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

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Motivation and Aim: The neuronal ceroid lipofuscinosis (NCLs) are neurodegenerative disorders, mostly of childhood onset [1]. They form a heterogeneous group of lysosomal storage diseases with a prevalence of 1:14000 to 1:1000000 worldwide, depending on the region [2]. 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*) [3]. In the Republic of Sakha (Yakutia), a case of neuronal ceroid lipofuscinosis type 6 was previously identified, the cause of which was a mutation c.396dupT in exon 4 of the *CLN6* gene. Given this fact, a study was continued to search for molecular genetic causes in patients with similar clinical signs. First of all, a mutation in the *CLN6* gene was excluded. Considering the severity of the course of the disease, the disability of patients, the fatal outcome and the lack of specific therapy, the study of neuronal ceroid lipofuscinosis in Yakutia is both a fundamental scientific problem and a medical and social task for the diagnosis and timely prevention of this hereditary pathology.

Methods and Algorithms: A total of 33 DNA samples from patients registered at the Medical Genetic Center of the National Center of Medicine (Yakutsk) with suspected NCL6 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: 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. In our patients we identified a homozygous frameshift variant c.396dupT (p.Val133CysfsTer18) in 4 exon of *CLN6,* parents are heterozygous carriers of the mutation. All patients of the Yakut ethnic group. 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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