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# MARKAZIY OSIYO ENDOKRINOLOGIK JURNALI

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# PRECOCIOUS PUBERTY: MOLECULAR GENETICS, MODERN APPROACHES TO THE DIAGNOSIS AND TREATMENT

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**ANNOTATION**

The article is devoted to the basic molecular-genetic mechanisms and novel approaches to the diagnosis and management of the development of central precocious puberty. Precocious puberty is the appearance of the secondary sexual characteristics before the age years in girls and before 9 years in boys. Prevalence varies greatly by study. The incidence is generally thought to be 1 in 5000-10000 children, but some countries around the world have seen an increase in the incidence, including the United States, Spain, France, Denmark, Korea and China since 1990. Complex interactions with genetic, nutritional and environmental factors play a decisive role in determining the timing of puberty. To date, mutations in four genes (KISS1, KISS1R, MKRN3, DLK1) have been confirmed as causal variants leading to central idiopathic Precocious Puberty.

**Key words:** precocious puberty (PP), central precocious puberty (CPP), peripheral precocious puberty (PPP), idiopathic, KISS1, KISS1R, MKRN3, DLK1, congenital adrenal hyperplasia, Mc-Cune Albright syndrome.

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# ПРЕЖДЕВРЕМЕННОЕ ПОЛОВОЕ СОЗРЕВАНИЕ: МОЛЕКУЛЯРНАЯ ГЕНЕТИКА, СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ И ЛЕЧЕНИЮ

**АННОТАЦИЯ**

Статья посвящена основным молекулярно-генетическим механизмам и новым подходам к диагностике и лечению центрального преждевременного полового созревания. Преждевременное половое созревание — это появление вторичных половых признаков до 8 лет у девочек и до 9 лет у мальчиков. Распространенность сильно варьируется в зависимости от исследования. Обычно считается, что заболеваемость составляет 1 на 5000-10000 детей, но в некоторых странах мира наблюдается рост заболеваемости, включая США, Испанию, Францию, Данию, Корею и Китай с 1990 года. Сложные взаимодействия с генетическими факторами, факторами питания и окружающей среды играют решающую роль в определении сроков полового созревания. На сегодняшний день мутации в четырех генах (KISS1, KISS1R, MKRN3, DLK1) были подтверждены как причинные варианты, приводящие к центральному идиопатическому преждевременному половому созреванию.

**Ключевые слова:** преждевременное половое созревание, центральное преждевременное половое развитие (ЦППР), периферическое преждевременное половое развитие (ППППР), идиопатическое, KISS1, KISS1R, MKRN3, DLK1, врожденная дисфункция коры надпочечников, синдром Мак-Кьюна-Олбрайта.

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## VAQTIDAN ILGARI JINSIY YETILISH: MOLEKULYAR GENETIK XUSUSIYATLARI, DIAGNOSTIKA VA DAVOLASHGA ZAMONAVIY YONDASHUVLAR

**ANNOTATSIYA**

Maqola markaziy erta jinsiy yetilishning asosiy molekulyar-genetik mexanizmlari, tashxislash va davolashning yangi yondashuvlariga bag’ishlangan. Vaqtidan ilgari jinsiy yetilish–bu qizlarda 8 yoshgacha va o'g'il bolalarda 9 yoshgacha ikkilamchi jinsiy belgilarning paydo bo'lishidir. Tarqalishi tadqiqotga qarab juda farq qiladi. Odatda 5000 dan 10000 gacha bo'lgan bolalarda kasallanish darajasi 1 deb hisoblanadi, ammo dunyoning ba'zi mamlakatlarida, xususan, AQSh, Ispaniya, Fransiya, Daniya, Koreya va Xitoyda tarqalish darajasining ortganligi kuzatilmoqda. ta'sirlari hal qiluvchi rol o'ynaydi. Bugungi kunga qadar to'rtta gendagi mutatsiyalar (KISS1, variantlari sifatida tasdiqlangan.

**Kalit so’zlar:** erta jinsiy yetilish (EJY), markaziy erta jinsiy yetilish (MEJY), periferik erta jinsiy yetilish (PEJY),idiopatik, KISS1, KISS1R, MKRN3, DLK1, buyrakusti bezi po’stlog’i.

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**Introduction.** Precocious Puberty (PP) is the appearance of secondary sexual characteristics up to 8 years in girls and up to 9 years in boys. The complex process of puberty depends on the interaction of genetic, socio-economic, nutritional and environmental factors [4]. Precocious puberty classified to gonadotropin-dependent (central, true), gonaotropin-independent (peripheral) and partial forms [40]. Understanding changes in the timing of sexual development is important because earlier puberty may be associated with psychosocial difficulties, is a risk factor for a younger age at the first sexual intercourse and has negative health consequences in the long term, including an increased risk of type 2 diabetes, obesity, cardiovascular diseases, depression and premature death. Large-scale genetic data suggests, that early puberty is associated with an increased risk of breast cancer in women, while, in men, earlier sexual development may increase the risk of prostate cancer [9]. Since the 1970s, the acceleration process has been registered, i.e., the acceleration of the development of

secondary sexual characteristics by 0.24 years every decade on a global scale [16]. Trends towards earlier onset of puberty among the general population, first recorded among girls from the USA in the 1990s [6]. 20 years later, European data showed a similar trend towards an earlier onset of puberty in girls and to a lesser extent in boys [29].

**Epidemiology.** One of the very few studies on the prevalence and incidence of premature puberty based on data from the national patient registry was a Danish report covering the period 1993-2001 [23]. Danish researchers estimated that 0.2% of girls had some forms of PP, while boys had less than 0.05%. The predominance of women ranged from 20 to 23 per 10,000 girls compared to boys, which was less than 5 per 10,000 boys [32]. A nationwide study in France determined that the incidence of idiopathic central PP in 2011-2013 was 2.68/10000 in girls under 9 years old and 0.24/10000 in boys under 10 years old [18]. A study conducted in South Korea showed that the frequency of central precocious puberty in girls increased from 0.33/10000 to 5.04/10000, and in boys – from 0.03/10000 to 0.12/10000 in the period from 2004 to 2010 [14]. Another observational study in carried out in Spain estimated the annual incidence of CPP between 0.02 and 1.07 cases per 100,000 children [30]. From the first of January 1998 to the first of December 2003, 65 cases of central precocious puberty were registered in health services in five cities of Tuscany, Italy, the prevalence of central puberty averaged 30.4 per 100,000 children in four cities and 161 per 100,000 children in another city due to environmental circumstances [39]. In 2010, in the USA, a study by Biro et al. It showed that in a cohort of 1,239 girls aged 7-7.99 years from three urban centers, the proportion of those who reached the degree of breast development 2 according to Tanner was 10.4% of white girls, 23.4% of black girls and 14.9% of Latin American girls [23]. In China, by Mingqiang Zhu et al. 18,707 primary and secondary school students were examined in six cities from October 2009 to October 2010, and the prevalence of precocious puberty was estimated at 0.43% (girls – 0.48%, boys – 0.38%) [21]. According to Yawen Zhang et al., the uncorrected and adjusted prevalence rates of premature puberty in Qufu City, Shandong Province, China were 5.01% (11.53% for girls and 1.41% for boys) and 6.29% (14.23% for girls and 1.54% for boys), respectively. The prevalence of PP in urban children was significantly higher (5.34%) than in suburban residents (2.36%, $p<0.05$). And the prevalence of PP in the overweight groups (21.43% in girls and 1.97% in boys), obesity (35.48% in girls and 4.6% in boys) and severe obesity (32.35% in girls and 3.38% in boys) was higher than in the normal body weight group (4% in girls and 0.54% in boys, $p<0.05$) [38]. In Uzbekistan, scientific studies on the prevalence and incidence of precocious puberty have not been conducted, and information on the epidemiology of PP in the Uzbek population is insufficient.

**Classification.** Gonadotropin-dependent (central, true), gonadotropin-independent (peripheral) and partial forms of PPR are distinguished [40]. The modern classification of premature sexual development was shown in Table 1 [40].

**Modern approaches to the diagnosis of PP.** Evaluation of children with PPR requires a thorough physical examination with measurement of height, weight and growth rate. In girls, estrogen determines the development of mammary glands (telarche), an increase in the labia majora and labia minora, and an increase and redistribution of fat in the body, mainly in the hips. In boys, the first physical changes are an increase in the average volume of the testicle by more than 3 ml. Testosterone is responsible for the growth of the testicles, penis and cricoid cartilage, facial hair growth, changes in body fat and muscle mass [4].The study of testicular volume is important in boys, since boys with CPP usually have symmetrical bilateral testicular enlargement at puberty (≥4 ml or >2.5 cm in length), unlike peripheral PP, who usually have disproportionately small testicles compared to the degree of virilization. The exceptions are PPP caused by tumors secreting human chorionic gonadotropin, and familial limited RPPR in men (testotoxicosis caused by a mutation of the LH receptor) [29].

The best initial screening test for detecting activation of the hypothalamic-pituitary-gonadal axis is the measurement of basal serum LH levels (ideally in the morning) using sensitive immunochemiluminescent methods with a lower detection limit of <0.1 mMU/ml. The remaining tests are determination of serum levels of FSH, estradiol in girls and testosterone in boys, assessment of thyroid function (TSH, free T4 and antibodies to TPO), radiography of the hand to determine bone age. The results are used for differential diagnosis of the central and peripheral forms of PP, which

then conducts additional testing [4]. Unstimulated prepubescent LH levels are usually less than 0.1 IU/l [22]. A basal LH level of more than 0.3 IU/l indicates a central PP. Levels below 0.3 indicate peripheral causes or benign variants [1]. However, even with hypersensitive tests, the diagnostic effectiveness of the basal LH level in serum for differentiating CPP from the prepubertal state differs in different studies [8].

The gold standard for the diagnosis of CPP is the GnRH stimulation test. Despite the fact, that various stimulation test protocols have been described and it has been reported that LH levels vary depending on the method used, the most commonly used threshold value for peak LH concentration during stimulation is 5 IU/L [17]. This test requires blood sampling to be performed several times to measure gonadotropins at a time in the range from 15 to 180 minutes after intravenous or subcutaneous GnRH administration [36]. The clinical guidelines of the Korean Society of Pediatric Endocrinology for Premature Puberty recommend sequential measurement of LH at intervals of 15-30 minutes from baseline to 90-120 minutes after the application of a standard dose of LHRH (100 mcg) by injection to stimulate GnRH. [35].

**Table 1. Modern classification of PP.** *Adapted from Shlomo Melmed et al., 2016*

| Classification of Sexual Precocity | |
|---|---|
| **True Precocious Puberty or Complete Isosexual Precocity (GnRH-Dependent Sexual Precocity or Premature Activation of the Hypothalamic GnRH Pulse Generator)** | **Females** |
| Idiopathic true precocious puberty | Ovarian cyst |
| CNS tumors | Estrogen-secreting ovarian or adrenal neoplasm |
| Optic glioma associated with neurofibromatosis type 1 | Peutz-Jeghers syndrome |
| Hypothalamic astrocytoma | **Both Sexes** |
| Other CNS disorders | McCune-Albright syndrome |
| Developmental abnormalities including hypothalamic hamartoma of the tuber cinereum | Hypothyroidism |
| Encephalitis | Iatrogenic or exogenous sexual precocity (including inadvertent exposure to estrogens in food, drugs, or cosmetics) |
| Static encephalopathy | **Variations of Pubertal Development** |
| Brain abscess | Premature thelarche |
| Sarcoid or tubercular granuloma | Premature isolated menarche |
| Head trauma | Premature adrenarche |
| Hydrocephalus | Adolescent gynecomastia in boys |
| Arachnoid cyst | Macroorchidism |
| Myelomeningocele | **Contrasexual Precocity** |
| Vascular lesion | **Feminization in Males** |
| Cranial irradiation | Adrenal neoplasm |
| True precocious puberty after late treatment of congenital virilizing adrenal hyperplasia or other previous chronic exposure to sex steroids | Chorioepithelioma |
| True precocious puberty due to gain of function mutations: | CYP11B1 deficiency |
| in *KISS1R/GRP54* gene | Late-onset adrenal hyperplasia |
| in *KISS1* gene | Testicular neoplasm (Peutz-Jeghers syndrome) |
| **Incomplete Isosexual Precocity (Hypothalamic GnRH-Independent)** | Increased extraglandular conversion of circulating adrenal androgens to estrogen |
| **Males** | Iatrogenic (exposure to estrogens) |
| Gonadotropin-secreting tumors | **Virilization in Females** |
| hCG-secreting CNS tumors (e.g., chorioepitheliomas, germinoma, teratoma) | Congenital adrenal hyperplasia |
| hCG-secreting tumors located outside the CNS (hepatoma, teratoma, choriocarcinoma) | CYP21 deficiency |
| Increased androgen secretion by adrenal or testis | CYP11B1 deficiency |
| Congenital adrenal hyperplasia (CYP21 and CYP11B1 deficiencies) | 3β-HSD deficiency |
| Virilizing adrenal neoplasm | Virilizing adrenal neoplasm (Cushing syndrome) |
| Leydig cell adenoma | Virilizing ovarian neoplasm (e.g., arrhenoblastoma) |
| Familial testotoxicosis (sex-limited autosomal dominant pituitary gonadotropin-independent precocious Leydig cell and germ cell maturation) | Iatrogenic (exposure to androgens) |
| Cortisol resistance syndrome | Cortisol resistance syndrome |
| | Aromatase deficiency |

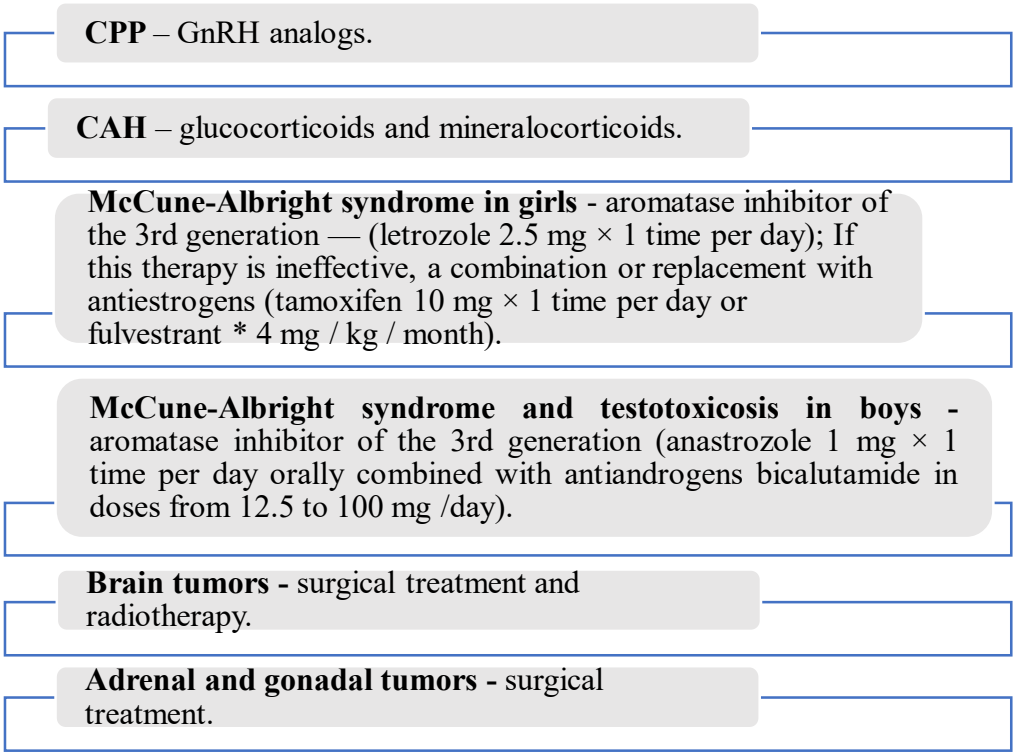
According to Shu-Nin Yeh et al. serum LH collected at the 30th minute after intravenous administration of gonadorelin in the GnRH stimulation test showed almost perfect sensitivity (99.5%) and specificity (100%) in predicting a positive result of the GnRH stimulation test [26]. According to Ruixuecao et al., A single 60-minute post-stimulated LH gonadotropin result (sensitivity 87.6% and specificity 86.6%) and the LH/FSH ratio (sensitivity 97.3% and specificity 93.0%) can be used instead of the GnRH agonist stimulation test, or samples can be taken only 0, 30 and 60 minutes after stimulation with GnRH agonist.

In boys with PP, mandatory determination is recommended to study the level of 17-hydroxyprogesterone (17-HP) in the blood to exclude congenital adrenal hyperplasia (CAH), alpha-fetoprotein, beta-subunit of human chorionic gonadotropin (β-hCG) to exclude germinogenic tumors, to study the level of dehydroepiandrosterone (DHEA) in the blood and/or dehydroepiandrosterone sulfate in the blood (DHEA-C) to exclude androgen-producing adrenal tumors. In girls with premature adrenarche, a mandatory study of the level of 17-HP and DHEA /DHEA-C is recommended to exclude CAH; blood androstenedione, DHEA /DHEA-C blood and total blood testosterone to exclude androgen-producing tumors of the ovaries or adrenal glands [40].

Girls under the age of six and all boys with premature puberty and children with neurological symptoms such as headache, vision changes or seizures should be checked using magnetic resonance imaging (MRI). Some experts do not approve of routine neuroimaging of asymptomatic girls aged six to eight years. Because pathology requiring treatment is extremely rare [6].

Ultrasound of the pelvic organs is not used to diagnose premature puberty, but in girls it helps to determine the volume of the uterus and ovaries and is a sensitive method for detecting cysts and neoplasms. Ovarian volume> 1.8 ml and uterine length> 3.4 cm indicate hormonal stimulation and may be an additional laboratory parameter for assessing the condition of girls with premature puberty [35]. It is recommended to conduct ultrasound of the scrotum for boys with clinical signs of PP to assess the age of the testicular volume, to exclude testicular tumors [40].

**Figure 3. Precocious Puberty Management.**




**Treatment options.** The standard treatment for CPP is a gonadotropin-releasing hormone (GnRHa) analog, a synthetic decapeptide that binds to GnRH receptors in the pituitary gland with

greater stability and a longer half-life than natural GnRH [10]. Treatment with GnRH analogues is recommended for patients with CPP, whose bone age at the time of the initial examination is <12.5 years in girls or <14 years in boys in order to preserve the growth potential. GnRH analogues are not recommended for the treatment of CPR in patients with markedly elderly bone age > 12.5 years in girls or > 14 years in boys at the time of diagnosis, since there are no positive results in the form of suppression of the hipotalamo-pituitary-gonadal axis or preservation of growth at an older age [2]. The treatment of various forms of PP, depending on the etiological factor, is shown in Figure 3.

**Genetic factors of PP.** Central preocious puberty is usually considered idiopathic, although by Vries et al. it was mentioned that family cases accounted for 27.5% (43 out of 156 children) of CPP, and segregationally analysis suggests autosomal dominant transmission with incomplete penetrance depending on gender [39].To date, mutations in four genes (KISS1, KISS1R, MKRN3, DLK1) have been confirmed as causal variants leading to the central idiopathic form of PP [31].

**MKRN3 Makorin Ring Finger Protein 3.** The MKRN3 gene is a maternal imprinted gene located next to the Prader-Willi syndrome region graft of chromosome 15q11.2. Thus, all affected individuals inherit the mutation from their fathers. The protein consists of five domains with zinc fingers: three fingers or C3H1 motifs responsible for RNA binding; one C3HCRING motif with ubiquitin ligase activity; and one MKRN-specific Cys-His domain.Currently, it is reported that mutations in the MKRN3 gene, including reading frame shift, nonsense and missense mutations, among different families, nationalities and geographical regions leads to the development of CPP [31]. Currently, MKRN3 mutations are the most commonly identified monogenetic cause of central PPD, with local prevalence rates ranging from 0 to 46%, depending on the study. A systematic review and meta-analysis conducted in 2019 showed that more than 800 people with CPPR from 14 studies demonstrated an overall prevalence of MKRN3 gene mutations of 9% [34], however, in other reports, the prevalence of this mutation varied from 0% to 20% in small cohorts of Italian and Bulgarian girls [6, 12]. Although most published studies describe mutations of loss of function in the coding region of MKRN3, defects in the regulatory regions of the genes have been described in two recent studies. In one of the studies, it was found that a four-nucleotide deletion (c.150 -147delTCAG) in the proximal region of the promoter of the MKRN3 gene is responsible for the occurrence of CPP [21]. The second study described the replacement of one nucleotide at position 19 (MKRN3:g.+19C>T) at the site of the beginning of transcription in the 5'-UTR region of the MKRN3 gene, which is associated with CPP [19]. By Pavlos F et al. in 2019, three new heterozygous mutations were found which is located in the proximal promoter and one in the 5'-UTR region of the MKRN3 gene in seven unrelated girls with CPP. Four of these girls had a common mutation MKRN3:g.-865G>A, one MKRN3:g.-166G>A, and another MKRN3:g.-886G>A, which are all localized in the proximal promoter of the MKRN3 gene [24].

Patients carrying MKRN3 mutations have typical clinical and biochemical signs of premature reactivation of the reproductive axis. Several studies have compared data from patients with and without mutations, and higher basal FSH levels and earlier age of onset of puberty have been described among girls with mutations, while affected boys have a later onset of puberty compared to patients with PP and no mutations. Thus, it is still unknown whether their phenotype differs from those without mutations [3]. According to Dominique et al., mean age at onset of puberty was the only parameter that differed significantly between girls with and without MKRN3 mutations (lower in girls with mutations, at 6.0 years). The narrow age range of onset of puberty in patients with MKRN3 mutations indicates that the activity of the encoded protein is critical at a certain point in time in the postnatal development of the GnRH neural network [7].

**Kisspeptin, a peptide product of the KISS1 gene**, and its receptor, G-protein signaling complex 54 **(GPR54)**, are important factors in pubertal activation of GnRH neurons [25, 28]. An increase in kisspeptin signaling caused by increased expression of the KISS1 and GPR54 genes at the onset of puberty contributes to the activation of the hypotalamo-pituitary-gonadal axis. The gene is located on chromosome 1q32-q41. It was first identified in 1996 as an agent that suppresses tumor metastasis [37]. Later, its role as a major regulator during puberty was confirmed. Two years after reports of mutations in the KISS1R gene in a patient with CPP, mutations with increased function in

the KISS1 gene were found in three Brazilian children [27]. A boy with a mutation in the KISS1 gene (p.Pro74Ser) manifested secondary sexual development at the age of 17 months. This mutation was inherited from his healthy mother and grandmother. Luan et al. evaluated the relationship between KISS1 gene mutations and CPLR in 272 Chinese girls with CPRD. They identified 8 mutation polymorphisms of this gene. One of them was new (P110T) and had a significant negative association with the disease [20]. Ko et al. studied mutations of the KISS1 gene and polymorphisms of this gene among 101 Korean girls with CPP. They found 8 polymorphisms (two polymorphisms) in the studied Korean girls. They also reported that P110T polymorphism is a rare polymorphism in the KISS1 gene mutation, which was supposed to have a protective effect on precocious puberty [15]. Tomiska et al. in Finland, the role of the KISS1 gene in the pathogenesis of CPP in 30 patients. They did not find any mutations and concluded that the KISS1 gene is not a common cause of CPP [33]. Krstevska Konstantinova et al. in Macedonia, a KISS1 mutation was studied in 28 girls with ICPP [15]. Their results were similar to those of Tomiska et al.

**DLK1 Delta-like noncanonical Notch ligand**. More recently, a mutation in the delta-like non-canonical Notch 1 ligand located on chromosome 14q32.2 has been described as a new genetic cause of CPP [5]. This region includes imprinted genes (DLK1-DIO3 domain) associated with Kagami-Ogata syndrome, which is associated with maternally expressed genes, and Temple syndrome, which is associated with paternally expressed genes. The DLK1 gene has 5 exons and encodes a transmembrane protein belonging to a family of proteins like epidermal growth factor that includes Notch receptors and Delta and Serrate ligands; this is part of the Delta Notch pathway, a signaling pathway that has been preserved in different species during evolution [1]. Recent studies illustrate the relationship between CPP and DLK1. In a study involving a family of five women diagnosed with CPLR, a complex partial deletion of chromosome 14 was identified, the 5'UTR and the first intron were removed, while the underlying structures were preserved [5]. DLK1 imprinting is controlled by two differentially methylated regions (DMRs), an intergenic differentially methylated region (IG-DMR) and a secondary MEG3-DMR obtained after fertilization [11]. Loss of DLK1 in combination with two other genes on the paternal chromosome, RTL1 and DIO3, leads to Temple syndrome [13].

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