F.M. Teryutin, N.A. Barashkov, N.A.Lebedeva.

A CASE OF WAARDENBURG SYNDROME TYPE II CAUSED OF NONSENSE VARIANT OF THE MITF GENE IN THE CONTEXT OF THE EPIGENETIC MOSAICISM HYPOTHESIS

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Waardenburg syndrome (WS) represents a very rare autosomal dominant disease. The prevalence of WS is estimated at 1 per 42,000 among the European population and people with congenital hearing loss 2-5% [3; 8; 5; 7; 9]. It is known that the most common causes of WS are mutations in the *PAX3*, *MITF*, *SOX10* and *SNAI2* genes [10; 12]. WS is divided into four types depending on phenotypic manifestations: WS type I (OMIM 193500); WS type II (OMIM 193510); WS type III Waardenburg-Klein syndrome (OMIM 148820); WS type IV – Waardenburg-Shah syndrome (OMIM 277580). Common phenotypic manifestations for all types of WS are hearing loss, impaired skin, hair and iris pigmentation, decreased visual acuity, changes in certain skeletal bones and weakened immune system. It is a well-known fact that clinical phenotypes of WS are extremely variable. In the case of WS, the literature often describes cases of significant phenotypic differences even between affected members of the same family carrying the same mutation [6]. Previously, the phenotypic variability of lesion observed in WS was associated mainly with the influence of modifier genes. Thus, a modifying effect of the *LEF-1* gene on *MITF* gene expression has been shown among patients with WS type II [11]. However, in 2021 R. Happle, based on clinical features of patients with asymmetric lesions of the sensory organs – sight and hearing – the hypothesis of a possible epigenetic influence on the phenotypic variability of WS was put forward [4]. A classic example of the role of epigenetic factors is imprinting in autosomal dominant diseases: Angelman syndrome ("off" maternal allele) and Prader-Willi syndrome ("off" paternal allele); in relation to WS [1], such hypothesis was first proposed.

In Yakutia in 2019, a clinical case of type II WS was described, in which a patient had iris heterochromia with a sectoral site of normal pigmentation on the affected iris, and asymmetric hearing loss (unilateral deafness) [2]. The described clinical case with of a patient with type II WS, with asymmetric lesions the sight and hearing organs is more in favor of the hypothesis of epigenetic mosaicism the proposed by R. Happle [4], than in favor of the hypothesis of the influence of modifier genes [11]. In our opinion, in cases of epigenetic mosaicism, uneven damage to sensory organs is theoretically more likely, than with the epigenetic influence of modifier genes, since in this case we would observe a more uniform damage (for example, bilateral damage to the organs of vision and hearing). Thus, despite WS is well-studied, the new hypothesis of epigenetic mosaicism in WS requires further study and suggests that new evidence of epigenetic control in other cases of irregular gene expression is needed.

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FSBSI YSC CMP: **TERYUTIN Fedor Mikhailovich** – MD, senior researcher, rest26@mail.ru, https://orcid.org/0000-0002-8659-0886; **BARASHKOV Nikolay Alekseevich** – Ph D, head of laboratory, e-mail: barashkov2004@mail.ru https://orcid.org/0000-0002-6984-7934; Medical Institute FSASI NEFU named after M.K. Ammosov: **LEBEDEVA Natalia Afanasyevna** – MD., e-mail: lebedeva-lor@mail.ru.

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