TBCK related encephalopathy

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Introduction

TBCK (TBC1-domain-containing kinase) is involved in the regulation of mTOR signal pathway, which is the central regulator for both cell proliferation and cell growth. Mutation of TBCK may cause TBCK related encephalopathy or TBCK syndrome characterized by dysmorphic face, hypotonia, global developmental delay and epilepsy.

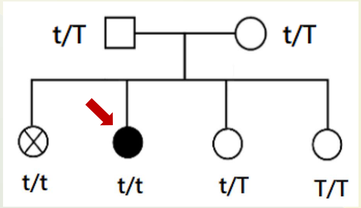
Objectives

The syndrome is a rare neurogenetic disease and scarcely reported in the literature. Recently we encountered this syndrome in one family.

Materials & Method

We followed up a family with unrelated, healthy parents who subsequently had initial two daughters suffering from developmental delay, intellectual disability and epilepsies. They later got birth to two normal daughters (Fig.1). To explore the genetic role, the family was requested to receive whole exome sequencing (WES) studies.

Figure 1. Family pedigree



Legend:

- The proband is a 28 y/o girl suffering from motor delay, intellectual disability and epilepsy.
- Elder sister had the same prototype, died of pneumonia at 14 y/o.
- The two younger sisters and parents were normal.

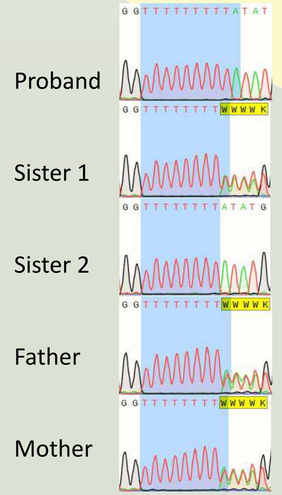
Results

While the 1st child died at 14 y/o without genetic testing, WES reported a TBCK mutation from the 2nd child (proband). Then through Sanger sequencing, both parents and the 3rd daughter were confirmed to have heterozygous TBCK mutation and the 4th daughter did not carry the mutation gene (Table 1 & Fig.2). The family pedigree demonstrated an autosomal recessive trait in transmission.

Table 1. Pedigree of TBCK mutation in the family

Name	Gene	Mutation	Zygosity	ACMG/ AMP 2015
Elder sister	?	?	?	?
Proband	TBCK	C.1370dup	Homo	pathogenic
Younger sister 1	TBCK	C.1370dup	Hetero	(-)
Younger sister 2	(-)	(-)	Normal	(-)
Father	TBCK	C.1370dup	Hetero	(-)
Mother	TBCK	C.1370dup	Hetero	(-)

Figure 2. Sanger sequencing



Conclusions

1. TBCK syndrome was first described in medical literature in 2016, and estimated over 100 members globally via TBCK foundation, 2023.
2. This report gives an example of autosomal recessive inheritance of a rare genetic disease.
3. With proper utilizing of the modern genetic testing such as next generation sequencing, more cases will be discovered and may be helpful for clinical understanding and genetic counselling.

References

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