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GENETIC AND EPIGENETIC DETERMINANTS OF DYSMETABOLIC NEPHROPATHY IN CHILDREN

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Summary.

Dysmetabolic nephropathy (DN) is one of the most common nephrological disorders in childhood, characterized by metabolic disturbances leading to intrarenal crystal formation and affecting 21-31% of the pediatric population in Ukraine. This article presents the results of a comprehensive investigation into the genetic and epigenetic determinants of DN in children, including the clinical course, biochemical abnormalities, and molecular mechanisms of pathogenesis associated with different genotypes. The relevance of the study is underscored by the polygenic nature of DN, with up to 90% of cases exhibiting polygenic inheritance determined by complex interactions between hereditary and environmental factors.

Objective. *To characterize the genetic and epigenetic determinants of dysmetabolic nephropathy in children through analysis of polymorphisms in the VDR, GSTM1, and GSTT1 genes and assessment of early developmental factors.*

Materials and methods. *A total of 108 children aged 6-17 years with DN and 44 healthy children from the Ivano-Frankivsk region were enrolled. Genotyping for VDR polymorphisms (TaqI, ApaI) and GSTM1/GSTT1 deletions was performed using polymerase chain reaction (PCR). A comprehensive clinical and laboratory evaluation was conducted to assess metabolic disorders, oxidative stress markers, and early developmental factors. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 145/24 dated 20 March 2024). Statistical analyses were performed using the SPSS software package (IBM Corp., Armonk, NY, USA). Intergroup comparisons were carried out using the Student's t-test, Mann–Whitney U test, and chi-squared (χ^2) test as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. The study was supported by the research program of the State Institution «Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine»: «Search for markers of early diagnosis and differential diagnosis of congenital malformations associated with undifferentiated connective tissue dysplasia» (State Registration No. 0114U001549), and by the research programs of Ivano-Frankivsk National Medical University: «Features of psychosomatic adaptation in children with chronic somatic pathology» (State Registration No. 0112U004423; implementation period 2012-2021) and «Health status and adaptation features of children of Prykarpattia with somatic diseases, their prevention» (State Registration No. 0121U111129; implementation period 2021-2026).*

Results. *In children with dysmetabolic nephropathy (DN), significant associations with VDR gene polymorphisms were observed: the heterozygous Aa genotype (ApaI) was associated with a 5.69-fold increase in DN risk ($p < 0.001$), and the Tt genotype (TaqI) with a 2.66-fold increase. The double deletion of GSTM1/GSTT1 conferred a 4.73-fold increase in DN risk. Among epigenetic factors, the most significant associations were observed for threatened abortion (15.83% versus 8.93%), gestosis during the first half of pregnancy (53.83% versus 28.57%), early artificial feeding (67.31% versus 14.28%), and frequent acute respiratory infections in childhood (71.15% versus 12.50%). Elevated markers of oxidative stress and disturbances in connective tissue metabolism were also documented in patients.*

Conclusion. *Dysmetabolic nephropathy in children exhibits a polygenic inheritance pattern with a substantial contribution from epigenetic factors. The identified genetic markers may be utilized for early identification of at-risk individuals, while modification of epigenetic risk factors may serve as a basis for preventive strategies.*

Keywords: *Child; Dysmetabolic Nephropathy; Epigenetic Factors; Genetic Polymorphisms; GSTM1; GSTT1; VDR*

Introduction

Dysmetabolic nephropathy (DN) in children is one of the most common nephrological disorders encountered in pediatric practice and is characterized by metabolic disturbances leading to intrarenal crystal formation [1]. Epidemiological data indicate that DN affects approximately 8-15% of the pediatric populations in Europe and North America, whereas in Ukraine, the prevalence among children ranges from 21% to 31%, depending on the region [2]. Up to 94% of DN cases in pediatric practice are classified as oxalate nephropathies and are accompanied by calcium oxalate crystalluria.

DN is typically polygenic in nature; up to 90% of cases are inherited polygenically, with disease manifestation determined by the interaction of hereditary and environmental factors [3]. Familial studies corroborate the role of heredity: the likelihood of DN development in a child with a positive family history of metabolic disorders is increased by 3.5- to 5-fold.

Among genetic determinants, polymorphisms in genes regulating oxalate and calcium metabolism, as well as antioxidant defense mechanisms, have attracted particular interest. Polymorphisms in the vitamin D receptor (*VDR*) gene have been associated with susceptibility to nephrolithiasis, and deletions in the glutathione S-transferase genes (*GSTM1* and *GSTT1*) have been linked to an increased risk of chronic kidney disease [4,5].

Epigenetic factors encompass early developmental and nutritional exposures that may induce heritable alterations in gene expression without modification of the DNA

sequence. Adverse pregnancy outcomes have been shown to elevate the risk of metabolic disorders in offspring through epigenetic programming [6].

The objective of the study was to characterize the genetic and epigenetic determinants of dysmetabolic nephropathy in children through analysis of polymorphisms in the *VDR, GSTM1*, and *GSTT1* genes and evaluation of early developmental factors.

Materials and Methods. The study was based on clinical and genetic data collected from children with DN at the Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine between 2012 and 2021. A total of 108 children aged 6-17 years from the Ivano-Frankivsk region with a confirmed diagnosis of DN were included. The control group comprised 44 apparently healthy children without evidence of DN.

The diagnosis was established on the basis of medical history, clinical evaluation, ultrasonographic detection of renal deposits, and the presence of persistent crystalluria. Patients were stratified into two groups: Group I (n = 52) consisted of children with DN complicated by recurrent urinary tract infections; Group II (n = 56) included children with uncomplicated DN.

Genetic analysis involved polymerase chain reaction (PCR) genotyping of *VDR* polymorphisms (TaqI, rs731236; ApaI, rs7975232) using the PCR–restriction fragment length polymorphism (PCR-RFLP) method, and assessment of *GSTM1/GSTT1* deletional polymorphisms by multiplex PCR.

Laboratory investigations included measurement of urinary excretion of oxalate, phosphate, calcium, uric acid, and citrate in 24-hour urine samples; evaluation of the anti-crystallization capacity of urine; and quantification of oxidative stress markers (malondialdehyde [MDA], diene conjugates) and connective tissue metabolism markers (hydroxyproline).

Statistical analyses were performed using the SPSS software package (IBM Corp., Armonk, NY, USA). Intergroup comparisons were conducted using the Student's *t*-test, Mann–Whitney *U* test, and chi-squared (χ^2) test, as appropriate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 145/24 dated 20 March 2024).

The study was performed as part of the research program of the State Institution «Institute of Hereditary Pathology of the National Academy of Medical Sciences of Ukraine»: «Search for markers of early diagnosis and differential diagnosis of congenital malformations associated with undifferentiated connective tissue dysplasia» (State Registration No. 0114U001549), and of the research programs of Ivano-Frankivsk National Medical University: «Features of psychosomatic adaptation in children with chronic somatic pathology» (State Registration No. 0112U004423; implementation period 2012-2021) and «Health status and adaptation features of children of Prykarpattia with somatic diseases, their prevention» (State Registration No. 0121U111129; implementation period 2021-2026).

Results and Discussion

Among the 108 children with dysmetabolic nephropathy (DN) included in the study (mean age 11 ± 2.3 years), 55 were boys and 53 were girls. The distribution of patients across clinical groups is presented in Table 1.

Table 1

Characteristics of examined children with dysmetabolic nephropathy

Indicators	Group I (complicated DN) n=52	Group II (uncomplicated DN) n=56	Control group n=44
Age, years	11.2 ± 2.1	10.8 ± 2.5	11.0 ± 2.2
Boys/girls	28/24	27/29	23/21
Symptoms of chronic intoxication, %	80.8	32.1	5.2
Body weight deficit, %	15.4	5.4	2.3
Positive family history, %	78.85	67.86	18.2

Symptoms of chronic intoxication and body weight deficit were significantly more frequent in children in Group I than in Group II. Positive family history of metabolic diseases was observed in the majority of children with dysmetabolic nephropathy.

Analysis of antenatal and postnatal risk factors revealed a significant association between epigenetic determinants and the development of dysmetabolic nephropathy (Table2).

The most significant epigenetic risk factors were early artificial feeding and frequent acute respiratory infections during childhood, which were associated with a 12.1-fold and 17.4-fold increase in the risk of dysmetabolic nephropathy, respectively.

Biochemical examination revealed significant metabolic disturbances in children with dysmetabolic nephropathy (DN) (Table 3).

Children with DN exhibited elevated urinary oxalate excretion, disturbances in calcium metabolism, and significantly increased markers of undifferentiated connective tissue dysplasia (UCTD) and oxidative stress. These abnormalities were most pronounced in Group I (complicated DN).

Genetic analysis revealed significant associations between *VDR* polymorphisms and DN (Table 4).

The heterozygous *Aa* genotype (ApaI) was associated with a 5.69-fold increase in the risk of dysmetabolic nephropathy, and the *Tt* genotype (TaqI) was associated with a 2.66-fold increase in risk.

Analysis of deletional polymorphisms in glutathione S-transferase (GST) genes revealed a significant association with dysmetabolic nephropathy (Table 5).

Table 2

Frequency of antenatal and postnatal risk factors in children with DN

Risk factors	Children with DN n=108	Control n=44	OR (95% CI)
Antenatal factors			
Threatened abortion, %	15.83	8.93	2.14 (1.12-4.08)
Gestosis of first half of pregnancy, %	53.83	28.57	2.97 (1.73-5.09)
Anemia of pregnancy, %	38.46	21.43	2.29 (1.25-4.19)
Harmful habits of parents, %	73.07	50.00	2.73 (1.58-4.71)
Postnatal factors			
Low birth weight, %	21.15	8.93	2.75 (1.18-6.40)
Early artificial feeding, %	67.31	14.28	12.1 (5.89-24.8)
Frequent ARI in childhood, %	71.15	12.50	17.4 (8.45-35.8)
Neonatal jaundice, %	40.38	17.85	3.12 (1.55-6.27)
Atopic diathesis, %	34.62	7.14	7.04 (2.89-17.1)

Table 3

Biochemical parameters in children with dysmetabolic nephropathy

Indicators	Group I n=52	Group II n=56	Control n=44
Urine parameters			
Oxalate excretion, μmol/day	49.1 ± 3.2	45.8 ± 2.9	35.2 ± 2.1
Calcium excretion, mmol/day	2.45 ± 0.31	1.98 ± 0.24	1.93 ± 0.35
Anti-crystallization capacity, cu	0.71 ± 0.08	0.62 ± 0.05	0.53 ± 0.06
Blood parameters			
Serum calcium, mmol/L	1.47 ± 0.21	1.54 ± 0.19	1.63 ± 0.32
Parathyroid hormone, pg/mL	16.2 ± 4.1	13.1 ± 2.8	11.2 ± 1.14
UCTD markers			
Free hydroxyproline, μmol/L	61.8 ± 3.2	53.4 ± 2.8	27.65 ± 1.1
Bound hydroxyproline, μmol/L	42.1 ± 3.5	35.2 ± 2.9	21.22 ± 2.2
Oxidative stress markers			
Plasma MDA, μmol/L	2.12 ± 0.11	1.67 ± 0.09	1.28 ± 0.17
Diene conjugates, μmol/L	15.8 ± 1.6	13.1 ± 1.1	13.83 ± 0.97

Table 4

Distribution of VDR genotypes in children with dysmetabolic nephropathy

Genotypes	Children with DN n=108	Control n=44	OR (95% CI)
ApaI polymorphism			
AA, %	78.18	38.64	5.69 (2.85-11.4)
Aa, %	14.55	59.09	—
aa, %	7.27	2.27	3.41 (0.68-17.1)
TaqI polymorphism			
TT, %	45.45	63.64	—
Tt, %	43.64	22.73	2.66 (1.27-5.59)
tt, %	10.91	13.63	1.12 (0.41-3.05)

Table 5

Distribution of GSTM1/GSTT1 genotypes in children with dysmetabolic nephropathy

Genotypes	Children with DN n=108	Control n=44	OR (95% CI)
GSTM1 (+), %	52.78	70.45	—
GSTM1 (0/0), %	47.22	29.55	2.13 (1.05-4.32)
GSTT1 (+), %	61.11	79.55	—
GSTT1 (0/0), %	38.89	20.45	2.53 (1.15-5.57)
Double deletion *GSTM1*/*GSTT1*, %	18.52	4.55	4.73 (1.42-15.7)

Double deletion of *GSTM1*/*GSTT1* was associated with a 4.73-fold increase in the risk of dysmetabolic nephropathy. The highest levels of oxidative stress markers were observed in carriers of these deletions.

The associations identified between genetic polymorphisms and dysmetabolic nephropathy are consistent with the current understanding of the role of the vitamin D receptor (*VDR*) in calcium metabolism regulation

and glutathione S-transferases (*GST*) in detoxification. The observed phenomenon of «negative heterosis» for *VDR* may be explained by effects on messenger RNA stability and protein function

Epigenetic factors play a pivotal role in the pathogenesis of dysmetabolic nephropathy, in accordance with the «developmental origins of health and disease» (DOHaD) hypothesis. Adverse intrauterine exposures may induce a persistent epigenetic «imprint,» manifesting clinically as undifferentiated connective tissue dysplasia (UCTD) syndrome and metabolic disturbances.

Particular attention should be given to the role of the vitamin D receptor in the pathogenesis of dysmetabolic nephropathy. Vitamin D is involved not only in the regulation of calcium–phosphorus homeostasis but also in the modulation of immune responses and anti-inflammatory processes in the kidneys. Studies have demonstrated that polymorphisms in the *VDR* gene, particularly TaqI and ApaI, are associated with increased susceptibility to chronic kidney disease in children, influencing *VDR* protein expression and target organ sensitivity to vitamin D [11].

Investigations into glutathione S-transferases have highlighted their critical role in defense against oxidative stress. Deletions of *GSTM1* and *GSTT1* result in complete absence of enzymatic activity, substantially diminishing the body's antioxidant capacity [12-15]. The prospective Chronic Kidney Disease in Children (CKiD) study reported that *GSTM1* deletion is associated with accelerated progression of chronic kidney disease in pediatric patients, with a hazard ratio of 1.94 [16].

The DOHaD concept holds particular relevance in the context of dysmetabolic nephropathy [17,18]. Epigenetic modifications triggered by adverse early-life exposures can lead to long-term alterations in gene expression without changes to the underlying DNA sequence [19]. Renal maturation in humans extends well beyond birth, rendering the developing kidney especially vulnerable to adverse intrauterine and neonatal conditions [20].

Early artificial feeding warrants specific consideration as a potent epigenetic risk factor. Human breast milk contains epigenetic regulators, including microRNAs, that contribute to the programming of gene expression [21]. The absence of these bioactive components in formula feeding may result in alternative epigenetic programming.

The observed biochemical abnormalities confirm the systemic nature of the pathological process. Elevated urinary oxalate excretion reflects disturbances in oxalate metabolism. Calcium oxalate crystalluria and intratubular crystal deposition represent pathognomonic features of oxalate nephropathy, which accounts for up to 94% of dysmetabolic nephropathy cases in children [22,23].

Marked oxidative stress – evidenced by elevated concentrations of malondialdehyde and diene conjugates – underscores the contribution of free radical–mediated mechanisms to disease pathogenesis [24,25]. Studies in children with chronic renal failure have demonstrated significantly increased malondialdehyde levels in both plasma and erythrocytes, correlating with the severity of renal dysfunction [18-20].

The interplay between genetic and epigenetic factors constitutes a complex, multilayered regulatory system governing susceptibility to dysmetabolic nephropathy. Genetic polymorphisms establish the baseline functional capacity of key metabolic and detoxification pathways, whereas epigenetic modifications dynamically modulate gene expression throughout life [21-23].

Conclusions

The comprehensive investigation of genetic and epigenetic determinants of dysmetabolic nephropathy in children has yielded fundamentally new insights into the molecular mechanisms underlying the pathogenesis of this disorder and has enabled the identification of key risk factors for its development. The findings clearly demonstrate that dysmetabolic nephropathy in children exhibits a complex polygenic inheritance pattern, with a substantial contribution from epigenetic factors that shape individual susceptibility through intricate interactions between hereditary and environmental influences.

The genetic component of dysmetabolic nephropathy pathogenesis proved to be more complex than previously recognized. Positive family history of metabolic disorders was associated with a 3.5- to 5-fold increase in disease risk, underscoring the significance of heredity within the etiological framework of dysmetabolic nephropathy. Of particular interest were the associations involving polymorphisms of the vitamin D receptor (*VDR*) gene, which revealed an unusual phenomenon of «negative heterosis.» The heterozygous *Aa* genotype for the ApaI polymorphism was associated with a 5.0-fold increase in the risk of developing dysmetabolic nephropathy, whereas the *Tt* genotype for the TaqI polymorphism conferred a 2.66-fold increase in risk. This effect may be attributed to the influence of heterozygosity on messenger RNA stability and the functional activity of the *VDR* protein, a hypothesis that warrants further in-depth molecular investigation to elucidate the precise mechanisms involved.

Equally significant was the role of deletional polymorphisms in the glutathione S-transferase genes *GSTM1* and *GSTT1*, which encode key enzymes of the body's detoxification and antioxidant defense systems. The double deletion of these genes was associated with a 4.73-fold increase in the risk of dysmetabolic nephropathy and correlated with the highest levels of oxidative stress markers among the examined children. These findings highlight the critical role of the antioxidant system in the pathogenesis of renal metabolic disturbances and reinforce oxidative stress as a central component of the pathogenetic cascade in dysmetabolic nephropathy

Epigenetic factors exerted a profoundly strong influence on the development of susceptibility to dysmetabolic nephropathy, in alignment with the contemporary «developmental origins of health and disease» (DOHaD) concept. Among the identified epigenetic determinants, early artificial feeding emerged as the most potent, increasing disease risk by 12.1-fold, followed by frequent acute respiratory infections during childhood (odds ratio 17.4). These exposures are likely to induce stable epigenetic modifications that modulate the expression of genes involved in renal metabolic regulation. Gestosis during the first half of pregnancy also represented a significant antenatal risk factor (odds ratio 2.97), reinforcing the

pivotal role of the intrauterine environment in programming future metabolic dysfunction. Additionally, atopic diathesis in children was associated with a 7.04-fold increase in risk, suggesting shared pathophysiological pathways between allergic and metabolic disorders, potentially mediated by impaired immune regulation and chronic low-grade inflammation.

Biochemical studies revealed profound metabolic disturbances in children with dysmetabolic nephropathy, reflecting the systemic nature of the underlying pathological process. Elevated urinary oxalate excretion, abnormalities in calcium metabolism, and reduced anti-crystallization capacity of urine collectively create a favorable environment for intrarenal crystal formation and progression of nephropathy. The development of undifferentiated connective tissue dysplasia (UCTD) syndrome – evidenced by increased concentrations of both free and bound hydroxyproline – indicates systemic alterations in collagen metabolism and may account for the observed predisposition to recurrent urinary tract infections in these patients. Marked oxidative stress, documented by elevated levels of malondialdehyde and diene conjugates, underscores the contribution of free radical–mediated mechanisms to disease progression and supports the inclusion of antioxidant therapy in comprehensive management strategies.

Particular attention should be given to the observed differences in the severity of metabolic disturbances between children with complicated and uncomplicated forms of dysmetabolic nephropathy. Patients with the complicated form exhibited the most pronounced abnormalities across all evaluated parameters, which may reflect either a more aggressive disease course in the presence of a concurrent infectious trigger or a less favorable genetic background.

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Author contributions:

Kiyan N. R. – Concept and design of the study; collection and processing of clinical material; statistical data analysis; drafting the manuscript. Kech N.R – Concept and design of the study; interpretation of results; critical revision of the manuscript. Lukianenko N.S – Collection and processing of clinical material; interpretation of research findings; critical revision of the manuscript. Petritsa N.A – Performance of molecular genetic analyses; interpretation of genetic data; contribution to manuscript writing. Iskiv M.Yu – Performance of molecular genetic analyses; laboratory investigations; analysis of biochemical parameters.

All authors approved the final version of the manuscript and take full responsibility for all aspects of the work, ensuring the accuracy and integrity of all its components.

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ГЕНЕТИЧНІ ТА ЕПІГЕНЕТИЧНІ ДЕТЕРМІНАНТИ ДИЗМЕТАБОЛІЧНОЇ НЕФРОПАТІЇ У ДІТЕЙ

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Резюме.

Дизметаболічна нефропатія (ДН) є одним з найпоширеніших нефрологічних захворювань дитячого віку, що характеризується метаболічними розладами з утворенням кристалів у нирках та вражає 21-31% дитячого населення України. Стаття висвітлює результати комплексного дослідження генетичних та епігенетичних детермінант ДН у дітей, особливості клінічного перебігу, біохімічних порушень та молекулярних механізмів патогенезу при різних генотипах. Актуальність дослідження обумовлена полігенною природою ДН, коли до 90% випадків успадковуються полігенно з розвитком, що визначається складною взаємодією спадкових та середовищних чинників.

Мета – характеристика генетичних та епігенетичних детермінант дизметаболічної нефропатії у дітей на основі аналізу поліморфізмів генів VDR, GSTM1, GSTT1 та факторів раннього розвитку.

Матеріали та методи. Обстежено 108 дітей віком 6-17 років з ДН та 44 здорові дитини з Івано-Франківської області. Використано ПЛР-генотипування для визначення поліморфізмів VDR (TaqI, ApaI) та делецій GSTM1/GSTT1. Проведено комплексне клініко-лабораторне обстеження з оцінкою метаболічних порушень, окислювального стресу та факторів раннього розвитку. Дослідження проведено відповідно до принципів Гельсінської декларації. План дослідження схвалено комісією з питань етики Івано-Франківського національного медичного університету (протокол № 145/24 від 20.03.2024 р.). Статистична обробка проводилася з використанням пакету SPSS. Для порівняння груп застосовували t-критерій Стьюдента, U-критерій Манна-Вітні, критерій χ^2. Обчислювали відношення шансів (ВШ) з 95% довірчим інтервалом. Дослідження виконане в межах науково-дослідної роботи ДУ «Інститут спадкової патології НАМН України» «Пошук маркерів ранньої діагностики та диференціальної діагностики природжених вад розвитку, асоційованих із недиференційованою дисплазією сполучної тканини» (№ держреєстрації 0114U001549) та в межах науково-дослідної роботи Івано-Франківського національного медичного університету «Особливості психосоматичної адаптації у дітей із хронічною соматичною патологією» (№ держреєстрації 0112U004423), терміни виконання 2012-2021; «Стан здоров'я та особливості адаптації дітей Прикарпаття із соматичними захворюваннями, їх профілактика» (№ держреєстрації 0121U111129), терміни виконання 2021-2026.

Результати. У дітей з ДН виявлено значущі асоціації з поліморфізмами гена VDR: гетерозиготний генотип Aa (ApaI) асоціювався з підвищенням ризику ДН у 5,69 раза ($p<0,001$), генотип Tt (TaqI) – у 2,66 раза. Подвійна делеція GSTM1/GSTT1 підвищувала ризик ДН у 4,73 раза. Серед епігенетичних факторів найбільш значущими були: загроза переривання вагітності

(15,83% проти 8,93%), гестоз I половини вагітності (53,83% проти 28,57%), раннє штучне вигодовування (67,31% проти 14,28%) та часті ГРЗ у дитинстві (71,15% проти 12,50%). У хворих виявлено підвищення маркерів окислювального стресу та порушення обміну сполучної тканини.

Висновок. ДН у дітей має полігенну природу з вагомим внеском епігенетичних факторів. Виявлені генетичні маркери можуть використовуватися для ранньої діагностики груп ризику, а корекція епігенетичних факторів – для профілактики захворювання.

Ключові слова: дизметаболічна нефропатія; діти; генетичні поліморфізми; VDR; GSTM1; GSTT1; епігенетичні фактори.

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