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Expanding the phenotype of the truncating eIF2? pathogenic variant p.(Ile465Serfs*4) identified in two brothers with MEHMO syndrom

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Abstract

We describe two brothers with a truncating variant in EIF2S3 and expand the phenotypic description of MEHMO. Our cases had the previously described facial dysmorphic features, severe microcephaly, hypoglycaemia, hypothyreosis, epilepsy, hypertonus, obesity, micropenis and death due to multiorgan failure. Additionally, we describe hypothermia and reduced umbilical blood flow.

Εξπανδινγ τηε πηενοτψπε οφ τηε τρυνςατινγ εΙΦ2γ πατηογενις αριαντ π.(Ιλε465Σερφς*4) ιδεντιφιεδ ιν τωο βροτηερς ωιτη MEHMO σψνδρομε

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ABSTRACT

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We describe two brothers with a truncating variant in *EIF2S3* and expand the phenotypic description of MEHMO. Our cases had the previously described facial dysmorphic features, severe microcephaly, hypoglycaemia, hypothyreosis, epilepsy, hypertonus, obesity, micropenis and death due to multiorgan failure. Additionally, we describe hypothermia and reduced umbilical blood flow.

Key words: MEHMO syndrome, *EIF2S3,* Whole exome sequencing

INTRODUCTION

There are many genetic conditions that are linked to various aspects of protein translation in humans, including Vanishing White Matter Disease and Wolcott–Rallison syndrome. The main regulatory step of translation is the initiation. To initiate protein translation in a mammalian cell, a ternary complex consisting of one GTP, the initiator methionyl-tRNA, and the translation initiation factor eIF2 is required. The core subunit is called eIF2γ, and is encoded by *EIF2S3* , located on the X-chromosome. The first paper linking this gene to disease appeared in 2012, when a missense variant was linked to a clinical phenotype with moderate-to-severe ID, microcephaly, short stature, and facial dysmorphic features in three male patients of the same family (Borck et al., 2012). Subsequently, a more severe phenotype with severe developmental delay, hypertonus, epilepsy and short lifespan was described to result from a truncating variant in *EIF2S3* (Moortgat et al., 2016). A genetic retrospective analysis of a clinical group of patients described in 1998 as suffering from MEHMO syndrome (MIM# 300148) (Steinmuller et al., 1998), revealed that this group had pathogenic variants in *EIF2S3* . The first description included**M** ental retardation, **E** pileptic seizures,**H** ypogonadism and -genitalism, **M** icrocephaly,**O** besity, and hence the acronym. Here, we describe an expanded MEHMO phenotype in two brothers with attenuating variants in*EIF2S3* .

MATERIAL AND METHODS

Key features

Microcephaly, Hypoglycaemia, Diabetes Mellitus, Hypothyreosis, Epilepsy, Hypertonus, Obesity, Micropenis

Ethics approval was given by the Regional Ethical Review Board in Stockholm, Sweden (ethics permit number 2012/2106-31/4). Written consent from the family was provided for genetic studies and for the publication of the cases including pictures.

Clinical summary

The index case was the third child of non-consangineous parents. He was delivered prematurely with C-section at age 34+4 due to reduced umbilical blood flow. It was noted that the umbilical cord was thick and had a jelly-like appearance. His weight was 1627 g (-3SD), his head circumference 28,5 cm (-3SD) and his length 39 cm (-4SD) (Fig1A). His APGAR was 9,10,10, and apart from an early hypoglycemic event, and one suspected seizure, he was stable during the neonatal period. Magnetic Resonance Imaging (MR) performed at age 2 months showed large ventricles with thin periventricular substance, underdeveloped corpus callosum, and a delayed myelination. Metabolic investigation did not reveal any cause. CGH-array did not show any alterations of significance. He initially had repeated episodes of hypoglycaemia, and was diagnosed with hyperinsulinemia, for which he received diazoxide. Unfortunally, this induced a lung edema, and was discontinued. He subsequently shifted to an insulin dependent diabetes instead. At age three months he developed epilepsy with multiple seizure types: generalized tonic-clonic, migrating focal, myoclonias and absenses. Virtually no response to anti-epileptic treatment was noted despite trying Levetiracetam, Lamictal, Lakosamide, Clonazepam, Fenobarbital and Zonisamid. He also had numerous central endocrinologic symptoms, including hypothyreosis, obesity and micropenis. In addition, he was often hypothermic, even at ambient room temperature, down to 32° C rectal temperature. He had a poor exocrine pancreatic function, with low pancreatic amylase, despite normal ultrasound of the abdomen, and required substitution of fat-soluble vitamins. He did however, never develop pancreatitis. He had until his death, in multiorgan failure, virtually no development. He had a progressive microcephaly, and obesity, despite adequate nutrition (Fig 1A, 1B).

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He had an older brother (Fig 1C), born in Germany 2001, with an almost identical clinical presentation, with the exception of the hypothyreosis. He also died at age 4 years.

RESULTS

Whole exome sequencing was performed and analysed as previously described(Tham et al., 2015) and revealed a hemizygous four basepair deletion in EIF2S3, c.1394_1397del, located on the X-chromosome in both boys and their mother who was a healthy heterozygous carrier of the variant. The variant leads to a premature stop codon p.(Ile465Serfs*4) in the final exon of the gene (Fig. 2).

DISCUSSION

We describe two boys with a clinical picture that included premature birth due to reduced umbilical blood flow, growth retardation, progressive microcephaly, hypothermia, micropenis, hypothyreosis, obesity, diabetes as well as exocrine pancreatic failure. We found that both boys carried a truncating pathogenic variant towards the C-terminal end of eIF2γ. , c.1394_1397del (p.Ile465Serfs*4). This is the exact same variant as described in the paper of Moortgat et al. 2016 (Moortgat et al., 2016). That family was of Spanish origin and the mother in our family originates from northern Sweden, and we do not suspect a common heritage indication that the variant has arisen independently at least twice. There are several similarities between the affected individuals in Family 2 described by Moortgat et al. (Moortgat et al., 2016) and the cases reported here; including characteristic facial dysmorphic features (fig 1B, 1C), poor development, severe microcephaly (-3SD vs -4SD), initial hypoglycaemia, epilepsy, hypertonia, micropenis and finally death due to multiorgan failure. In contrast, our patients survived longer (4 years vs 12 months), which may partially explain the additional phenotypes. Some phenotypes were known from other MEHMO cases, such as diabetes, poor pancreas function and obesity (Borck et al., 2012, Gregory et al., 2019, Skopkova et al., 2017, Stanik et al., 2018, Steinmuller et al., 1998, Kotzaeridou et al., 2020). However, nor the hypothermia, neither the reduced umbilical blood flow, that resulted in premature delivery in our boys was previously described.

Human body temperature is sensed by a system of thermoreceptors located in the core and the periphery, in order to detect real and anticipated temperature alternations, respectively. Signals from these are connected to the lateral parabrachial nucleus (LBP) of the pons and the pre optic area (POA) located just by the anterior hypothalamus. Signals indicating low temperature will activate physiological responses such as vasoconstriction, shivering and non-shivering brown adipose thermogenesis. Structural damage to the LBP is known to abolishes behavioural temperature responses (Yahiro et al., 2017). POA is key to activation of all the physiological responses. Our patients had signs of vasoconstriction with colder extremities, though they were never seen shivering, indicating a partial failure to activate compensating systems. In addition, the anterior hypothalamus is important for thyroid regulation, growth hormone and gonadotropic hormones, all affected in our boys. Structural defects in the hypothalamus were not detected in our patients, but the MR investigations were not optimized to study the hypothalamus.

The ultrasounds performed during pregnancy indicated initial normal fetal growth, but in mid pregnancy (week 31) reduced fetal growth was noted. The boys were delivered by C-section at 34+4 and 35+3 due to absent umbilical artery end diastolic flow, indicating primary increased placental resistance or secondary such due to fetal hypoxia. Neither the MR performed, nor the clinical picture, indicated chronic or acute hypoxia. The molecular cause remains elusive.

The 2 novel phenotypes, hypothermia and reduced umbilical flow has to our knowledge not been associated with any related condition such as Vanishing White Matter disease (MIM# 606686, MIM# 606454, MIM# 606273, MIM# 606687, MIM# 603945; EIF2B1, EIF2B2, EIF2B3, EIF2B4 and EIF2B5), varinats in PPP1R15B, Wolcott Rallisson syndrome (MIM# 226980; EIF2AK3), or MEDS syndrome (MIM# 614231; IER3IP1).

A recent paper has unravelled the exact molecular mechanism of this specific variant (Young-Baird et al., 2020). The authors show that the variant impairs eIF2 function and leads to a chronic activation of the integrated stress response and neuronal differentiation results. Intriguingly, this can be reversed by the small

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molecule ISRIB, which raises treatment hopes in this devasting disease.

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CONFLICTS OF INTEREST

None declared.

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FIGURE LEGENDS

Figure 1.

A. Growth chart showing head circumference, weight and length, in relation to standard curves from sibling born 2015.

B. Picture of sibling born 2015 and 1C picture of sibling born 2001.

Figure 2.

On top, a schematic drawing of the eIF2γ protein. The location of the variant in the 3' end is indicated with a black line and a screen shot from the Integrative Genomics Viewer (IGV) illustrating the 4 bp deletion. Below the EIF2S3 protein structure is outlined with the variant indicated as well as conservation in four different species.

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`FIG1 EIF2S3.pptx` available at https://authorea.com/users/452471/articles/550534-expanding-the-phenotype-of-the-truncating-eif2-pathogenic-variant-p-ile465serfs-4-identified-in-two-brothers-with-mehmo-syndrom