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
- Steinmüller 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 to 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 stigmata (full cheeks, downturned mouth corners, almond-shape eyes , long eye lashes, hypotelorism, large thick ears), axial hypotonia, edematous hands and feet, tapered fingers, epilepsy (severes a day despite combination of antiepileptic drugs)
- kyphorachism, microopen, 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-consanguineus parents, no other boys from the side of the mother - mother's mother had 1 miscarriage (gender 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 (IllumagenExe, 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

Figure 2: Co-segregation 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.

<table>
<thead>
<tr>
<th>Chr position</th>
<th>Ref</th>
<th>All</th>
<th>Locus</th>
<th>MAF</th>
<th>Effect</th>
<th>Pheno/Phenocens</th>
<th>NFT/Prov/Phen/Phen-2</th>
<th>Mutation Taster</th>
<th>Associated phenotype</th>
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</thead>
<tbody>
<tr>
<td>26043124</td>
<td>G</td>
<td>A</td>
<td>MAPD7D2</td>
<td>-</td>
<td>R121W</td>
<td>0.001</td>
<td>D</td>
<td>-</td>
<td>Trapped gene – no phenotype</td>
</tr>
<tr>
<td>21392748</td>
<td>A</td>
<td>AGG</td>
<td>CNKRS2</td>
<td>-</td>
<td>5 UTR</td>
<td>0.199</td>
<td>D</td>
<td>-</td>
<td>ID, microcephaly, epilepsy</td>
</tr>
<tr>
<td>21392943</td>
<td>T</td>
<td>A</td>
<td>CNKRS2</td>
<td>-</td>
<td>5 UTR</td>
<td>0.280</td>
<td>D</td>
<td>-</td>
<td>ID, microcephaly, epilepsy</td>
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<tr>
<td>24094873</td>
<td>ACAAT</td>
<td>A</td>
<td>EIF25</td>
<td>-</td>
<td>16565s*4</td>
<td>0.133</td>
<td>D</td>
<td>-</td>
<td>ID, ID=microcephaly</td>
</tr>
<tr>
<td>9825256</td>
<td>G</td>
<td>A</td>
<td>DYNL1</td>
<td>-</td>
<td>intron</td>
<td>0.008</td>
<td>D</td>
<td>-</td>
<td>Parkinson's disease</td>
</tr>
<tr>
<td>5357826</td>
<td>G</td>
<td>A</td>
<td>HUE1</td>
<td>-</td>
<td>P2999</td>
<td>0.030</td>
<td>D</td>
<td>-</td>
<td>ID</td>
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<tr>
<td>60861200</td>
<td>CCA</td>
<td>CCAC</td>
<td>EFNB1</td>
<td>-</td>
<td>3 UTR</td>
<td>0.077</td>
<td>D</td>
<td>-</td>
<td>Caudatefrontal sp.</td>
</tr>
<tr>
<td>16684307</td>
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<td>MAPD7D2</td>
<td>-</td>
<td>R121W</td>
<td>0.001</td>
<td>D</td>
<td>-</td>
<td>Trapped gene – no phenotype</td>
</tr>
</tbody>
</table>

EIF253 encodes a y subunit of eukaryotic translation initiation factor 2 (eIF2) - responsible for transporting the initiator Met-tRNAMet to the 40S ribosomal subunit.

Protein eIF2y has 472 aminoacids. The variant p.I4665s*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 evaluates this change as disease causing.

Other known variants - point mutations in this gene were previously described in families with intellectual disability:
- 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.I4665s*4 of EIF253 in both of our MEHMO patients.

Our results support the role of EIF253 as a candidate gene, disruption of which might significantly contribute to severe clinical symptoms of MEHMO syndrome.

REFERENCES


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