

# THE ROLE OF GENETIC POLYMORPHISMS IN BONE TISSUE REGENERATION FOLLOWING INJURY

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## ABSTRACT:

Individual variations in fracture healing have sparked interest in genetic polymorphisms; however, the inconsistency of the reported associations has limited their utility for the early prediction of delayed union or nonunion. The objective of this study was to critically synthesize existing data on the role of genetic polymorphisms in post-traumatic bone regeneration and to define the conditions under which they might be used for prognostic purposes. The study drew upon Russian and international publications from 2022–2026, sourced from PubMed, Europe PMC, and various scientific journals, as well as official data from the Ministry of Health of the Russian Federation. A qualitative comparative analysis was conducted, encompassing clinical studies of polymorphisms, research on gene expression, and experimental models of bone regeneration. Key parameters—such as sample characteristics, the timing of healing assessments, outcome definitions, the inclusion of clinical covariates, and the presence of independent validation—were compared; no quantitative meta-analysis was performed. The author examined polymorphisms in genes related to the inflammatory response, osteogenic differentiation, and bone metabolism. In a study of 108 patients, an association with impaired bone union was identified for the GG genotype of the  $-174C>G$  variant in the *\*IL6\** gene, whereas no significant differences in the frequencies of the *\*IL1B\** genotypes were observed. A prognostic model incorporating variants of *\*TNFRSF11B\**, *\*TGFB1\**, and *\*IL6\** demonstrated a sensitivity of 83% and a specificity of 84%; however, variations in clinical outcomes and a lack of independent validation have limited the generalizability of these findings. This comparison allowed for a distinction to be made between the functional roles of specific genes and the evidence supporting the prognostic value of their variants. To assess the added value of genotyping, it was proposed to compare a clinical model with a model augmented by genetic markers, using an independent prospective cohort.

**KEYWORDS:** genetic polymorphisms, bone regeneration, fracture healing, delayed union, non-union, candidate genes, genetic prediction.

## INTRODUCTION

Genetic polymorphisms are considered one factor underlying individual differences in the timing and outcomes of fracture union. Their prognostic significance remains uncertain: an established association does not necessarily permit early identification of delayed union or nonunion. Improving the prediction of healing is increasingly important as the number of detected and surgically treated fractures rises. According to an August 2024 statement by the Russian Ministry of Health, fracture detection increased by 110% and the number of surgical interventions by 126% during 2020–2023 [45]. These figures describe changes in detection and surgical treatment, not the incidence of delayed union or nonunion. Predicting such complications requires separate evaluation of factors contributing to impaired regeneration, including genetic variants. Accordingly, this review seeks to establish which genetic associations have clinical confirmation and whether their inclusion improves prediction beyond clinical characteristics alone.

Known risk factors for adverse healing provide the starting point. In a meta-analysis of 30 studies, S. S. Jensen, N. M. Jensen, P. H. Gundtoft and colleagues associated nonunion with infection, open fracture, smoking, diabetes mellitus and obesity [4]. A. M. Miromanov, K. A. Gusev, A. N. Staroselnikov and colleagues examined genetic regulation of inflammation and bone metabolism as components of the pathogenesis of impaired union [5]. M. Sadat-Ali and colleagues summarized inherited variants associated with nonunion [6]. Differences in study samples, outcome definitions and adjustment for clinical factors hinder comparisons of their prognostic significance. This study aimed to critically evaluate the association between genetic polymorphisms and post-traumatic bone regeneration, the reproducibility of reported associations and prospects for individual risk prediction.

**Materials and Methods.** This analytical review covers publications from 2022 to 2026. Sources included World Health Organization materials, Russian specialist journals, PubMed and Europe PMC records, and abstracts and full texts available from publishers. Searches combined the Russian equivalents of 'genetic polymorphism', 'bone regeneration', 'delayed union' and 'fracture nonunion' with the English terms 'genetic polymorphism', 'fracture healing', 'delayed union' and 'nonunion'. Studies reporting fracture-healing outcomes were prioritized; investigations of cellular mechanisms were included to

interpret potential functional relationships. Clinical polymorphism studies were analyzed separately from gene-expression studies and experiments altering gene activity. When reviews were used, the dates of the original observations and independent replication of associations were considered. Studies of fracture incidence or bone mineral density were not equated with investigations of post-traumatic repair. Evidence was compared by study design, injury characteristics, outcome definition, clinical covariates, functional verification and independent validation. No quantitative meta-analysis was conducted.

### **Biological Stages of Post-Traumatic Bone Regeneration**

Fracture healing involves overlapping phases of inflammation, cartilage and bone callus formation, mineralization and remodeling. A. Kotsifaki, G. Kalouda, S. Maroulaki and colleagues link nonunion to disturbances in osteogenic activity, growth-factor action and the inflammatory microenvironment [7]. According to F. Staubli, R. M. T. ten Ham, J. E. Bergsma and colleagues, repair requires coordination of immune, vascular, neural and skeletal signals [8]. Initiation and timely resolution of inflammation serve distinct purposes. K. H. Molitoris, M. Huang and G. S. Baht discuss the temporal organization of the cellular response [9]. A genetic variant may alter the amount or properties of a regulatory protein or tag another functionally important region. The mechanism of an association therefore requires validation with respect to the phase of repair: one regulator may exert different effects on callus formation and remodeling.

Experimental investigations clarify the cellular mechanisms of these changes. A. Julien, S. Perrin, E. Martínez-Sarrà and colleagues identified a shared activation program in periosteal and skeletal-muscle progenitor cells; inactivation of *Bmpr1a* in the studied population impaired healing [10]. J. Xu, Y. Wang, Z. Li and colleagues demonstrated the contribution of periosteal cells exhibiting platelet-derived growth factor receptor alpha reporter activity to regenerate formation [11]. Suppression of the mechanosensitive channel *Piezol* impaired repair, whereas its activation enhanced osteochondrogenic processes in experiments by Y. Liu, H. Tian, Y. Hu and colleagues [12]. W. Wu and colleagues reviewed the influence of the mechanical environment on cellular responses [13]. These genes warrant further study, but effects of experimental gene inactivation cannot be directly extrapolated to common human polymorphisms.

### **Genetic Factors in Osteogenic Differentiation and Bone Matrix Formation**

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### **Polymorphisms of Inflammatory Response and Angiogenesis Genes**

Russian clinical data permit comparison of IL6 and IL1B findings. A. M. Miromanov, K. A. Gusev, A. N. Staroselnikov, O. B. Mironova and N. A. Miromanova examined 108 patients with long-bone fractures of the lower extremities: 62 healed without complications, 46 developed delayed union, and the control group comprised 92 individuals [20]. The GG genotype of the IL6 -174C>G variant was associated with impaired union. No significant differences were found in the frequencies of the IL1B genotypes examined; thus, associations for IL6 cannot be extended to other inflammatory genes without separate testing. A. N. Staroselnikov and colleagues describe the involvement of these interleukins in bone resorption and repair [21], while C. A. Capobianco, K. D. Hankenson and A. J. Knights describe changes in immune-stromal interactions during healing [22]. Cytokines in study [20] were measured on day 60 after injury. Such a measure reflects a particular phase of repair; its prognostic significance depends on whether it precedes the outcome being predicted.

The inflammatory response is linked to blood supply in the developing callus. J. Burgan, M. Rahmati, M. Lee and A. M. Saiz describe innate immunity as a sequence of responses from injury to repair [23]. H. Wang and colleagues reviewed the functions of T-cell subsets during bone formation and remodeling [24]; C. Song and colleagues described disturbances of the immune microenvironment in nonunion [25]. R. E. Kostiv, N. Yu. Matveeva and S. G. Kalinichenko identified heterogeneous distributions of growth, inflammatory and apoptotic markers in hypertrophic nonunion tissues from five patients [26]. Genetic evidence includes *CYR61* and *NOS2* variants reviewed by M. Sadat-Ali and colleagues [6]. The coupling of angiogenesis and osteogenesis described by F. van Brakel, Y. Zhao and B. C. J. van der Eerden [28] suggests that blood supply may mediate these relationships. Its role can be tested by jointly assessing genotype, vascular supply and healing outcome.

## Polymorphisms of Mineral Metabolism and Bone Remodeling Genes

Genetic differences also affect resorption and mineralization of the regenerate. A. M. Miromanov and colleagues compared TNFRSF11B 1181G>C, IL6 -174C>G, TGFB1 Arg25Pro and EGFR 2073A>T variants with concentrations of osteoprotegerin, interleukin-6, transforming growth factor  $\beta$ 1 and epidermal growth factor [29]. Carriers of the TNFRSF11B CC genotype had higher osteoprotegerin levels. The IL6 GG, TGFB1 Pro/Pro and EGFR TT genotypes were associated with lower concentrations of interleukin-6, transforming growth factor  $\beta$ 1 and epidermal growth factor, respectively [29]. An association between genotype and a post-injury protein measure does not itself establish value for early prediction. EGFR requires separate interpretation: it encodes the epidermal growth factor receptor, so measuring the growth factor itself does not measure the protein encoded by this gene.

The BsmI variant of the vitamin D receptor gene (VDR) has also been studied in models predicting fracture union [37, 38]. Vitamin D supplementation studies address a different question: whether treatment changes healing outcomes. T. Gatt, A. Grech and H. Arshad summarized 14 studies involving 2,734 patients and found no consistent evidence that vitamin D alone improves union [30]. Prespecified comparisons in a randomized trial by G. P. Slobogean, S. Bzovsky, N. N. O'Hara and colleagues involving 102 patients likewise revealed no clinically meaningful differences in the main healing outcomes [31]. M. Chandran and colleagues described discrepancies between experimental and clinical findings on the effects of osteoporosis on repair [32]. T. Zhang and colleagues demonstrated age-related remodeling changes in mice [33], whereas F. Perut and colleagues considered the prognostic value of circulating bone-turnover markers insufficiently established [34]. Vitamin D treatment results do not validate the predictive value of VDR variants or justify genotype-guided treatment.

Clinical studies associate genotype with fracture outcomes, whereas experimental and tissue studies characterize regenerative mechanisms. Table 1 combines these findings and identifies their interpretive limits.

Table 1 – Clinical Genetic and Functional Studies of Post-Traumatic Bone Regeneration

| Gene or gene group                        | Feature examined                                 | Type of evidence                 | Limit of interpretation                                                                                     |
|-------------------------------------------|--------------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------|
| IL6, -174C>G variant                      | Delayed union; interleukin-6 concentration       | Russian clinical study [20]      | Association identified in a regional sample                                                                 |
| IL1B, 3953C>T variant (authors' notation) | Interleukin-1 $\beta$ concentration and union    | Russian clinical study [20]      | Protein-level changes were not accompanied by significant between-group differences in genotype frequencies |
| BMPR1A, BMPR2                             | Fracture healing                                 | Clinical study [16]              | No significant association between the examined variants and healing was established                        |
| TNFRSF11B, TGFB1, IL6                     | Protein measures and prediction of delayed union | Russian studies [29, 38]         | Sample independence and external validation must be assessed                                                |
| WNT1, LGR6, PIEZO1                        | Osteogenesis and regenerate formation            | Experimental models [12, 14, 15] | Functional involvement of a gene does not establish a role for a human polymorphism                         |
| FOS and other expression regulators       | Molecular profile of nonunion                    | Human tissue studies [18, 19]    | Transcriptional changes do not establish that the disorder is inherited                                     |

Comparison of IL6 and IL1B shows that cytokine involvement in repair does not imply identical genetic findings. Signaling-pathway data explain candidate selection, but the clinical relevance of a variant depends on its association with a specific outcome. Further evaluation therefore requires distinct outcome definitions and verification that observations are independent.

## Reproducibility of Genetic Associations and Reasons for Divergent Results

Comparing associations begins with defining the outcome. A. M. Miromanov and colleagues assessed delayed union two months after injury [20], whereas A. V. Bondarenko and colleagues assessed absence of union after eight months [3]. These time points represent different conditions. The universal classification proposed by L. N. Solomin, A. A. Semenistyy, A. V. Komarov and colleagues accounts for the location and morphology of long-bone nonunion [35]. C. Siverino, W.-J. Metsemakers, R. Sutter and colleagues also discuss the need for clearer diagnosis and definitions [36]. Combining early delayed healing, aseptic nonunion and infectious complications can alter estimated genetic associations even when the same variants are studied.

Reproducibility also depends on sample independence. A single research group may successively investigate genotypes, protein measures and prediction models in wholly or partly overlapping samples. Such publications add descriptive

information but do not constitute independent replication. The associations of nonunion with infection, smoking, diabetes and injury characteristics identified by S. S. Jensen and colleagues require adjustment for these factors in genotype analyses [4]. Persistence of an association after clinical adjustment and replication in another sample increases its credibility. Suitability for individual prediction must be evaluated separately.

Table 2 lists seven criteria for evaluating genetic associations, from outcome definition to independent evaluation of a prediction model.

Table 2 – Criteria for assessing the reliability of genetic associations with impaired fracture union

| Criterion                    | What must be checked                                                  | Consequence of inadequate control                                            |
|------------------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------|
| Outcome definition           | Distinction between delayed union, nonunion and infection             | Combining biologically different conditions                                  |
| Comparison group             | Patients with comparable fractures and favorable healing              | Confounding predisposition to fracture with predisposition to impaired union |
| Clinical factors             | Injury severity, fixation, blood supply, smoking, diabetes            | Attributing the effects of associated conditions to genotype                 |
| Genetic data                 | Genotyping quality, participant ancestry, variant frequencies         | Spurious association due to technical or population differences              |
| Statistical analysis         | Multiple comparisons, effect sizes, confidence intervals              | Overstating the strength of a chance finding                                 |
| Independence of publications | Potential overlap between samples                                     | Counting the same observations more than once                                |
| Prediction assessment        | External validation, calibration and comparison with a clinical model | Overestimating model applicability                                           |

Genotyping quality and adjustment for multiple comparisons are necessary to assess the credibility of associations. The usefulness of a marker for prediction additionally depends on model calibration and testing in independent data. These requirements define the transition from comparisons of genotype groups to individual risk assessment.

#### Prospects for Genetic Prediction and Directions for Future Research

Russian studies have incorporated genetic indicators into models of impaired union. A. M. Miromanov, K. A. Gusev, A. N. Staroselnikov and V. A. Mudrov reported 91.7% classification accuracy using a neural network [37]. A model published in 2026 by A. M. Miromanov, K. A. Gusev and A. N. Staroselnikov that included TNFRSF11B, TGFB1 and IL6 variants achieved sensitivity of 0.83, specificity of 0.84 and an area under the receiver operating characteristic curve of 0.88 (95% confidence interval 0.81–0.95) [38]. These figures cannot be used to rank the models because classification accuracy and area under the curve measure different properties. Clinical implementation requires determining whether results hold in another sample and what genotyping adds to patient and fracture characteristics.

Joint evaluation of genotype and changing molecular measures may expand prediction. F. L. Breulmann, L. P. Hatt, B. Schmitz and colleagues identified microRNAs potentially associated with nonunion but noted study heterogeneity [39]. S. S. Iyer discussed DNA methylation, histone modifications and noncoding RNAs as regulators of healing [40]. In an experiment by D. Xiao and colleagues, systemic inflammation altered epigenetic regulation in progenitor cells [27]. C. Del Toro Runzer, E. R. Balmayor and M. van Griensven reviewed cell-, protein- and gene-based methods of bone repair [41]; G. Xu and colleagues reviewed monitoring and modification of the fracture microenvironment [42]. Challenges in clinical implementation of biological approaches described by J. P. Johnson and colleagues [43] limit the translation of experimental results into treatment decisions. The value of genetic prediction must be confirmed both by model validation and by assessing decisions made using the model.

#### LIMITATIONS OF THE REVIEW

Clinical associations, expression data and experimental manipulation of signaling pathways were compared qualitatively; no pooled effect size was calculated. The review by M. Sadat-Ali and colleagues, published in 2023, searched literature from 2000 onward [6]. Its publication date does not mean that every included association had recently been replicated: the age of primary observations was considered separately.

Only abstracts were available for some studies, limiting assessment of statistical adjustments, genotype subgroup composition and potential sample overlap. Incomplete reporting was not interpreted as evidence that a procedure had not been performed. Conclusions concerning molecular profiling therefore took into account the need for clinical verification emphasized by M. Panteli and colleagues [44].

Synthesis of Findings and Recommendations. Among the Russian studies reviewed, IL6, TGFB1 and TNFRSF11B have been investigated most extensively, but the evidence is insufficient to establish a universal predictive panel. Its incremental contribution over clinical risk assessment remains undetermined. Future work should prioritize testing this contribution using identical sets of clinical variables in the models compared.

Two models are proposed: a clinical model and a model augmented with genetic indicators, using identical inclusion criteria and outcome assessment. Their performance should be compared in an independent prospective cohort not involved in model development. Follow-up intervals and union criteria must be prespecified to distinguish delayed union from nonunion. The practical benefit of improved risk estimates should be assessed through changes in monitoring frequency, timing of additional investigations and appropriateness of treatment decisions.

## CONCLUSION

IL6, TGFB1 and TNFRSF11B variants are of interest for predicting impaired fracture union, but the evidence reviewed does not establish a universal risk panel. Clinical associations require independent replication, while functional studies explain potential mechanisms without demonstrating the predictive suitability of every variant. Genetic-marker assessment should compare their performance with clinical factors and use consistent healing criteria. The reviewed studies provide no basis for choosing treatment solely according to genotype.

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