

# Association of COL1A1 Rs1800012 Gene Polymorphism with The Development of Primary Empty Sella Syndrome

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## Abstract

*This article discusses the possible role of the COL1A1 rs1800012 polymorphism in the development of primary empty sella syndrome. Special attention is given to the relationship between this genetic variant and structural changes of the sellar diaphragm, which is an important connective tissue formation involved in the pathogenesis of the syndrome. In patients with primary empty sella syndrome, the T allele and T/T genotype were observed more frequently than in the control group, especially in cases with the complete form of the disease. These findings suggest that the COL1A1 rs1800012 polymorphism may be associated with connective tissue weakness, reduced mechanical stability of the sellar diaphragm, and progression of morphological changes. The obtained data support the view that this polymorphism may be considered as one component of a multifactorial risk model for primary empty sella syndrome.*

**Keywords:** Empty sella syndrome, COL1A1, rs1800012, polymorphism, sellar diaphragm, connective tissue, genetic risk.

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## 1. Introduction

Primary empty sella syndrome is characterized by the herniation of the subarachnoid space into the sella turcica, leading to varying degrees of pituitary gland compression [7,27]. While the etiology of this condition is often linked to increased intracranial pressure and obesity, emerging evidence suggests that structural variations in connective tissue proteins may also play a crucial role in its pathogenesis [13,28]. Specifically, the COL1A1 gene, which encodes the pro- $\alpha 1$  chain of type I collagen, is essential for the structural integrity of the diaphragm sellae. Alterations in this gene,

particularly the rs1800012 polymorphism, potentially compromise the tensile strength of this collagenous structure, thereby facilitating the herniation of arachnoid tissue into the pituitary fossa. Given the pivotal role of collagen composition in maintaining the sella turcica's mechanical barriers, investigating this genetic variant may clarify why certain individuals develop symptoms of pituitary compression while others remain asymptomatic [11]. Furthermore, the prevalence of this condition, often identified incidentally during neuroimaging [8], may reflect an underlying susceptibility to connective tissue laxity that warrants investigation alongside established radiological markers

like sella turcica morphology and pituitary volume [23]. Existing clinical data indicate that although primary empty sella syndrome is frequently identified as an incidental radiological finding, a subset of patients exhibits significant endocrine dysfunction that necessitates comprehensive monitoring [5,11]. Patients with this syndrome commonly report chronic headaches and visual disturbances, reflecting the mechanical stress exerted on the surrounding neural and pituitary structures [1,6]. Beyond these mechanical manifestations, the resulting sellar anatomy can lead to varied clinical presentations ranging from asymptomatic morphological findings to profound hypogonadotropic hypogonadism or hyperprolactinemia [1]. Despite these clinical implications, the precise genetic underpinnings governing the structural integrity of the diaphragma sellae remain poorly defined. Therefore, identifying specific molecular markers like the COL1A1 rs1800012 polymorphism could offer significant insights into the pathogenesis of this condition, especially regarding the mechanical incompetence of the diaphragma sellae which is frequently implicated in the development of primary empty sella [20,22]. This hypothesis gains support from existing studies identifying COL1A1 variants as potential drivers of connective tissue laxity and associated pituitary-hypothalamic dysregulation [12,24]. Building on this potential genetic susceptibility, analyzing the correlation between this polymorphism and the degree of pituitary displacement may elucidate the spectrum of symptoms observed in clinical practice, ranging from incidental radiological findings to severe neurological complications [9,25]. Such advancements in molecular diagnostics could shift the current paradigm from viewing the empty sella primarily as a consequence of mechanical pressure to recognizing it as a phenotypic expression of systemic connective tissue heterogeneity [4,21]. Integrating these genetic findings with clinical assessment facilitates a more nuanced, multidisciplinary diagnostic approach that accounts for both anatomical pituitary deformities and systemic connective tissue status [15,16]. This approach is particularly vital given that the clinical spectrum of primary empty sella often fluctuates from asymptomatic presentations to complex endocrine deficiencies that require long-term longitudinal monitoring [14]. However, the current diagnostic framework often overlooks these genetic factors, leading to prolonged diagnostic delays as patients navigate disparate specialist consultations before receiving an accurate assessment [30]. Consequently, a targeted analysis of the COL1A1

rs1800012 polymorphism may establish a more predictive diagnostic model, potentially identifying individuals at risk for pituitary structural failure before the onset of profound endocrine abnormalities [10,31]. Furthermore, examining such genetic biomarkers may provide a molecular basis for the connective tissue laxity observed in patients with cerebral venous outflow disorders, which are increasingly recognized as contributors to the clinical phenotype of pituitary-related symptoms [19]. By shifting the focus toward the hereditary architecture of the collagenous matrices, researchers may better delineate how localized variations in type I collagen contribute to the mechanical failure of the diaphragma sellae [35]. This shift in perspective aligns with findings that emphasize the delicate orchestration of intracranial structures, where structural deviations in the sellar region often manifest as the clinical cost of altered physiological homeostasis. Such investigations parallel broader anthropological inquiries into how evolutionary cranial base remodeling renders specific neurocranial niches susceptible to functional decline when connective tissue homeostasis is disrupted [29]. Consequently, future research must prioritize cross-referencing genetic predispositions, such as collagen-related variants, with radiographic indices of sella morphology to better predict disease progression. Moreover, implementing large-scale multicenter screenings will be essential to validate these associations and mitigate the selection biases inherent in current, smaller-scale clinical observations [27]. In addition to genetic analysis, systematic longitudinal studies addressing the discrepancy between incidental radiographic findings and genuine clinical hypopituitarism are required to resolve persistent uncertainties regarding the prevalence of hormone dysregulation [2]. Establishing standardized protocols for endocrine screening in patients presenting with these anatomical variants will be critical for distinguishing between benign empty sella and clinically significant pituitary insufficiency [17]. Such robust investigations must concurrently address the limitations of existing cross-sectional data, which often fail to account for the variability in patient endocrine parameters or the potential for symptom progression over time [3]. Integrating patient-specific genetic profiles with longitudinal endocrine tracking may ultimately unveil whether specific collagen mutations serve as predictive biomarkers for pituitary stalk disruption [34]. Furthermore, experimental models utilizing these genetic variants could elucidate the mechanical consequences of

altered matrix composition on the sellar diaphragm's resilience, mirroring strategies employed in understanding other connective tissue pathologies [18,32]. Such mechanistic insights are crucial, as they may parallel the complex interplay observed in other hereditary connective tissue disorders, where collagen-related structural instabilities manifest as widespread systemic or localized anatomical phenotypes [33]. This framework mirrors the multidimensional diagnostic approach necessary for identifying cryptic pituitary syndromes, where the integration of genomic, proteomic, and biochemical data is increasingly viewed as essential for achieving precision in personalized clinical outcomes. Ultimately, the validation of these genetic markers through standardized imaging protocols and comprehensive longitudinal monitoring will be necessary to shift current management toward a more predictive and patient-centered framework. Furthermore, advancements in genetic screening technologies are likely to improve the characterization of these developmental factors, providing clinicians with the granular insight required to refine current diagnostic and treatment paradigms for patients with complex pituitary phenotypes [26].

**2. Aim of the study:** to assess the prognostic significance of the COL1A1 rs1800012 polymorphism in the development of primary empty sella syndrome and to determine its association with the complete and developing forms of the disease.

### 3. Methods

A total of 140 patients with primary empty sella syndrome (PESS) were under our observation, including 26 men and 114 women. The mean age of patients in the overall group was  $42.1 \pm 1.02$  years:  $38.8 \pm 2.5$  years in men and  $42.9 \pm 1.1$  years in women.

The group with the complete form of PESS included 100 patients, with a mean age of  $43.41 \pm 1.19$  years. Among them, there were 12 men and 88 women. The mean age was  $41.75 \pm 4.01$  years in men and  $43.63 \pm 1.25$  years in women.

The group with the developing form of PESS consisted of 40 patients, including 14 men and 26 women (Tables 1, 2; Figures 1, 2).. The mean age in this group was  $38.85 \pm 1.89$  years:  $36.2 \pm 3.16$  years in men and  $40.27 \pm 2.35$  years in women.

**Table 1. Distribution of PESS patients by syndrome form**

| Total number of patients with PESS | Complete form | Developing form |
|------------------------------------|---------------|-----------------|
| PESS, n=140                        | 100 (71%)     | 40 (29%)        |

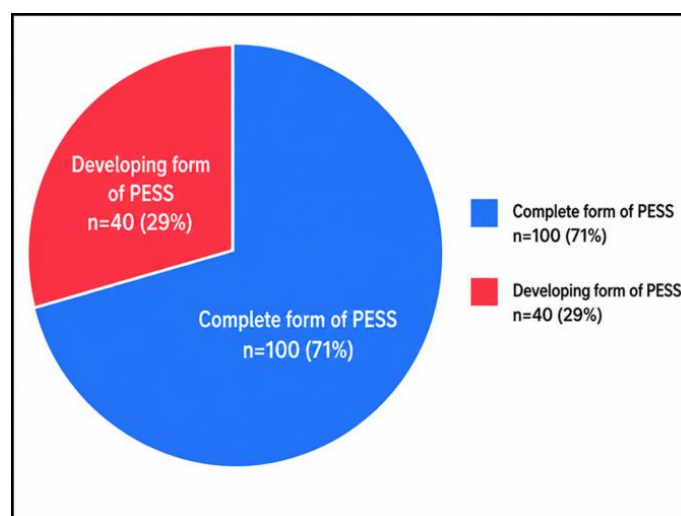
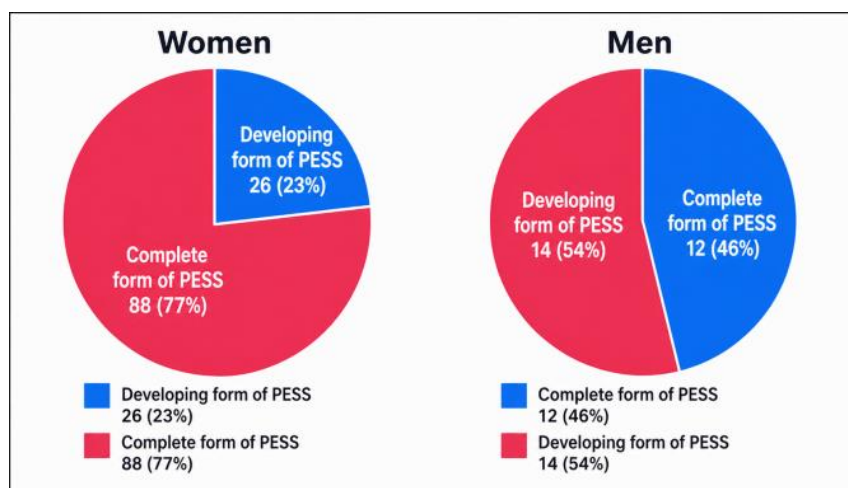


**Figure 1. Distribution of patients by disease form**

**Table 2. Distribution of patients with PESS by sex**

| Sex          | Complete PESS | Developing PESS |
|--------------|---------------|-----------------|
| Men, n=26    | 12 (46%)      | 14 (54%)        |
| Women, n=114 | 88 (77%)      | 26 (23%)        |

**Figure 2. Distribution of PESS patients according to sex and clinical-morphological form**

From the overall cohort of patients with primary empty sella syndrome, a separate subgroup was selected for the molecular genetic stage of the study. This subgroup included 36 patients with primary ESS and represented an in-depth pilot molecular genetic analysis within the larger clinical cohort.

Considering that insufficiency of the sellar diaphragm and possible genetically determined weakness of the connective tissue framework are regarded as important factors in the pathogenesis of primary ESS, these patients underwent analysis of the COL1A1 rs1800012 polymorphism. This gene encodes the  $\alpha 1$  chain of type I collagen and may be associated with the mechanical integrity of connective tissue structures.

The molecular genetic study included 36 patients with primary ESS: 19 patients with the complete form and 17 patients with the developing form of the disease. The control group consisted of 36 individuals without signs of ESS.

The mean age of the examined patients was  $39.78 \pm 2.3$  years. All patients were divided into two groups depending on the clinical and morphological form of the disease.

The inclusion criterion was the presence of primary empty sella syndrome, confirmed by magnetic resonance imaging. The exclusion criteria were previous surgical, radiation, or medical treatment of tumors of the pituitary region, since such cases are classified as secondary empty sella syndrome.

The diagnosis was established based on brain MRI findings. The complete form of the syndrome was defined as a marked reduction in the vertical height of the pituitary gland to  $\leq 2$  mm. The developing form was considered the initial stage of the pathological process, in which the vertical height of the pituitary gland was  $>2$  mm.

All participants underwent molecular genetic testing for the COL1A1 rs1800012 polymorphism at the Viamed molecular genetic laboratory. Genomic DNA was isolated from leukocytes of venous blood using the NK-Magnit Base-96 kit manufactured in Russia.

Allelic variants of the COL1A1 rs1800012 polymorphism were determined by restriction fragment analysis, based on enzymatic digestion of amplified genomic DNA fragments. Amplification of the COL1A1 rs1800012 DNA fragment was performed by polymerase

chain reaction (PCR) using specific oligonucleotide primers. The primer annealing temperature during amplification was 65°C.

The analysis was carried out using a DT lite 5S1 thermal cycler manufactured by DNA-Technology, Russian Federation, with test systems produced by Litekh, Russia. Genotypes were visualized by electrophoretic separation of the obtained restriction fragments.

Statistical analysis included determination of allele and genotype frequencies, comparison of groups using Pearson's  $\chi^2$  test, calculation of relative risk, odds ratio, and 95% confidence intervals. Differences were considered statistically significant at  $p \leq 0.05$ . Calculations were performed using OpenEpi 2009, Version 9.2.

#### 4. Results

Analysis of the distribution of alleles and genotypes of

**Table 3. Distribution frequency of alleles and genotypes of the COL1A1 rs1800012 polymorphism in patients with primary ESS and in the control group**

| Gro<br>ups                                             | G n | G %       | T n | T %       | G/G<br>n | G/G<br>%  | G/T<br>n | G/T<br>%  | T/T<br>n | T/T<br>%  |
|--------------------------------------------------------|-----|-----------|-----|-----------|----------|-----------|----------|-----------|----------|-----------|
| I —<br>Mai<br>n<br>grou<br>p<br>(MG<br>,<br>(n=3<br>6) | 46  | 63,8<br>9 | 26  | 36,1<br>1 | 17       | 47,2<br>2 | 12       | 33,3<br>3 | 7        | 19,4<br>4 |
| II —<br>Com<br>plete<br>form<br>(n=1<br>9)             | 22  | 57,8<br>9 | 16  | 42,1<br>1 | 8        | 42,1<br>1 | 6        | 31,5<br>8 | 5        | 26,3<br>2 |
| III<br>—<br>Dev<br>elopi<br>ng<br>form                 | 24  | 70,5<br>9 | 10  | 29,4<br>1 | 9        | 52,9<br>4 | 6        | 35,2<br>9 | 2        | 11,7<br>6 |

the COL1A1 rs1800012 polymorphism in patients with primary empty sella syndrome showed that the frequency of the T allele was higher in patients with PESS than in the control group. In the main group, it was 36.11%, whereas in the control group it was 18.06%. In contrast, the G allele was more frequently detected in the control group — 81.94% compared with 63.89% in patients with PESS.

When assessing the clinical and morphological forms of the disease, the highest frequency of the T allele was found in patients with the complete form of PESS — 42.11%. In patients with the developing form, this value was 29.41%.

A similar pattern was observed in the analysis of the T/T genotype: its frequency was 26.32% in the complete form of PESS and 11.76% in the developing form, whereas in the control group it was only 2.78%. The data are presented in Table 3, Figure3.

|                                                     |    |       |    |       |    |       |    |       |   |      |
|-----------------------------------------------------|----|-------|----|-------|----|-------|----|-------|---|------|
| (n=17)                                              |    |       |    |       |    |       |    |       |   |      |
| IV – Control group (CG), healthy individuals (n=36) | 59 | 81,94 | 13 | 18,06 | 24 | 66,67 | 11 | 30,56 | 1 | 2,78 |

Distribution of COL1A1 rs1800012 alleles and genotypes by groups

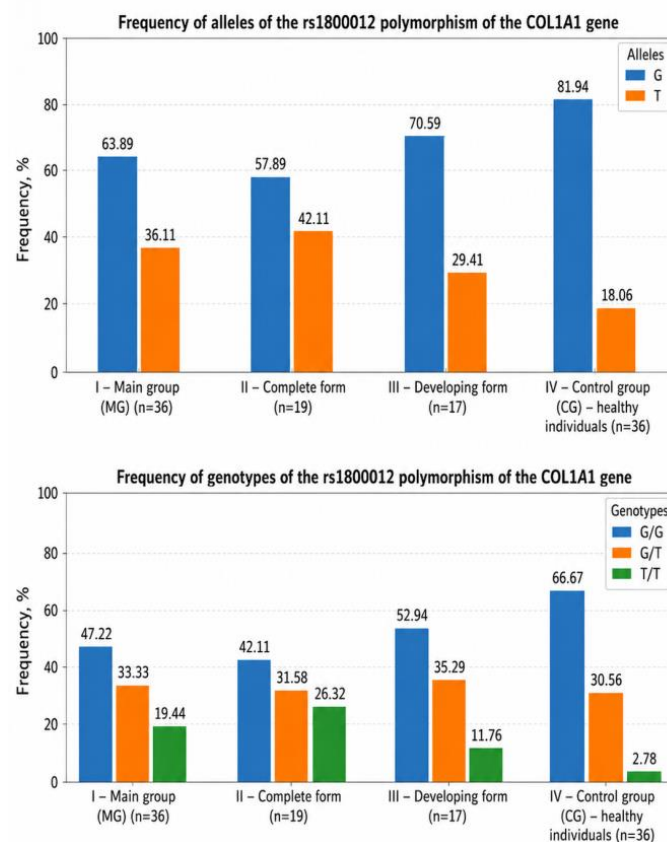


Figure 3. Distribution of alleles and genotypes of the COL1A1 rs1800012 polymorphism across the study groups

At the next stage, a comparative analysis of the distribution of allelic and genotypic variants of the

COL1A1 rs1800012 polymorphism was performed in patients with the complete form of PESS and in the

control group. The most pronounced differences were identified in this subgroup.

In patients with the complete form of PESS, the frequency of the T allele was significantly higher than in controls: 42.1% versus 18.1%, respectively ( $\chi^2=7.4$ ;  $p=0.01$ ). The odds ratio was  $OR=3.3$ , indicating an association of the T allele with an increased risk of developing the complete form of the disease. In contrast, the G allele was more frequent in the control group — 81.9% versus 57.9% in patients with the complete form of PESS, which allows it to be considered a potentially protective variant.

The most significant differences were observed for the T/T genotype. Its frequency in patients with the complete

form of PESS was 26.3%, whereas in the control group it was 2.8%. The differences were statistically significant ( $\chi^2=7.1$ ;  $p=0.01$ ). The relative risk was  $RR=9.5$ , and the odds ratio was  $OR=12.5$ , indicating a strong association between the T/T genotype and the complete form of primary ESS. The data are presented in Table 4 Figure 4.

To clarify the possible role of the COL1A1 rs1800012 polymorphism in disease progression, patients with complete and developing forms of PESS were compared. No statistically significant differences were found between these subgroups. However, a certain trend was observed: the T allele was more frequent in the complete form of PESS — 42.1% versus 29.4% in the developing form. The T/T genotype was also detected more often in patients with the complete form: 26.3% versus 11.8%.

**Table 4. Comparative analysis of allelic and genotypic variants of the COL1A1 rs1800012 polymorphism in patients with the complete form of PESS and in the control group**

| Alleles and genotypes | Complete form n | Complete form % | Control group n | Control group % | $\chi^2$ | p    | RR  | 95% CI      | OR   | 95% CI       |
|-----------------------|-----------------|-----------------|-----------------|-----------------|----------|------|-----|-------------|------|--------------|
| G                     | 22              | 57,9            | 59              | 81,9            | 7,4      | 0,01 | 0,7 | 0,27 – 1,83 | 0,3  | 0,13 – 0,72  |
| T                     | 16              | 42,1            | 13              | 18,1            | 7,4      | 0,01 | 1,4 | 0,62 – 3,26 | 3,3  | 1,4 – 7,8    |
| G/G                   | 8               | 42,1            | 24              | 66,7            | 3,1      | 0,19 | 0,6 | 0,15 – 2,67 | 0,4  | 0,12 – 1,12  |
| G/T                   | 6               | 31,6            | 11              | 30,6            | 0,0      | 0,93 | 1,0 | 0,22 – 4,77 | 1,0  | 0,32 – 3,48  |
| T/T                   | 5               | 26,3            | 1               | 2,8             | 7,1      | 0,01 | 9,5 | 3,1 – 28,91 | 12,5 | 1,95 – 80,24 |

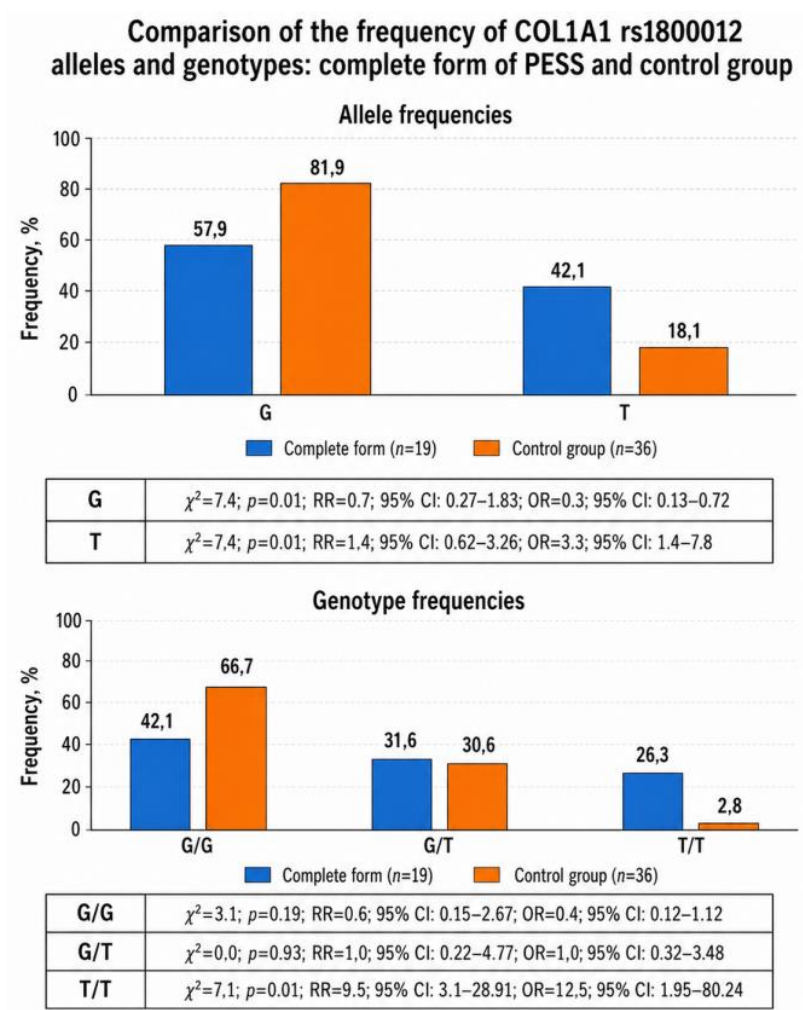


**Figure 4. Allele and genotype frequencies in complete PESS and controls.**

Despite the absence of statistical significance, the risk estimates for the T/T genotype were higher in the complete form of the disease: RR=2.2; OR=2.7. This may indicate a possible role of this genotype not only in

the development of primary ESS, but also in the transition of the disease from the developing to the complete form. The data are presented in Table 5 Figure 5.

**Table 5. Comparison of complete and developing forms of PESS by the distribution of alleles and genotypes of the COL1A1 rs1800012 polymorphism**

| Alleles and genotypes | Complete form n | Complete form % | Developing form n | Developing form % | $\chi^2$ | p    | RR  | 95% CI   | OR  | 95% CI    |
|-----------------------|-----------------|-----------------|-------------------|-------------------|----------|------|-----|----------|-----|-----------|
| G                     | 22              | 57,9            | 24                | 70,6              | 1,3      | 0,42 | 0,8 | 0,35–1,9 | 0,6 | 0,22–1,52 |

|     |    |      |    |      |     |      |     |                   |     |                    |
|-----|----|------|----|------|-----|------|-----|-------------------|-----|--------------------|
| T   | 16 | 42,1 | 10 | 29,4 | 1,3 | 0,42 | 1,2 | 0,41<br>–<br>3,65 | 1,7 | 0,66<br>–<br>4,63  |
| G/G | 8  | 42,1 | 9  | 52,9 | 0,4 | 0,74 | 0,8 | 0,23<br>–<br>2,75 | 0,6 | 0,17<br>–<br>2,41  |
| G/T | 6  | 31,6 | 6  | 35,3 | 0,1 | 0,92 | 0,9 | 0,24<br>–<br>3,36 | 0,8 | 0,21<br>–<br>3,39  |
| T/T | 5  | 26,3 | 2  | 11,8 | 1,2 | 0,41 | 2,2 | 0,69<br>–<br>7,27 | 2,7 | 0,46<br>–<br>15,47 |

**Figure 2. Comparison of allele and genotype frequencies between the complete form of PESS and the developing form**

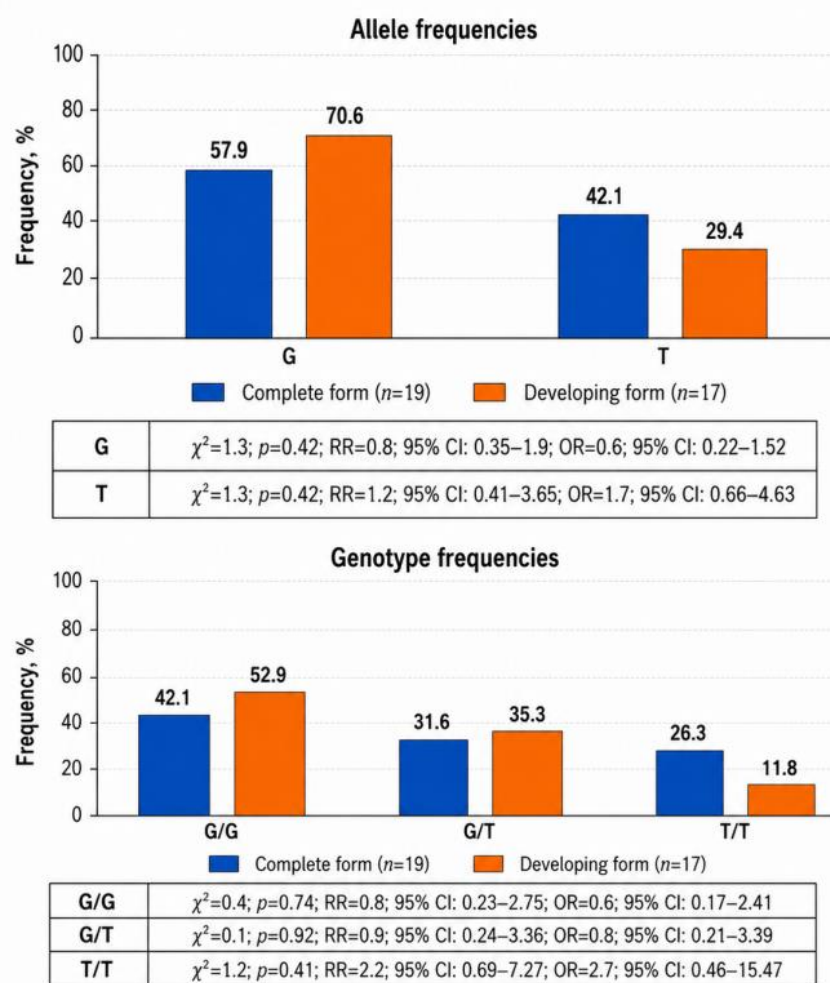


**Figure 5. COL1A1 rs1800012 allele and genotype frequencies in two forms of PESS**

Thus, the analysis showed an increased frequency of the T allele and T/T genotype of the COL1A1 rs1800012 polymorphism in patients with primary ESS. The most pronounced and statistically significant association was observed in the complete form of the disease, where the T/T genotype occurred significantly more often than in the control group.

When comparing the complete and developing forms, no statistically significant differences were obtained. However, the higher frequency of the T allele and T/T genotype in the complete form suggests that this polymorphism may be considered a possible component of a multifactorial risk model for the development and progression of primary empty sella syndrome.

## 5. Discussion

The obtained results allow the COL1A1 rs1800012 polymorphism to be considered a potential genetic factor associated with the development of primary empty sella syndrome. The most important finding of the study is the increased frequency of the T allele, and particularly the T/T genotype, in patients with this syndrome compared with the control group.

The biological significance of the identified association may be explained by the role of COL1A1 in the formation of type I collagen. The sellar diaphragm is a connective tissue structure whose mechanical stability depends on the integrity of the collagen framework. In the presence of genetic variants affecting the regulation of collagen synthesis, the strength of the diaphragm may be reduced. This creates conditions for prolapse of the subarachnoid space into the sella turcica, cerebrospinal fluid accumulation, pituitary compression, and subsequent development of the syndrome.

Of particular importance is the fact that the most pronounced association between the rs1800012 polymorphism and the disease was identified specifically in patients with the complete form of the syndrome. This suggests that the T/T genotype may be associated not only with a predisposition to the development of ESS, but also with greater severity of morphological changes.

In the developing form of the disease, differences in the frequency of the T allele and T/T genotype did not reach statistical significance. However, the observed trend was consistent with the findings in the overall group and in patients with the complete form. This may reflect the early stage of the pathogenetic process, when genetic

predisposition is already present, but morphological changes have not yet reached their maximum severity.

It should be emphasized that the obtained data do not allow the COL1A1 rs1800012 polymorphism to be considered as the sole diagnostic criterion for empty sella syndrome. Most likely, the development of the disease is multifactorial and depends on a combination of anatomical, cerebrospinal fluid dynamic, connective tissue, endocrine, and genetic factors. Within this model, the COL1A1 polymorphism may be regarded as one of the components of pathogenetic predisposition.

A limitation of the study is the relatively small sample size, which may have influenced the achievement of statistical significance in some comparisons. Nevertheless, the consistent direction of the observed changes, high odds ratio values, and the most pronounced association in the complete form of the disease indicate the scientific relevance of the obtained results and support the need for further studies in larger patient cohorts.

From a practical perspective, assessment of the COL1A1 rs1800012 polymorphism may be useful not as a mass screening test, but as an additional clarifying marker in patients with MRI-confirmed empty sella syndrome, particularly in cases of the complete form of the disease, signs of connective tissue insufficiency, or the presence of endocrine dysfunction.

## 6. Conclusions

1. In patients with primary empty sella syndrome, an increased frequency of the T allele of the COL1A1 rs1800012 polymorphism was found compared with the control group.
2. The T/T genotype was more frequently observed in patients with empty sella syndrome, particularly in those with the complete form of the disease.
3. The strongest association was established between the T/T genotype and the complete form of primary empty sella syndrome, as confirmed by high values of relative risk and odds ratio.
4. The G allele and G/G genotype may be considered potentially protective variants, as they were more frequent in the control group.
5. The COL1A1 rs1800012 polymorphism should be regarded not as an isolated diagnostic marker, but as a

component of a multifactorial risk model for the development and progression of empty sella syndrome.

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