Sepsis genomics: Stepping forward toward sepsis prevention?

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ABSTRACT

The era of personalized medicine has already begun and now it is time to initiate personalized prevention strategies against diseases. Infectious diseases have a higher mortality than any other illness, especially in developing countries. Among newborns and young children the situation is even worse. The microorganisms are becoming resistant to almost all known antibiotics. Hence, it is imperative to improve the preventive strategies against infections. ‘Pathogens are everywhere, but not every individual is getting diseased,’ — this basic logical thinking needs to look into the genetic predisposition/host susceptibility to sepsis. Interestingly, genetic studies have shown that the type of infecting organism, outcome of infections, and mortality can be predetermined by analyzing an individual's genome. Exploration of inter-individual genetic variations and their association with sepsis will help in the development of new prognostic markers to provide novel personalized therapeutics and predict the outcome. In this review article, we discuss the genetic variations and their association with sepsis, studied by various researchers in different regions.

Key words: Diagnostic, genetic association, genomics, prognostic marker, sepsis

INTRODUCTION

Genetic risk factors are the recent prognostic/diagnostic markers that save numerous lives from various diseases like cancer. Sepsis susceptibility and outcome are predictable by decoding the genomics of an individual. Although several confounding factors are involved in sepsis progression and mortality, the host immune response to infections is based on the genetic nature of each individual. Genetic association studies have shown that sepsis susceptibility, mortality, and even the type of infecting pathogen are associated with genetic variations. This article provides insights into the genomics associated with sepsis and its applicability in clinical practice.

Candidate gene polymorphisms

For more than a decade, the candidate genes involved in the pathophysiology of sepsis have been analyzed for the association of their single-nucleotide polymorphisms (SNPs) with sepsis and its outcome, like multiple organ dysfunction (MOD), shock, and mortality.

Tumor necrosis factor

Among the most studied cytokine polymorphisms, the tumor necrosis factor alpha (TNF-α) polymorphism has drawn more attention from genomic researchers, especially the 308 G/A polymorphism. Although the polymorphism has been studied very descriptively, yet its association with sepsis remains uncertain. Several studies have claimed that TNF-α-308A is associated with sepsis susceptibility and mortality. However, some studies have shown no association with either susceptibility or outcome or both.¹⁻³ Other than 308G/A, SNPs like 238G/A, 376G/A, +489G/A, and -863C/A
were also studied. Table 1 highlights some TNF-α polymorphisms associated with sepsis.

Phumeetham et al., have found no association of the TNF-α (−308) polymorphism with sepsis/septic shock in Thai pediatric patients. [17] Contrastingly, a significant association was found between these in Brazilian pediatric patients by Azevedo et al. [7]

The NcO1 TNFB1/B2 polymorphism in the tumor necrosis factor beta (TNF-β) gene was analyzed in post-traumatic patients, and it was found that the homozygous TNFB2 is associated with severe sepsis. [18] Further studies are required to identify the significance of TNF polymorphisms in clinical situations.

Interleukins

Interleukins include both pro- and anti-inflammatory cytokines. IL-1β may lead to septic shock and organ failure and serves as a primary mediator of systemic inflammatory response syndrome (SIRS). [19] IL-6 acts as a potential diagnostic marker for infections. IL-10, an anti-inflammatory cytokine, also plays a significant role in the inflammatory pathway of sepsis. Variations in the structure of these genes may lead to altered gene expression, which may result in the modification of the host immune system. Some of the interleukin polymorphisms are tabulated below [Table 2].

An in vitro study by Kang et al., has shown that −1082G > A of IL-10 interacts with the nuclear protein, PARP-1 (Poly ADP-ribose polymerase 1), which is a transcription repressor and regulates the production of IL-10. [36]

**Toll-like receptors**

Toll-like receptors act as sensors against pathogen invasion, triggering the host’s immune response. They also play the role of receptors for endogenous ligands that may lead to tissue damage. [37] Changes in toll-like receptor (TLR) expression may cause favorable/adverse

### Table 1: TNF-α polymorphisms associated with sepsis and its outcome

| Mutation | Genotype | Number of cases/controls | Association |
|----------|----------|--------------------------|-------------|
| −308 G/A | GA+AA 278/115 | Risk of sepsis and septic shock[4] |
|          | GA+AA 432/624 | Susceptibility to severe sepsis, but not mortality[8] |
|          | AA 1057/- | Increased mortality and ventilator duration[9] |
|          | GA 490/610 | Protection against ARDS* and sepsis mortality[7] |
|          | GA 123/- | Predictor of ICU mortality[10] |
|          | AA 106/- | High survival rate[6] |
|          | GA+AA -/- | Associated with sepsis, but not mortality[11] |
|          | GA+AA 306/- | Associated with sepsis[11] |
|          | GA+AA 69/- | Increased mortality risk[12] |
|          | GA+AA 173/- | Increased sepsis mortality, but did not affect sepsis development[13] |
|          | GA+AA 159/- | Increased risk for severe sepsis[14] |
|          | GA 197/214 | Risk of sepsis and poor outcome[15] |
| −238 G/A | GA+AA 278/115 | Risk of sepsis and septic shock[4] |
|          | GA+AA 233/- | Increased mortality[16] |
|          | −376 G/A GA+AA 278/115 | Risk of sepsis and septic shock[4] |
|          | +489 G/A GA+AA 278/115 | Risk of sepsis and septic shock[4] |
| −863 C/A | CA 490/610 | Risk for ARDS in sepsis patients[11] |

*ARDS = Acute respiratory distress syndrome, ICU = Intensive care unit

### Table 2: Interleukin polymorphisms associated with sepsis

| Gene | Mutation | Number of cases/controls | Association |
|------|----------|--------------------------|-------------|
| IL-1β | −511 C/T | 21/60 | C allele associated with sepsis susceptibility[20] |
| IL-4 | −589 T/C | 308/- | Affect Th1/Th2 balance and sepsis susceptibility[21] |
| IL-6 | −572 C/G | 348/105 | Risk for sepsis[22] |
|      |          | 421/644 | Sepsis susceptibility and severity predictor[23] |
|      | −174G/C | 112/- | Associated with shock in sepsis[24] |
|      |          | 326/- | GG genotype is significantly associated with improved survival[25] |
|      |          | 293/- | Risk for sepsis in ventilated VLBW infants[26] |
|      |          | 421/644 | Sepsis susceptibility and severity predictor in children[27] |
| IL-8 | −251 A/T | 467/- | Increased risk of PaO2/FiO2 and IL-8 mRNA expression[28][23] |
| IL-10 | −1082 G/A | 293/- | Risk for sepsis in ventilated VLBW infants[29] |
|      |          | 333/202 | Risk for sepsis[28] |
|      |          | 106/- | Associated with type of organism[30] |
|      |          | 71/109 | Association in the sepsis outcome[29] |
|      |          | 33/53 | GG genotype influences the sepsis outcome[29] |
|      |          | 116/140 | An A allele has high risk for sepsis, while G allele has increased mortality[31] |
|      | −819 C/T | 116/140 | Susceptibility to severe sepsis[21] |
|      | −592 C/A | 97/207 | Potential predictor for sepsis[32] |
|      |          | 67/132 | An A allele is associated with increased mortality[33] |
| IL-17A rs1974226 | 517/679 | GG genotype is associated with gram-positive infection and G allele has increased mortality[34] |
| IL-18 | −607 C/A | 90/123 | CA genotype has a high risk for sepsis[35] |

*VLBW = Very low birth weight
effects in the host immune response. Polymorphism in TLRs has been studied in various populations, yet its functional significance in sepsis remains unexplored. TLR4 polymorphisms and their association with sepsis have given more conflicting results, in particular the SNPs, Asp299Gly (+896 A/G) and Thr399Ile (+1196 C/T). In Table 3, we have listed some of the polymorphisms analyzed in TLRs associated with sepsis.

In contrast to the above discussed studies [Table 3], Shan et al., did not find any association of TLR4 (Asp299Gly and Thr399Ile) polymorphisms with sepsis, but suggested a large study on the TLR2 Arg753Gln polymorphism among Chinese Han children. A meta-analysis that included 17 studies in the Caucasian population, with a total of 2,212 cases and 3,880 controls showed that TLR4 polymorphisms, Asp299Gly and Thr399Ile, were not associated with sepsis susceptibility. In vitro studies by Figueroa et al., showed that D299G TLR4 polymorphism interfered with TLR4 dimerization and assembly of intracellular docking platforms for recruitment of adapters like MyD88 and TRIF.

Apart from TLRs, other receptors like CD14 also play a major role in innate immunity during sepsis. CD14 along with TLR4 and MD2 forms the lipopolysaccharide (LPS) receptor complex. Polymeric variants in CD14 and other cell surface receptors are given in Table 4.

Fcgamma RIIA polymorphisms are widely studied in association with the antibody response in pneumonia, malaria, autoimmune diseases like systemic lupus erythematosus (SLE), and inflammatory diseases like rheumatoid arthritis. As the cell surface receptors play a vital role in the triggering of infection and molecular mechanism of the inflammatory pathway, polymorphism in its genetic structure may lead to significant alterations in disease conditions.

**Recently studied single-nucleotide polymorphisms and their association with sepsis**

Genetic studies related to sepsis have been found in abundance during recent years. The research is now extended to the genes, other than the innate immunity genes. Apart from the generally studied genes like TNF-α, and interleukins, tremendous knowledge has been created about associated genes by recent studies. This shows the rapid and vigorous growth of genomics and its applicability in clinical settings. In Table 5, we have listed the polymorphisms analyzed in the last three years, in the different protein molecules involved in sepsis pathophysiology.

**Haplotype tagging single-nucleotide polymorphisms**

Tag SNPs are single nucleotide polymorphisms that are non-randomly associated with alleles at other loci in the chromosome. Analysis of Tag SNP reduces the burden of studying each individual SNP separately, and is highly beneficial in genetic association studies that use whole-genome sequencing. Tag SNPs are usually identified using the HapMap database by Linkage Disequilibrium analysis or PHASE (software used to reconstruct haplotype and estimation of the recombination rate).

Tag SNPs or hSNPs (haplotype tagging SNPs) in the MD-2 gene was studied by Zeng et al., in two different populations in China (Chongqing in southwestern China and Zhejiang in eastern China), using the pyrosequencing method. They found three SNPs, rs7843858, rs11465996, and rs2114169, to be hSNPs, but...
Table 5: Association of various SNPs with sepsis and its outcome

| Gene                | Mutation | Association                                                                 |
|---------------------|----------|-----------------------------------------------------------------------------|
| VEGF                | +936 C/T | CC genotype has increased risk of AKI in severe sepsis[^7]                   |
| IRAK-M              | +22148 G/A | High risk of sepsis with GG genotype[^56]                                   |
| IRAK1               | rs1059702 | Septic susceptibility and severity[^59]                                     |
| HSP90β              | −144 C/A | AA genotype is associated with inflammatory response and severity of organ failure[^62] |
| ACE                 | ins/del | D allele is associated with ARDS in severe sepsis[^51]                      |
| NFXB1               | −94 ins/del | Increased 30-day mortality and innate immune system response[^62]          |
| NOS2                | Exon 16 G/A | An A allele is associated with increased susceptibility to septic shock[^63] |
| SOD2                | 47 C/T | A C allele is associated with high frequency of septic shock[^64]          |
| HMOX1               | −413 A/T | AA genotype shows higher 28-day mortality[^55]                             |
| PBEF                | −1543 C/T | A T allele acts as a protective factor for ALI[^1] and sepsis[^65]         |
| TRAF6               | Intron C/G | A C allele frequency is higher in the sepsis-alone group than in the sepsis-induced ALI group[^62] |
| TREM-1              | Ser25Thr | Associated with sepsis prognosis[^66]                                     |
| BCL2                | rs8094315, rs12457893 | Both SNPs are associated with decreased risk for AKI[^69]                  |
| DDAH2               | −449 G/C | A G allele is associated with low plasma ADMA[^2] and high risk of cold septic shock[^70] |
| NOD2/ CARD15        | R702W, G908R, Leu1007fsinsC | All three polymorphisms are associated with sepsis susceptibility in children. Leu1007fsinsC carriers showed high mortality[^71] |
| LBP                 | rs2232618 | Sepsis susceptibility and MODS[^72]                                         |
| HMGB1               | rs2249825 | Risk for sepsis and MODS[^73]                                               |
| MBL                 | B allele | Risk for neonatal sepsis and pneumonia[^74]                                |
| NLRP3               | rs2027432, rs12048215 | Increased sepsis susceptibility and MODS[^75] |
| AQP5                | −1364 A/C | C allele is associated with an increased 30-day survival[^76]              |
| AGTR1               | rs11121816 | GG genotype is associated with an increased 28-day mortality in septic shock[^77] |
| LTA                 | +252 A/G | AA genotype is associated with sepsis morbidity and MODS[^78]              |
| eNOS                | 894 G/T | GT genotype is associated with shock and impaired organ function[^79]      |
| LNPEP               | rs4869317 | TT genotype is associated with a 28-day mortality[^80]                    |

[^7] AKI = Acute kidney injury, ^[1] ALI = Acute lung injury, ^[2] ADMA = Asymmetrical dimethylarginine

Yang et al. found that the mtDNA haplogroup R can be used to predict the outcome of septic encephalopathy in the Chinese Han population. The R haplogroup delivers high probability of neurological recovery, when compared to the non-R haplogroup.[^57] Previously in the same population, they had found that the R haplogroup was a predictor of sepsis outcome and was associated with long-term survival in sepsis patients.[^85] The MHC haplotype, AH8.1, was found to confer a protective effect toward septic shock in chronic obstructive pulmonary disease (COPD) patients, in the Caucasian population.[^86] Baudouin et al., showed that the mtDNA haplogroup H is a predictor of the outcome and is associated with 180 days of survival in European patients with severe sepsis.[^90]

Haplogroups

Haplogroups are used to define genetic populations, with similar haplotypes having the same SNPs. Y-chromosome (Y-DNA) haplogroups and mitochondrial DNA (mtDNA) haplogroups are the widely known haplogroups. Haplogroups have a common ancestor and are restricted to geographical locations. Identification of a single SNP and its association with a disease in a haplogroup serves as a prognostic marker for the entire population.

Tandem repeats or microsatellites

Tandem repeats are the repetition of two or more nucleotides and are adjacent to each other. When two to six nucleotides are repeated, it is called microsatellites or short tandem repeats. Microsatellite instability, which is caused by a defect in the DNA mismatch repair may act as a significant risk factor for diseases like cancer[^91] and schizophrenia.[^92] In sepsis, microsatellites in genes like HMox1[^65] TNFα and β[^93] eNOS[^64] and IL-10[^95] were studied. Flores et al., showed association of the CXCL2 −665(AC)n microsatellite with sepsis susceptibility in the Spanish population.[^96]

Copy number variations

Copy Number Variations (CNVs) are found throughout the human genome. CNVs may alter gene expression only if they lead to changes in gene dosage or structure. Microdeletions and microduplications are other common types of CNVs. Large CNVs, particularly those involving multiple genes, can lead to severe health outcomes, such as intellectual disability and autism. Studies have shown that CNVs are associated with a wide range of conditions including autism, schizophrenia, and intellectual disability. Furthermore, CNVs are not only associated with diseases, but they also contribute to individual differences in susceptibility to various diseases. Therefore, understanding the role of CNVs in disease susceptibility is crucial for personalized medicine and genetic counseling.
Epigenomics: The next?

Before experiencing the entire sweetness of epigenomics, researchers cracked out a new concept, ‘Epigenomics,’ which may explain the host’s non-genetic risk factors that alter disease conditions, via modifying the underlying gene expression. DNA methylation and Histone modification are the two major processes involved in epigenomics. MicroRNAs (miRNAs) also play a vital role in epigenetic processes.

Immunosuppression that follows severe sepsis is regulated by immune-related genes. The expression of these genes can be modified by histone acetylation/methylation. Repressive histone methylation has been found in the promoter region of IFN-γ and GATA-3 transcription factors in naïve CD4+ T-cells, in sepsis mice models.[100] Histone acetylation is controlled by histone acetylases and histone deacetylases (HDACs). Studies performed by Li et al., revealed that septic shock caused hypoacetylation of nuclear proteins, can be reversed by administering HDAC inhibitors (HDACI). The HDACIs prevented cell death, reduced inflammation, and eventually improved survival of the animal models in septic shock.[101] An in vitro study by Gazzar et al., showed that silencing of TNF-α expression during endotoxin tolerance occurs by the combined action of H3K9 methylation and CpG (TNF-α promoter) methylation. H3 histone is methylated on lysine 9 by histone methyltransferase, G9a. TNF-α promoter CpG methylation is catalyzed by Dnmt3a/b (DNA methyltransferases) and HPI (Heterochromatin protein 1).[102]

The role of miRNAs in the diagnosis of sepsis was very clearly stated in the recent studies. In particular, miR-146a and miR-223 are significant prognostic/diagnostic markers of sepsis.[103,104] Some other significant miRNAs are miR-150,[103,104] miR-499-5p,[106] miR-15a, and miR-16.[107] These potential biomarkers are also capable of distinguishing sepsis from the systemic inflammatory response syndrome.

Future direction for sepsis genomics studies

Lack of potential diagnostic or prognostic markers for sepsis makes it a dreadful disease, which holds the highest mortality. Genetic association studies build up hope for newer diagnostic/prognostic methods in the treatment of sepsis. In this modern era, a large number of small scale researches have been done on the genetic association of sepsis. The sensitivity and specificity to use genetic variations as prognostic markers is yet to be determined. Large-scale studies like Genome Wide Association Studies have already begun and started cracking this hurdle. Multicentric studies are required to understand the significance of genetic variations in different populations. The bridge between bench to bedside has to be built to put genetic associations into clinical practice. For overcoming such obstacles, hopefully, sepsis genomics will help us in directing treatment against infectious pathogens and possibly the eradication of sepsis.

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