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Novel large deletions of the PAX6 gene in aniridia patients from Russia.

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Aniridia is a congenital ocular disorder caused by the mutations of the PAX6 gene coding a paired box DNA-binding protein. We carried out an investigation of 21 aniridia patients from Russia and determined a specific PAX6 mutations spectrum with a significant rate of de novo mutations. Missense, nonsense, indel mutations, small insertions and deletions were identified by sequencing in 16 out of 21 cases. Here we focus on revealed by MLPA large deletions (in 4 cases). The latter type of mutations makes up a quarter of all identified in our study PAX6 changes. Large deletions of 11p13 region just outside the PAX6 gene and/or invading the PAX6 gene cause phenotype of aniridia with complications of a broad range: from uncomplicated aniridia to one with associated ocular abnormalities and/or disorders of other body systems. Lack of the close to the PAX6 gene portion of DNA sequence leads to similar defects as known intragenic point mutations do. Defects seem to be more complex and severe in patients with a lack of an area downstream of the PAX6 gene including the RCN gene and a part of the WT1 gene.

Four patients with revealed rearrangements have bilateral total iris absence. One of them has aniridia combined with microcornea and cataract, three patients do not have any other ocular associated pathology. One of these three patients has aniridia combined with bilateral nephroptosis, other one with nephropyelitis and adiposis, and one of the patients without auxillary ocular associated pathology has an uncomplicated isolated aniridia. The patients are from unrelated families; all of them undergo ophthalmic examination and DNA-testing. The DNA was extracted from periferal blood leucocytes with Promega DNA isolation kit according to the manufacturer protocol. DNA-testing includes initial sequencing of PAX 6 gene 14 exons and subsequent MLPA analysis with the help of the MRC Holland SALSA MLPA probmix P219-B2 PAX6.

MLPA analysis revealed in 4 patients without identified by sequencing point mutations large deletions invading PAX6 and/or close neighbor genes: a) 31307603_31650221del, spanning from DCDC1 gene exon 4 to exon 9 ELP4 gene not including the PAX6 gene (approximately 342 618 bp deletion distal of the PAX6 gene), b) 31650221_32417549del, spanning from ELP4 gene exon 9 and including genes PAX6, RCN, gene WT1 exon 5 (approximately 767 328 bp deletion distal & proximal of the PAX6 gene), c) c.(-316-?)_724+?del inside the PAX6 gene from intron 1 to exon 8 (approximately 23 000 bp), d) 31817459_31369675del, invading distal of PAX6 genes: DCDC1, IMMP1L, ELP4 and PAX6 gene intron 1 (approximately 450 000 bp). The exact borders of identified large deletions are to be determined.

All but one detected mutations are novel (the deletion inside PAX6 gene from intron 1 to exon 8 was described earlier). Together with novel identified point mutations, high frequency of de novo mutations inclusively revealed large rearrangements, specific large deletions of chromosome 11 make up the peculiarity of the mutations spectrum in patients from Russian Federation.