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Clinical description of Familial Cavernous Malformations

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INTRODUCTION

We describe a case report of father and son of Armenian origin diagnosed with Familial Cavernous Malformations.

CLINICAL MANIFESTATIONS

✓ Father, 78 years old:
- left n. abducens palsy with diplopia to the left has been persisting for 1 year
- rare generalized tonic-clonic seizures in 3-th and 4-th decade
- secondary diffuse, tension-type, relapsing headache has been persisting for 2 year
- rapidly growing soft-elastic neck lump, about 20 cm in diameter, histologically confirmed as benign epithelial cyst (Fig. 1.)

✓ Son, 34 years old:
- a cluster of 2 generalized tonic-clonic seizures in 2011

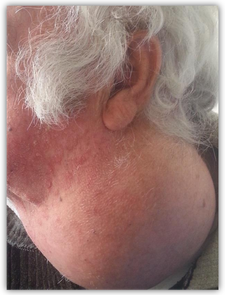


Fig. 1. Soft-elastic neck lump (father)

LABORATORY INVESTIGATIONS AND IMAGING

✓ Laboratory tests (FBC, basic metabolic panel, lipid panel) – no abnormalities
✓ ELISA IgM negative for Toxocariasis, Toxoplasmosis and Echonococcosis (father)
✓ Genetic testing: negative for Von Hippel-Lindau Syndrome; detected c.1061_1064dup mutation
✓ Imaging:
- abdominal CT and fundoscopy – no specific findings
- head MRT – typical finding of multiple brain cavernomas (Fig. 2. and 3.)

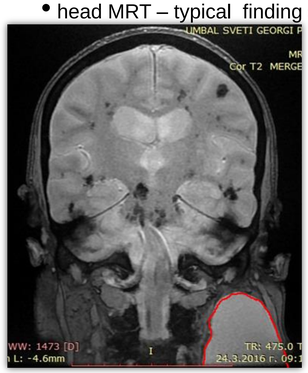


Fig. 2. Coronal MRT Cor 2 MERGE image (father) – multiple hypointense sub- and supratentorial lesions
***additional finding (red line) - homogenous liquid equivalent lesion in left neck region**

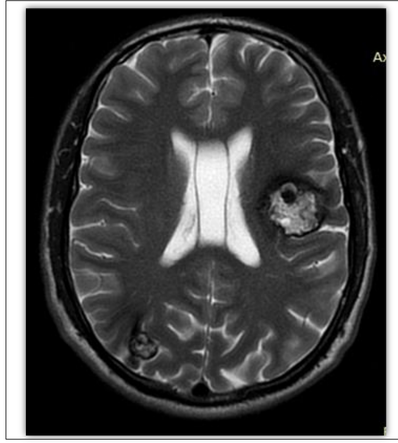


Fig. 3. Transversal MRT T_2 image (son) – two supratentorial lesions with typical "pop-corn like" image

GENETICS

Table 1. Domains, binding targets and function of Krev interaction trapped protein 1

DOMAIN	BINDING TARGET	FUNCTION
ICAP-1α (Integrin cytoplasmic domain-associated protein alpha)	β_1 integrin subunit cytoplasmic domain	cell migration, adhesion and proliferation
4 Ankeryn repeats	nuclear, extracellular and intracellular protein-protein interactions	signal transduction
RAP1A (Krev Interaction Trapped-1)	RAS GTPase	RAP1A-dependent sell proliferation
FERM (4.1 ezrin/radixin/moezsin) domain	F-actin and integral membrane proteins	signal transduction and cytoskeleton

Table 2. Confirmed genetic characteristics of KRIT1 and mutation

INHERITANCE PATTERN	Autosomal Dominant	heterozygous carriers of pathogenic variant
GENE	KRIT1, ankeryn repeat containig	with 19 exons
PROTEIN	Krev interaction trapped protein 1	with 736 amino acids
LOCUS	7q21.2	in exon 11
MUTATION	c.1061_1064dup	frameshift
RESULT	p.Ser356ThrfsX2	replacement of Serine in 356 place with Threonine and cease of translation

Fig 4. Scheme of c.1061_1064dup mutation

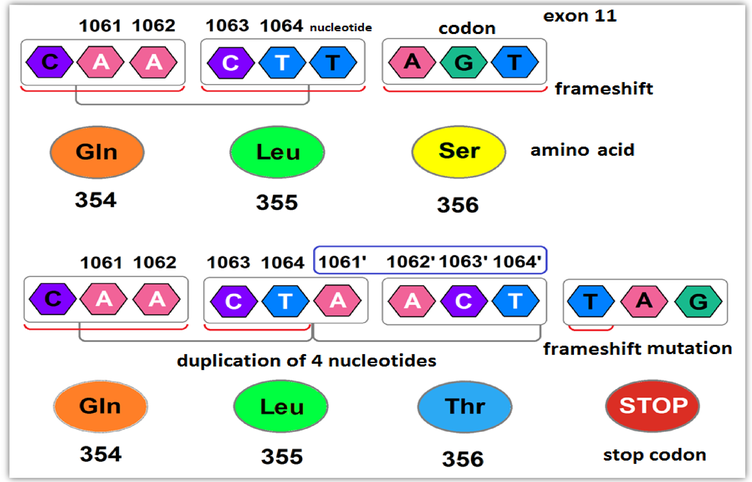
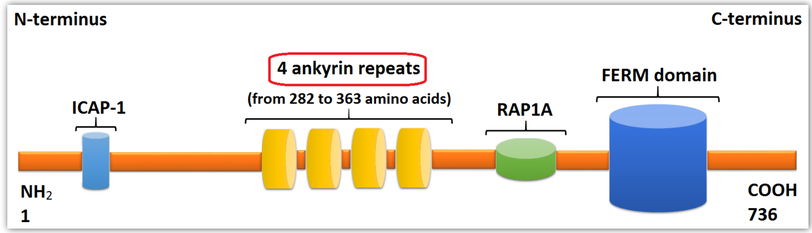


Fig. 5. Domains of Krev interaction trapped protein 1



CONCLUSION

1. The case report is the first genetically confirmed family with cerebral cavernous malformations in Bulgaria.

2. In contrast to the multiple lesions in the brain stem, cerebellum and subcortical white matter, typical symptoms of mild severity are present - epileptic seizures and abducens nerve palsy.

3. The case report will be helpful for the improvement of the etiological classification of brain vascular malformations through genetic testing. That will be crucial for their diagnosis, therapeutical approach and prognosis.