Mutation c.396dupT in the *CLN6* gene – the main cause of neuronal ceroid lipofucinosis in Yakutia

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Introduction

The neuronal ceroid lipofuscinosis (NCLs) are neurodegenerative disorders, mostly of childhood onset. They form a heterogeneous group of lysosomal storage diseases with a prevalence of 1:14000 to 1:1000000 worldwide, depending on the region. The clinical features of NCL include visual loss, seizures, ataxia, epilepsy and both mental and motor deterioration. Today, at least 14 affected genes are implicated, from *CLN1* to *CLN14*, 13 of which have been identified (*CLN1-8* and *CLN10-14*).

Aim

To investigate a mutation c.396dupT in 4 exon of *CLN6* gene among patients diagnosed with suspected neuronal ceroid lipofuscinosis

Materials and methods

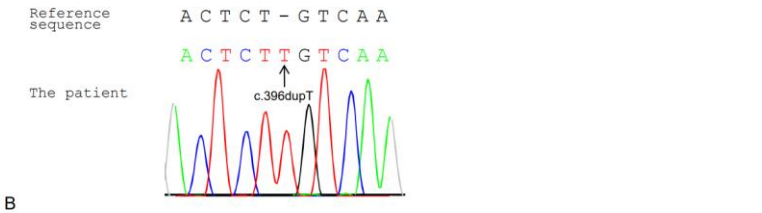
A total of 33 DNA samples from patients registered at the Medical Genetic Center of the National Center of Medicine (Yakutsk) with were studied.

3 patients were subjected to molecular genetic testing using exome sequencing using the TruSight Inherited Disease panel (Illumina, USA) on the MiSeq genetic sequencer (Illumina, USA). The results were validated by Sanger direct sequencing.

The remaining 30 patients were analyzed with commercial kits made to order (TestGene, Russia) by real-time PCR.

RESULTS

A



B

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                                                  *
H.sapiens     100 LIERSPRTLPRSITYVSIIIFIMGASIHLVGDSVNHRLLFSGYQHHLSVR 149
C.lupus       101 LIERSPRTLPRSVIYVSIITFVMGASIHLVGDSVNHRLLFSGYQHHLSVR 150
B.taurus      100 LIERCPRTLPRSLIYVSIITFIMGASIHLVGDSVNHRLIFSGYQNHLSVR 149
M.musculus     97 LIERSPRTLPRSIVYVSIITFIMGASIHLVGDSVNHRLLFSGYQHHLSVR 146
R.norvegicus   97 LMERSPRTLPRSIIYVSIITFIMGASIHLVGDSVNHRLLFSGYQHHLSVR 146
G.gallus      100 LIERSPKTLPRSMVYVSIITFVMGASIHLVGDSVNHRLIFSGYQHHLSVR 149
X.tropicalis   90 LIERSPKTLPNSVIYVSIITFVMGASIHLVGDSVNHRLIFSGYQLHLSVR 139
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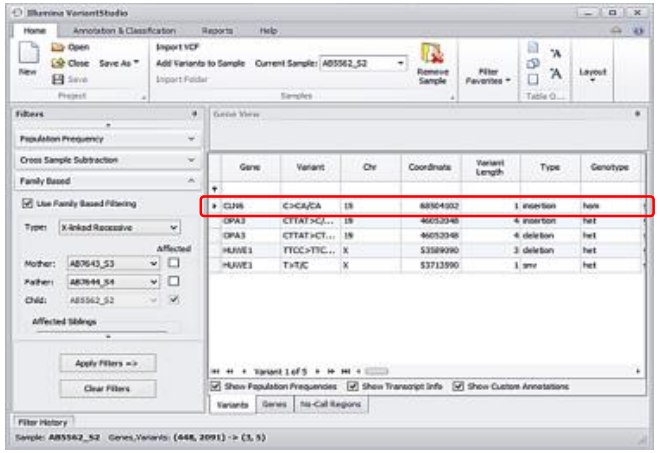
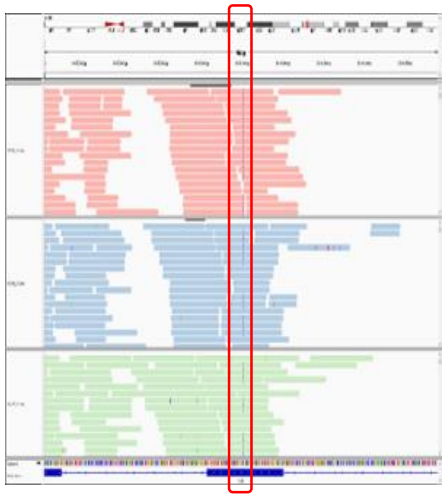
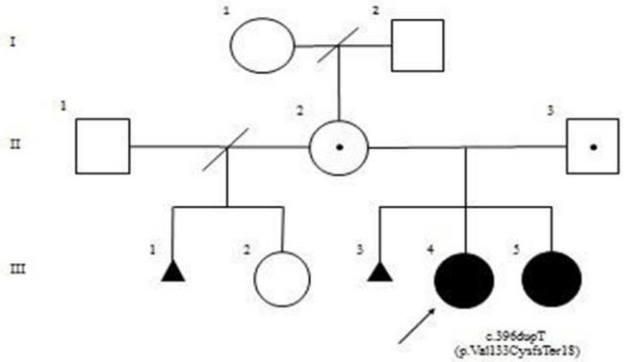
A - Results of Sanger sequencing of the Yakut family, showing a homozygous variant of c.396dupT in exon 4 of the *CLN6* gene;

B - Analysis of the amino acid sequence of the *CLN6* gene using the MUSCLE Sequence Alignment Tool shows that Val133 is highly conserved in vertebrates.



- Of 33 patients, 26 cases had of neuronal ceroid lipofuscinosis type 6, in 7 patients a mutation in the *CLN6* gene was excluded, and are currently registered with a diagnosis of leukodystrophy.
- All patients of the Yakut ethnic group.





Fragment of the pedigree of a family with NCL6
Type of inheritance: autosomal recessive

The clinical picture: the onset of the disease at the age of 3-4 years, impaired coordination, frequent falls, regression of psychomotor development, seizures, atrophy or subatrophy of the optic nerves, the development of dementia in the later stages.

CONCLUSION

In Yakutia, the most common form of neuronal ceroid lipofuscinosis is type 6, caused by a mutation c.396dupT in 4 exon of *CLN6* gene. Perhaps the reason for the accumulation of this disease is also the founder effect, as in other monogenic diseases common in Yakutia, this requires further study. Also, in 7 patients, the study will be continued to clarify the diagnosis.

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