COHEN SYNDROME IN FAMILY MEMBERS: A CASE REPORT

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Cohen syndrome is a rare autosomal-recessive disorder characterized by intellectual disability, myopia, hypotonia, and skeletal malformations. Its clinical diagnosis is impeded by marked inter- and intrafamilial phenotypic variability. Gene *VPS13B* that carries disease-associated mutations has 62 exons, making Sanger sequencing of the entire gene unsuitable for routine clinical use due to high costs. In this work we report a case of Cohen syndrome in a brother and sister born to a mixed Abazin-Circassian marriage and diagnosed with moderate mental retardation. Both patients had psychomotor retardation, were unable to study at school, and never learned to read, write and count. Although the patients shared a few nonspecific phenotypic characteristics, phenotypic differences made it impossible to arrive at a clear diagnosis. Therefore, whole exome sequencing was performed revealing the single nucleotide variant c.7603C>T that results in the premature stop codon R2535* in *VPS13B*. This mutation was found in the mother, the affected sibs and one of the two other healthy sibs. The second mutation remained undetected. Considering the identified mutation and the analyzed phenotypic traits, we concluded Cohen syndrome in both patients.

Keywords: intellectual disability, familial nonspecific intellectual disability, whole exome sequencing, Cohen syndrome, nonsyndromic intellectual disability

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СЕМЕЙНЫЙ СЛУЧАЙ СИНДРОМА КОЭНА: КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ

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Синдром Коэна — редкое аутосомно-рецессивное заболевание, характеризующееся умственной отсталостью, миопией, гипотонией, ожирением и деформацией костей. Заболевание имеет выраженный меж- и внутрисемейный клинический полиморфизм, что затрудняет его клиническую диагностику. Ген *VPS13B*, мутации в котором приводят к развитию синдрома, имеет 62 экзона, и полный его анализ в практике не применяется. Нами описан семейный случай синдрома Коэна. Брат и сестра из метисированного абазино-черкесского брака имеют диагноз «умственная отсталость в стадии имбецильности». У обоих пробандов с рождения отмечена задержка психомоторного развития. В школе учиться не смогли, писать, читать, считать не научились. Несмотря на некоторые общие неспецифические признаки, различия в фенотипе не позволили установить диагноз, и был назначен полноэкзомный анализ. Найдена однонуклеотидная замена c.7603C>T, приводящая к образованию преждевременного стоп-кодона R2535* в гене *VPS13B*. Носителями мутации оказались мать, больные сибсы и один из двух здоровых сибсов. Вторую мутацию найти не удалось. По итогам детального анализа фенотипа и с учетом выявленной мутации установлен синдрома Коэна у обоих пациентов.

Ключевые слова: умственная отсталость, семейная неспецифическая умственная отсталость, полноэкзомный анализ, синдром Коэна, несиндромальная умственная отсталость

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Cohen syndrome is an inherited autosomal recessive disorder (OMIM# 216550). It was first reported in 1973 by Cohen et al. who noticed a shared pattern of anomalies in a few patients, including hypotonia, obesity, intellectual disability, limb and facial dysmorphisms, and ocular anomalies [1]. As early as 1994 a group of Finnish researchers mapped the *VPS13B* (*COH1*) gene to chromosome 8 [2], but it was not until 2003 that it became clear that the syndrome is caused by mutations in this particular gene [3]. An extensive search for *COH1* mutations was carried out in 76 patients from 59 families preliminarily diagnosed with Cohen syndrome [4]. In the course of their study, the researchers described a total of 22 mutations, 19 of which were reported for the first time. A number of studies were dedicated to the study of Cohen syndrome in Finnish and British patients [4, 5]; but altogether the literature reports only a few hundreds of verified cases in different countries and across

different populations, including Germany and Poland [6], Italy [7], Greece [8], Belgium [9], Middle East and Africa [6, 10, 11], Japan [10, 12] and the US [6, 11, 13]. Therefore, the assumed rarity of the disease makes it difficult to accurately access its prevalence. The variability of clinical manifestations both within and between families impedes accurate diagnosis, resulting in the underestimation of real prevalence of the syndrome. For example, Rauch et al. [14] diagnosed Cohen syndrome in 0.7 % of patients with undifferentiated intellectual disability, while clinical exome sequencing verified Cohen syndrome only in 0.1% of patients showing signs of genetic disorder [15].

Cohen syndrome is an inherited disorder affecting many parts of the body and characterized by mild microcephaly, high degree myopia, progressive retinal dystrophy, joint hyperextensibility and specific facial features. Patients tend to have thick hair and eyebrows, long lashes, a peculiar eye shape (down slanting palpebral fissures and almond-shaped eyesantimongoloid slant or arched eyelids), a rounded nasal tip, a short philtrum, maxillary hypoplasia, and prominent upper incisors. A combination of the three latter signs often causes open mouth appearance [16]. Other signs and symptoms may include narrow hands and feet and long fingers. Lab tests reveal low levels of leukocytes (neutropenia) leading to recurrent infections [17]. Patients can show various combinations of the aforementioned symptoms which do not have to co-occur in Cohen syndrome.

Differential diagnosis is often hindered by the variability of clinical manifestations, including those accompanying age-related changes. Cohen syndrome should be differentiated from such syndromes as Prader–Willi, Bardet–Biedl, Alström, Angelman, Marfan, and Sotos. A rare Mirhosseini–Holmes–Walton syndrome (OMIM# 268050) is considered to be allelic to Cohen syndrome, and their clinical manifestations overlap to a great extent [18, 19].

Genetically, the syndrome is caused by mutations in the gene *VPS13B* (*COH1*) [3]. Mutations in this gene can also lead to non-syndromic intellectual disability [20] and autism [21]. The gene *VPS13B* encodes for a transmembrane protein constituting the Golgi apparatus. Its major role is to regulate vesicular transport and sort proteins inside the cell. Besides, VPS13B is involved in glycosylation. The expression analysis has demonstrated the highest levels of VPS13B production in the cortical neurons of the brain [22].

Most often, patients with Cohen syndrome have mutations that cause protein shortening and therefore loss of protein function. It has been shown that reduced protein synthesis leads to a drop in the amount of neurons in hypoccampal cultures, which may explain microcephaly and intellectual disability. The abnormal distribution of body fat in such patients may be caused by disrupted glycosylation [23].

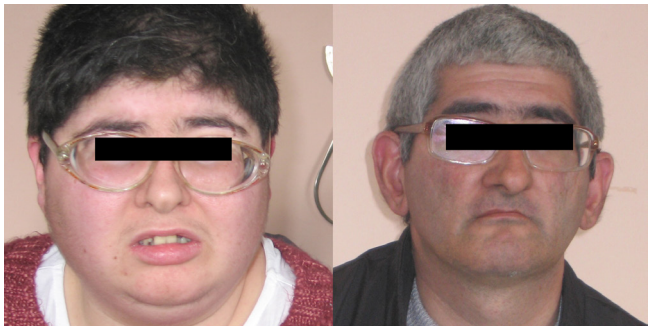
Targeted sequencing can be very instrumental in the verification of Cohen syndrome in populations where mutations are frequent. For example, in Finnish patients with Cohen syndrome 75 % of mutant alleles are represented by the deletion c.3348_3349delCT [3], and in the isolates obtained from the American Amish suffering from this disorder the founder pathogenic variants c.8459T>C and 9258_9259insT account for 99 % of all alleles. Other diagnostic options include multiplex ligation-dependent probe amplification (MLPA) and chromosomal microarray analysis, considering that up to 30 % of cases are caused by deletions/duplications [24]. Sanger sequencing of the entire gene is not recommended because the gene in question has 62 exons rendering the whole procedure too costly. NGS-panels and exome sequencing may also be good alternatives; the latter is increasingly used to as part of the diagnostic routine in patients with intellectual disability [25]. Exome sequencing can confirm Cohen syndrome in 70 % of patients [5].

Case description

A mixed Abazin-Circassian family sought advice of a medical geneticist. Both parents were healthy; of their 4 children two were also healthy, while the other (a son of 36 and a daughter of 23 years of age) were disabled and diagnosed with moderate mental retardation back in childhood. Both probands had suffered psychomotor retardation since birth and had been unable to study at school failing to learn to read, write and do simple sums. Their speech was impoverished, with a tendency to primitive grammatical structures. Mental development matched that of a 3 to 5-year old child. Physical examination showed intellectual disability, microcephaly (52.5 cm in the man and 53 cm in the woman). The patients had thick bushy hair and eyebrows, low hairlines, high degree myopia, short philtra, thin upper lips, hypoplasia of the maxilla (more prominent in the man), and beak-shaped noses with rounded tips. Both had pronounced limbar scoliosis, planovalgus feet, and long fingers. The male patient had a long proximal phalanx of the little finger, low-set protruding ears, and synophrys. The woman was 158–160 cm tall and obese (first to second degree), had a more severe intellectual disability, attached earlobes, a widow's peak, an open mouth with prominent front incisors, dental caries, hypotonia, striae all over the body, lack of menarche (see the Figure).

Due to the differences in the clinical manifestation, the diagnosis had not been arrived at by the time of the consultation, therefore we suggested that the male patient should undergo massively parallel whole-exome sequencing, which revealed a previously described mutation, namely *rs386834107* [6, 26]. It is a single nucleotide variant (c.7603C>T) which results in a premature stop-codon R2535* in exon 42 of *VPS13B*. Since *VPS13B* has 62 exons, the encoded protein is only two-thirds of its natural length. We also conducted Sanger sequencing to test all family members for this particular mutation. The mother, the diseased sibs and one of the two other healthy sibs turned out to be carriers, which does not contradict the autosomal recessive manner of inheritance.

In an effort to detect the second mutation, all single nucleotide variants identified in the sequenced gene were analyzed, and a manual search for possibly undetected mutations was performed. The following variants were found: M3265*, G3432R, and D903N. They are not pathogenic, nor were they confirmed by Sanger sequencing in our study. The analysis of evenness of coverage and the presence of heterozygous variants did not allow us to conclude an allelic deletion.



Sibs with Cohen syndrome: the sister, 23 years of age (on the left), and the brother, 32 years of age (on the right)

Phenotypes of both patients were additionally analyzed using the Face2Gene app (FDNA, Israel). The clinical signs (intellectual disability, microcephaly, myopia, thick hair, a low hairline, a rounded nasal tip, prominent front incisors) were also suggestive of Cohen syndrome.

Based on the complex clinical examination, we assume that Cohen syndrome has been verified in our patients.

Case discussion

The considerable variability of clinical manifestations in patients with Cohen syndrome hinders its accurate diagnosis, especially when verification lab tests cannot be run straightaway (e. g., in expeditionary research and genetic counselling). In these cases, high-throughput methods of molecular genetic testing are the only diagnostic solution. Molecular genetic testing demonstrated considerable allelic heterogeneity of the syndrome which was thought to be the reason of clinical variability [6, 16]. However, intrafamilial variability was almost ignored (OMIM# 216550) and published photos of the affected sibs were conclusive of mainly similar phenotypes [6, 16].

The studied family demonstrated a marked variability of clinical manifestations against the background of many shared features. The second mutation could have provided a possible explanation for clinical heterogeneity, had it been detected. Further diagnostic tests might include a search for deletions or duplications in the gene. However, given the gene length and the absence of robust methods for its analysis, this would be very difficult. Deletions and duplications of one or two exons, as well as inversions, have been described in many patients with Cohen syndrome: 9 (53 %) out of 17 cases [27]. However, there have been a few cases in which only one of two heterozygous mutations was detected (including the one that we identified in our patients) [6]. Therefore, molecular genetic testing for Cohen syndrome requires the use of various methods in order to accurately detect and identify point and lengthy mutations or inversions. Previously we proposed an algorithm for diagnosing intellectual disability, which includes the use of whole-exome sequencing or chromosomal microarray analysis [25]. Still, in some cases both of these methods fail to detect the second mutation.

CONCLUSIONS

Cohen syndrome is characterized by a considerable variability of the phenotypes within a family, which may present a problem for clinical diagnosis. Massively parallel sequencing is very instrumental in arriving at an accurate diagnosis, as it helps to differentiate this disease from other syndromes involving intellectual disability.

References

1. Cohen MM Jr, Hall BD, Smith DW, Graham CB, Lampert KJ. A new syndrome with hypotonia, obesity, mental deficiency, and facial, oral, ocular, and limb anomalies. J Pediatr. 1973 Aug; 83 (2): 280–4.
2. Tahvanainen E, Norio R, Karila E, Ranta S, Weissenbach J, Sistonen P, et al. Cohen syndrome gene assigned to the long arm of chromosome 8 by linkage analysis. Nat Genet. 1994 Jun; 7 (2): 201–4.
3. Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Träskelin AL, et al. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet. 2003 Jun; 72 (6): 1359–69.
4. Kolehmainen J, Wilkinson R, Lehesjoki AE, Chandler K, Kivitie-Kallio S, Clayton-Smith J, et al. Delineation of Cohen syndrome following a large-scale genotype-phenotype screen. Am J Hum Genet. 2004 Jul; 75 (1): 122–7.
5. Balikova I, Lehesjoki AE, de Ravel TJ, Thienpont B, Chandler KE, Clayton-Smith J, et al. Deletions in the VPS13B (COH1) gene as a cause of Cohen syndrome. Hum Mutat. 2009 Sep; 30 (9): E845–54.
6. Hennies HC, Rauch A, Seifert W, Schumi C, Moser E, Al-Taji E, et al. Allelic Heterogeneity in the COH1 Gene Explains Clinical Variability in Cohen Syndrome. 2004 Jul; 75 (1): 138–45.
7. Katzaki E, Pescucci C, Uliana V, Papa FT, Ariani F, Meloni I, et al. Clinical and molecular characterization of Italian patients affected by Cohen syndrome. J Hum Genet. 2007; 52 (12): 1011–7.
8. Bugiani M, Gyftodimou Y, Tsimpouka P, Lamantea E, Katzaki E, d'Adamo P, et al. Cohen syndrome resulting from a novel large intragenic COH1 deletion segregating in an isolated Greek island population. Am J Med Genet A. 2008 Sep 1; 146A (17): 2221–6.
9. Peeters K, Willekens D, Steyaert J, Fryns JP. The long term evolution of 6 adult patients with Cohen syndrome and their behavioral characteristics. Genet Couns. 2008; 19 (1): 1–14.
10. Mochida GH, Rajab A, Eyaid W, Lu A, Al-Nouri D, Kosaki K, et al. Broader geographical spectrum of Cohen syndrome due to COH1 mutations. J Med Genet. 2004 Jun; 41 (6): e87.
11. Taban M, Memoracion-Peralta DS, Wang H, Al-Gazali LI, Traboulsi EI. Cohen syndrome: Report of nine cases and review of the literature, with emphasis on ophthalmic features. J AAPOS. 2007 Oct; 11 (5): 431–7.
12. Kondo I, Shimizu A, Asakawa S, Miyamoto K, Yamagata H, Tabara Y, et al. COH1 analysis and linkage study in two Japanese families with Cohen syndrome. Clin Genet. 2005 Mar; 67 (3): 270–2.
13. Falk MJ, Feiler HS, Neilson DE, Maxwell K, Lee JV, Segall SK, et al. Cohen syndrome in the Ohio Amish. Am J Med Genet A. 2004 Jul 1; 128A (1): 23–8.
14. Rauch A, Hoyer J, Guth S, Zweier C, Kraus C, Becker C, et al. Diagnostic Yield of Various Genetic Approaches in Patients with Unexplained Developmental Delay or Mental Retardation. Am J Med Genet A. 2006 Oct 1; 140A (18): 2063–74.
15. Yang Y, Muzny DM, Xia F, Niu Z, Person R, Ding Y, et al. Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing. JAMA. 2014 Nov 12; 312 (18): 1870–9.
16. Seifert W, Holder-Espinasse M, Spranger S, Hoeltzenbein M, Rossier E, Dollfus H, et al. Mutational spectrum of COH1 and clinical heterogeneity in Cohen syndrome. J Med Genet. 2006 May; 43 (5): e22.
17. Wang H, Falk MJ, Wensel C, Traboulsi EI. Cohen syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2017. 2006 Aug 29 [updated 2016 Jul 21].
18. Norio R, Raitta C. Are the Mirhosseini-Holmes-Walton Syndrome and the Cohen Syndrome Identical? Am J Med Genet. 1986 Oct; 25 (2): 397–8.
19. Horn D, Krebsová A, Kunze J, Reis A. Homozygosity mapping in a family with microcephaly, mental retardation, and short stature to a Cohen syndrome region on 8q21.3-8q22.1: Redefining a clinical entity. Am J Med Genet. 2000 Jun 5; 92 (4): 285–92.
20. Karaca E, Harel T, Pehlivan D, Jhangiani SN, Gambin T, Coban Akdemir Z, et al. Genes that Affect Brain Structure and Function Identified by Rare Variant Analyses of Mendelian Neurologic Disease. Neuron. 2015 Nov 4; 88 (3): 499–513.
21. Yu TW, Chahrour MH, Coulter ME, Jiralerspong S, Okamura-Ikeda K, Ataman B, et al. Using whole-exome sequencing to

identify inherited causes of autism. Neuron. 2013 Jan 23; 77 (2): 259–73.
22. Seifert W, Kühnisch J, Maritzen T, Horn D, Haucke V, Hennies HC. Cohen syndrome-associated protein, COH1, is a novel, giant Golgi matrix protein required for Golgi integrity. J Biol Chem. 2011 Oct 28; 286 (43): 37665–75.
23. Seifert W, Kühnisch J, Maritzen T, Lommatzsch S, Hennies HC, Bachmann S, et al. Cohen syndrome-associated protein COH1 physically and functionally interacts with the small GTPase RAB6 at the Golgi complex and directs neurite outgrowth. J Biol Chem. 2015 Feb 6; 290 (6): 3349–58.
24. El Chehadeh-Djebbar S, Faivre L, Moncla A, Aral B, Missirian C, Popovici C, et al. The power of high-resolution non-targeted array-CGH in identifying intragenic rearrangements responsible for Cohen syndrome. J Med Genet. 2011 Nov; 48 (11): e1.
25. Lavrov AV, Bannikov AV, Chausheva AI, Dadali EL. [Genetics of mental retardation]. Rossiyskiy vestnik perinatologii i pediatrii. 2016; 61 (6): 13–20. Russian.
26. Xiong HY, Alipanahi B, Lee LJ, Bretschneider H, Merico D, Yuen RK, et al. RNA splicing. The human splicing code reveals new insights into the genetic determinants of disease. Science. 2015 Jan 9; 347 (6218): 1254806.
27. El Chehadeh-Djebbar S, Blair E, Holder-Espinasse M, Moncla A, Frances AM, Rio M, et al. Changing facial phenotype in Cohen syndrome: towards clues for an earlier diagnosis. Eur J Hum Genet. 2013 Jul; 21 (7): 736–42.

Литература

1. Cohen MM Jr, Hall BD, Smith DW, Graham CB, Lampert KJ. A new syndrome with hypotonia, obesity, mental deficiency, and facial, oral, ocular, and limb anomalies. J Pediatr. 1973 Aug; 83 (2): 280–4.
2. Tahvanainen E, Norio R, Karila E, Ranta S, Weissenbach J, Sistonen P, et al. Cohen syndrome gene assigned to the long arm of chromosome 8 by linkage analysis. Nat Genet. 1994 Jun; 7 (2): 201–4.
3. Kolehmainen J, Black GC, Saarinen A, Chandler K, Clayton-Smith J, Träskelin AL, et al. Cohen syndrome is caused by mutations in a novel gene, COH1, encoding a transmembrane protein with a presumed role in vesicle-mediated sorting and intracellular protein transport. Am J Hum Genet. 2003 Jun; 72 (6): 1359–69.
4. Kolehmainen J, Wilkinson R, Lehesjoki AE, Chandler K, Kivitie-Kallio S, Clayton-Smith J, et al. Delineation of Cohen syndrome following a large-scale genotype-phenotype screen. Am J Hum Genet. 2004 Jul; 75 (1): 122–7.
5. Balikova I, Lehesjoki AE, de Ravel TJ, Thienpont B, Chandler KE, Clayton-Smith J, et al. Deletions in the VPS13B (COH1) gene as a cause of Cohen syndrome. Hum Mutat. 2009 Sep; 30 (9): E845–54.
6. Hennies HC, Rauch A, Seifert W, Schumi C, Moser E, Al-Taji E, et al. Allelic Heterogeneity in the COH1 Gene Explains Clinical Variability in Cohen Syndrome. 2004 Jul; 75 (1): 138–45.
7. Katzaki E, Pescucci C, Uliana V, Papa FT, Ariani F, Meloni I, et al. Clinical and molecular characterization of Italian patients affected by Cohen syndrome. J Hum Genet. 2007; 52 (12): 1011–7.
8. Bugiani M, Gyftodimou Y, Tsimpouka P, Lamantea E, Katzaki E, d'Adamo P, et al. Cohen syndrome resulting from a novel large intragenic COH1 deletion segregating in an isolated Greek island population. Am J Med Genet A. 2008 Sep 1; 146A (17): 2221–6.
9. Peeters K, Willekens D, Steyaert J, Fryns JP. The long term evolution of 6 adult patients with Cohen syndrome and their behavioral characteristics. Genet Couns. 2008; 19 (1): 1–14.
10. Mochida GH, Rajab A, Eyaid W, Lu A, Al-Nouri D, Kosaki K, et al. Broader geographical spectrum of Cohen syndrome due to COH1 mutations. J Med Genet. 2004 Jun; 41 (6): e87.
11. Taban M, Memoracion-Peralta DS, Wang H, Al-Gazali LI, Traboulsi EI. Cohen syndrome: Report of nine cases and review of the literature, with emphasis on ophthalmic features. J AAPOS. 2007 Oct; 11 (5): 431–7.
12. Kondo I, Shimizu A, Asakawa S, Miyamoto K, Yamagata H, Tabara Y, et al. COH1 analysis and linkage study in two Japanese families with Cohen syndrome. Clin Genet. 2005 Mar; 67 (3): 270–2.
13. Falk MJ, Feiler HS, Neilson DE, Maxwell K, Lee JV, Segall SK, et al. Cohen syndrome in the Ohio Amish. Am J Med Genet A. 2004 Jul 1; 128A (1): 23–8.
14. Rauch A, Hoyer J, Guth S, Zweier C, Kraus C, Becker C, et al. Diagnostic Yield of Various Genetic Approaches in Patients with Unexplained Developmental Delay or Mental Retardation. Am J Med Genet A. 2006 Oct 1; 140A (18): 2063–74.
15. Yang Y, Muzny DM, Xia F, Niu Z, Person R, Ding Y, et al. Molecular Findings Among Patients Referred for Clinical Whole-Exome Sequencing. JAMA. 2014 Nov 12; 312 (18): 1870–9.
16. Seifert W, Holder-Espinasse M, Spranger S, Hoeltzenbein M, Rossier E, Dollfus H, et al. Mutational spectrum of COH1 and clinical heterogeneity in Cohen syndrome. J Med Genet. 2006 May; 43 (5): e22.
17. Wang H, Falk MJ, Wensel C, Traboulsi EI. Cohen syndrome. B: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH и др., редакторы. GeneReviews® [Интернет]. Seattle (WA): University of Washington, Seattle; 1993–2017. 29 августа 2006 г. [дополнено: 21 июля 2016 г.].
18. Norio R, Raitta C. Are the Mirhosseini-Holmes-Walton Syndrome and the Cohen Syndrome Identical? Am J Med Genet. 1986 Oct; 25 (2): 397–8.
19. Horn D, Krebsová A, Kunze J, Reis A. Homozygosity mapping in a family with microcephaly, mental retardation, and short stature to a Cohen syndrome region on 8q21.3-8q22.1: Redefining a clinical entity. Am J Med Genet. 2000 Jun 5; 92 (4): 285–92.
20. Karaca E, Harel T, Pehlivan D, Jhangiani SN, Gambin T, Coban Akdemir Z, et al. Genes that Affect Brain Structure and Function Identified by Rare Variant Analyses of Mendelian Neurologic Disease. Neuron. 2015 Nov 4; 88 (3): 499–513.
21. Yu TW, Chahrour MH, Coulter ME, Jiralerspong S, Okamura-Ikeda K, Ataman B, et al. Using whole-exome sequencing to identify inherited causes of autism. Neuron. 2013 Jan 23; 77 (2): 259–73.
22. Seifert W, Kühnisch J, Maritzen T, Horn D, Haucke V, Hennies HC. Cohen syndrome-associated protein, COH1, is a novel, giant Golgi matrix protein required for Golgi integrity. J Biol Chem. 2011 Oct 28; 286 (43): 37665–75.
23. Seifert W, Kühnisch J, Maritzen T, Lommatzsch S, Hennies HC, Bachmann S, et al. Cohen syndrome-associated protein COH1 physically and functionally interacts with the small GTPase RAB6 at the Golgi complex and directs neurite outgrowth. J Biol Chem. 2015 Feb 6; 290 (6): 3349–58.
24. El Chehadeh-Djebbar S, Faivre L, Moncla A, Aral B, Missirian C, Popovici C, et al. The power of high-resolution non-targeted array-CGH in identifying intragenic rearrangements responsible for Cohen syndrome. J Med Genet. 2011 Nov; 48 (11): e1.
25. Лавров А. В., Банников А. В., Чаушева А. И., Дадали Е. Л. Генетика умственной отсталости. Рос. вестн. перинатол. и педиатр. 2016; 61 (6): 13–20.
26. Xiong HY, Alipanahi B, Lee LJ, Bretschneider H, Merico D, Yuen RK, et al. RNA splicing. The human splicing code reveals new insights into the genetic determinants of disease. Science. 2015 Jan 9; 347 (6218): 1254806.
27. El Chehadeh-Djebbar S, Blair E, Holder-Espinasse M, Moncla A, Frances AM, Rio M, et al. Changing facial phenotype in Cohen syndrome: towards clues for an earlier diagnosis. Eur J Hum Genet. 2013 Jul; 21 (7): 736–42.