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SIGNIFICANCE OF SOD2 GENE C60T (C/C, C/T, T/T)

POLYMORPHISM IN CHRONIC
MYELOPROLIFERATIVE NEOPLASMS

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✎ ABSTRACT: *Chronic myeloproliferative neoplasms (MPNs) are a group of clonal hematologic malignancies characterized by the proliferation of hematopoietic stem cells in the bone marrow. The pathogenesis of these disorders is primarily driven by mutations in genes such as **JAK2**, **CALR**, and **MPL**. However, recent evidence suggests that **oxidative stress and mitochondrial dysfunction** also play an important role in disease biology.*

*The **superoxide dismutase 2 (SOD2)** gene encodes a key mitochondrial antioxidant enzyme responsible for detoxifying reactive oxygen species (ROS). The **SOD2 C60T (rs4880, Ala16Val)** polymorphism may alter mitochondrial targeting efficiency and enzymatic activity, thereby influencing oxidative stress levels.*

*This article reviews the potential role of **C/C, C/T, and T/T genotypes of SOD2 C60T polymorphism** in disease susceptibility, clinical severity, thrombotic complications, and progression of MPN.*

🔑 KEYWORDS: *MPN, SOD2, C60T, Ala16Val, oxidative stress, ROS, JAK2 V617F, thrombosis, mitochondrial dysfunction.*

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INTRODUCTION

Chronic myeloproliferative neoplasms (MPNs) are a group of clonal hematopoietic stem cell disorders characterized by abnormal proliferation and impaired differentiation within the bone marrow, leading to pathological hematopoiesis.

MPNs include three major clinical entities:

- Polycythemia vera (PV)
- Essential thrombocythemia (ET)
- Primary myelofibrosis (PMF)

The common pathological feature of these diseases is uncontrolled proliferation of hematopoietic stem cells, resulting in overproduction of erythroid, megakaryocytic, or fibrotic lineages. Clinically, these disorders manifest with thrombosis, bleeding complications, splenomegaly, and bone marrow fibrosis.

The central molecular hallmark of MPNs is the presence of **driver mutations**, including:

- **JAK2 V617F mutation**, leading to constitutive activation of the JAK-STAT pathway
- **CALR mutations**, promoting megakaryocytic proliferation
- **MPL mutations**, activating thrombopoietin receptor signaling

Recent molecular and translational studies suggest that MPN pathogenesis is not solely driven by genetic mutations. Instead, the **bone marrow microenvironment, immune dysregulation, and oxidative stress** play crucial roles.

Increased levels of inflammatory cytokines (IL-6, TNF- α , TGF- β) promote clonal selection and fibrosis. In addition, elevated reactive oxygen species (ROS) contribute to DNA damage and the accumulation of somatic mutations. These findings support the concept that MPNs represent **complex**

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clonal disorders influenced by both genetic and microenvironmental factors.

Thus, current understanding of MPN pathogenesis involves three major components:

1. Genetic driver mutations
2. Bone marrow microenvironment and inflammation
3. Oxidative stress and epigenetic alterations

Oxidative Stress and MPN

Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense systems, including glutathione, superoxide dismutase, and catalase.

In MPNs, oxidative stress plays a central role in disease pathogenesis. Studies have demonstrated:

- Increased ROS levels
- Elevated oxidative DNA damage (e.g., 8-OHdG)
- Enhanced proliferation and survival signaling in hematopoietic stem cells

ROS contributes to disease progression through multiple mechanisms, including DNA strand breaks, activation of signaling pathways (JAK-STAT, MAPK, NF- κ B), and promotion of genomic instability.

Furthermore, ROS interacts with inflammatory signaling, creating a self-perpetuating cycle of **inflammation and oxidative stress**, which sustains clonal hematopoiesis.

Role of SOD2 Gene

SOD2 (superoxide dismutase 2) is a mitochondrial antioxidant enzyme that converts superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2), which is further detoxified by catalase and glutathione peroxidase into water and oxygen.

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SOD2 plays a critical role in maintaining mitochondrial redox balance, particularly in metabolically active tissues.

SOD2 in MPN Pathogenesis

In MPNs, dysregulation of SOD2 may contribute to:

- Increased mitochondrial ROS production
- Oxidative DNA damage
- Genomic instability in hematopoietic stem cells

Reduced SOD2 activity leads to mitochondrial dysfunction, impaired ATP production, and activation of cellular stress responses.

Signal Transduction Effects

Impaired SOD2 function may enhance:

- JAK-STAT pathway activation
- NF-κB-mediated inflammatory signaling
- MAPK-driven proliferation

SOD2 C60T Polymorphism

The SOD2 C60T polymorphism (rs4880) is located in the mitochondrial targeting sequence (MTS) of the gene and affects mitochondrial import efficiency.

This polymorphism results in an amino acid substitution:

- **C allele → Alanine (Ala)**
- **T allele → Valine (Val)**

Genotype Functional Differences

☐ **C/C genotype (Ala/Ala)**

- Efficient mitochondrial import
- Optimal enzyme activity
- Lower ROS levels
- Better genomic stability

☐ **C/T genotype (Ala/Val)**

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- Intermediate mitochondrial import
- Moderate ROS levels
- Partial antioxidant impairment
- **T/T genotype (Val/Val)**
 - Reduced mitochondrial import efficiency
 - Decreased SOD2 activity
 - Increased ROS accumulation
 - Higher oxidative stress and mitochondrial dysfunction

MPN Risk and SOD2 C60T

Evidence suggests that the SOD2 C60T polymorphism may act as a modifier of oxidative stress burden in MPNs.

The T allele is associated with:

- Reduced mitochondrial antioxidant defense
- Increased ROS levels
- Higher mutation susceptibility
- Favorable conditions for clonal hematopoietic expansion

However, this association remains hypothetical and requires further validation.

Thrombotic Complications

Thrombosis is one of the major clinical complications in MPNs.

Oxidative stress contributes through:

- Endothelial dysfunction
- Platelet activation
- Pro-inflammatory signaling
- Vascular damage

The T/T genotype may theoretically increase thrombotic risk due to higher oxidative stress levels, although this remains unconfirmed clinically.

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Disease Progression

MPN progression from ET or PV to PMF or acute leukemia is a complex biological process.

The SOD2 C60T T/T genotype may contribute to:

- Increased oxidative stress in bone marrow microenvironment
- Fibroblast activation and collagen deposition
- Stem cell stress and exhaustion
- Enhanced inflammatory signaling

This may increase the risk of:

- Progression to PMF
- Accelerated fibrosis
- Aggressive disease phenotype

However, these associations are not fully established.

□ DISCUSSION

The pathogenesis of MPNs is multifactorial and cannot be explained solely by driver mutations.

Key mechanisms include:

- Constitutive JAK-STAT activation
- Chronic inflammation
- Oxidative stress imbalance
- Bone marrow microenvironment remodeling

Although JAK2 V617F is the central driver mutation, germline polymorphisms such as SOD2 C60T may act as **disease modifiers**.

Potential role of SOD2 C60T

- Not a disease-initiating mutation
- Modifies redox balance in hematopoietic microenvironment
- Increases mitochondrial ROS levels
- Enhances oxidative DNA damage

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- Provides selective advantage to malignant clones

Thus, SOD2 C60T likely functions as a **modulator rather than a driver mutation**.

🔗 Clinical Relevance

Currently:

- SOD2 C60T is not used as a diagnostic marker
- It is not a validated prognostic biomarker
- It is not included in routine clinical testing

However, it remains an active area of research in molecular hematology.

✦ CONCLUSION

The SOD2 C60T polymorphism (C/C, C/T, T/T genotypes) is not a primary cause of MPN and is not classified as a driver mutation.

However, it may act as a **modifier of disease biology** by influencing oxidative stress and mitochondrial function.

The T/T genotype is potentially associated with:

- Increased ROS levels
- Reduced antioxidant capacity
- Possibly more aggressive clinical behavior

Therefore, SOD2 C60T may be considered a **risk-modifying genetic factor in MPN**, although further large-scale studies are required for clinical validation.

📖 REFERENCES

1. Vainchenker, W., & Kralovics, R. *Myeloproliferative Neoplasms: Molecular Pathogenesis and Clinical Implications*. Nature Reviews Cancer.
2. Tefferi, A. *Primary Myelofibrosis and Molecular Pathogenesis*. New England Journal of Medicine / Blood Reviews.

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3. Harrison, C. N. *Pathophysiology of Myeloproliferative Neoplasms*. Hematology/Oncology Clinics.
4. NCBI. SOD2 gene polymorphism rs4880 database.
<https://www.ncbi.nlm.nih.gov>
5. MDPI Journals. Oxidative stress in hematologic malignancies.
6. PubMed Central (PMC). ROS and JAK-STAT signaling in MPN.
7. Landrigan, P. J., et al. Oxidative stress and clonal hematopoiesis.
8. Vannucchi, A. M., & Harrison, C. N. Emerging molecular pathways in MPN. Blood.