed by **Sanger sequencing** in patient and his family.

RESULTS

Candidate variant identification process

whole exome sequencing → **22** new variants on X chr. → **18** confirmed by Sanger sequencing → **4** shared by the patient, his mother and grandmother → **1** in the Xp21.1-p22.13 region

Figure 2: Cosegregation analysis in the family – all 18 new variants and 6 common SNPs were used as markers for X-chromosome haplotyping.

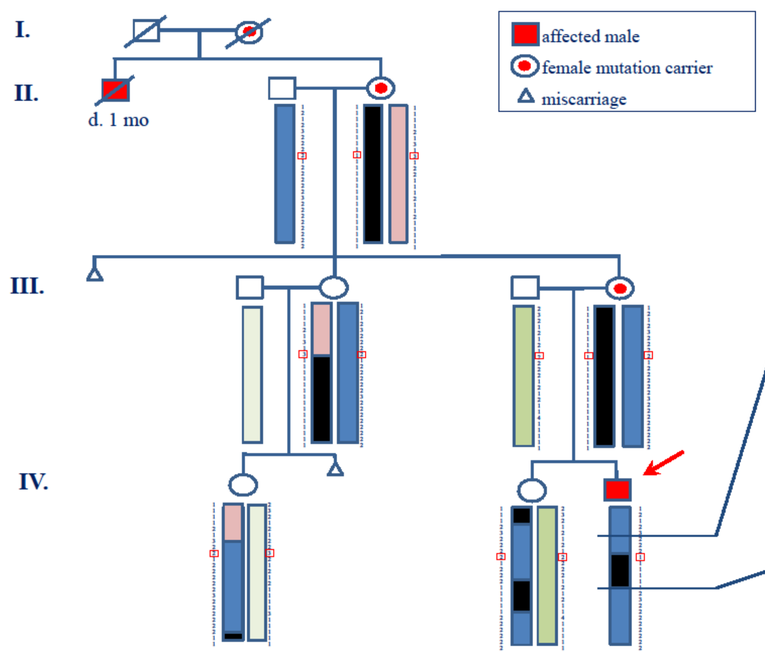


Table 1: Variants in the region of interest.

Chr. position hg19	Ref	Alt	Locus	MAF	Effect	PhyloP/ PhastCons	SIFT/ Provean/ PolyPhen-2	Mutation Taster	Associated phenotype
20043124	G	A	***MAPD7D2***	-	R412W	4.9/1	0.001/-7.9/1	D	Trapped gene – no phenotype
21392748	A	AGCC	***CNKSR2*** (rs76791548)	-	5 UTR	-/-	-/-/-	P	ID, microcephaly, epilepsy
21392943	T	A	***CNKSR2***	-	5 UTR	0.29/0.96	-/-/-	D	
24094873	ACAAT	A	***EIF2S3***	-	I465Sfs*4	5.131/ 1 0.191/ 1 4.177/ 1 4.177/ 1	-/-12.6/-	D	ID, ID+microcephaly
30254361	G	A	rs2071308	0,47	R107H				
37700372	C	G	***DYNLT3***	-	intron	0.08/0.001	-	P	Parkinson s disease
53578326	G	A	***HUWE1***	-	P2999	-1/0.02	-	P	ID
68061200	C	CCA	***EFNB1***	-	3 UTR	-/-	-	D	Craniofrontonasal sy.
88008807	G	A	rs5984611	0,23	R131H				

phyloP score: negative sign indicates faster-than expected evolution, while positive values imply conservation
PhastCons score: is a probability that each nucleotide belongs to a conserved element
SIFT: Variants with a score below 0.05 are considered "damaging„ ; *Provean:* Variants with a score equal to or below -2.5 are considered "deleterious„. *PolyPhen-2:* 1-probably damaging, 0-benign; *MutationTaster:* P - polymorphism, D – disease causing
ID – intellectual disability

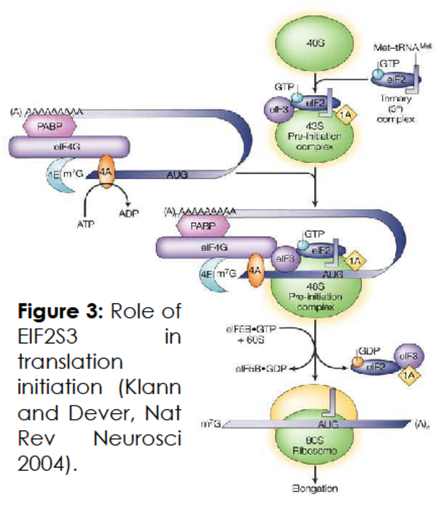


Figure 3: Role of EIF2S3 in translation initiation (Klann and Dever, Nat Rev Neurosci 2004).

EIF2S3 encodes a γ subunit of eukaryotic translation initiation factor 2 (eIF2) - responsible for transporting the initiator Met-tRNA$_i^{Met}$ to the 40S ribosomal subunit.
Protein eIF2γ has 472 aminoacids. The variant **p.I465Sfs*4 found in both of our probands** is a frame-shift mutation with a premature stop codon influencing 8 last amino acids of the protein conserved in vertebrates (Figure 4). *In silico* analysis evaluate this change as disease causing.

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422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTSQQ---------  467  HUMAN_I465S*fs4
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  HUMAN
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  ORANGUTAN
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  COW
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  RAT
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  MOUSE
422  ADLGKIVLTNPVCTEVGEKIALSRRVEKHWRLIGWGQIRRGVTIKPTVDDD----  472  CHICK
421  GDLAKIVLTTPVCTEKGEKIALSRRVENHWRLIGWGQIFGGKTITPVLDSQVAKK  475  DROSOPHILA
480  ADMARLQLTSPACTEINEKIALSRRIEKHWRLIGWATIKKGTTLEPIA--------  527  YEAST
     .*:.:: **.*.***  ********:*:*******. *  * *
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Figure 4: Alignment of the C-terminal end of I465S*fs4 variant with eIF2γ of other vertebrates, Drosophila and the yeast.

Other known variants - point mutations in this gene were previously described in families with intellectual disability:
- Tarpey et al., 2009 – **p.V151L** in one and **p.K125R** in 8 families with ID, no further phenotype specified.
- Borck et al., 2012 – **p.I222T** in one family with 3 affected male members with ID, microcephaly, and short stature, plus generalized seizures in one and microgenitalism and obesity in another patient.

CONCLUSIONS

We have identified a novel mutation p.I465Sfs*4 of EIF2S3 in both of our MEHMO patients.
Our results support the role of EIF2S3 as a candidate gene, disruption of which might significantly contribute to severe clinical symptomatology of MEHMO syndrome.

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