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REVIEW

How to manage rheumatoid arthritis according to classic biomarkers and polymorphisms?

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OBJECTIVES: Single nucleotide polymorphisms (SNPs), genetic background, and epigenetics play important roles in rheumatoid arthritis (RA). These factors can be useful in RA diagnosis, prognosis, and treatment response evaluation, particularly with the growing trends in personalized medicine. Therefore, categorizing classic genes and SNPs in RA can present an appropriate guideline for RA management.
DISCUSSION: Prognostic and diagnostic biomarkers play important roles in RA diagnosis and treatment. Categorizing SNPs is not an easy process yet, but selecting classic SNPs can be useful worldwide, according to basic similarities that exist in genomes. In this review, we compiled some of these RA-associated SNPs and biomarkers in a table, according to newly identified factors. The role of epigenetics in RA is undeniable; using epigenetic biomarkers like histone deacetylase (HDACs) can be useful in RA diagnosis and treatment. miRs such as miR-146a, miR-155, and miR-222 are useful in diagnosis and can be used in treatment by interfering with other factors' functions. Interleukins (ILs) seem to be good prognostic and diagnostic markers and can be targeted in RA treatment.
CONCLUSION: Using multiple types of biomarkers, such as genes, SNPs, and epigenetic biomarkers like HDACs can be useful in RA management and treatment. *PTPN22*, *HLA-DR* polymorphisms, miRs, and HDACs are considerable in RA susceptibility; hence, they can be valuable biomarkers in future studies. This article gathered separate information from approximately 100 articles to present useful biomarkers and polymorphisms in one review.

Keywords polymorphism, rheumatoid arthritis, miRs, HLA-DR, epigenetics

Introduction

Rheumatoid arthritis (RA) is a multifactorial disease affecting approximately 1% of people worldwide (Guo et al., 2014). Still, the exact mechanism of RA pathogenesis is unknown (Chimenti et al., 2015). On the other hand, early diagnosis and treatment are effective for controlling disease severity (Zengin et al., 2016). There are several diagnostic and prognostic biomarkers that are useful in RA management including instant Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) (Gavrilă et al., 2016). In addition, inflammatory cytokines such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) can reflect the inflammatory status in the body (Chimenti et al., 2015; Lavric et al., 2016). Biomarkers such as Cartilage Oligomeric Matrix Protein (COMP) are useful for predicting cartilage destruction (Deane and El-Gabalawy, 2014). Genetic biomarkers have important roles in RA development and severity, and affect therapeutic response as well (Ospelt, 2016). Epigenetics seems to also be responsible for RA susceptibility and inflammatory response (2e).

This review presents two tables representing diagnostic, prognostic, and therapeutic response biomarkers, as well as golden SNPs associated with RA severity and therapeutic response. These tables can be useful in RA management because this review gathered considerable information from studies conducted worldwide to offer an impactful insight regarding classic and genetic biomarkers to rheumatologists.

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Overview of rheumatoid arthritis

RA is known as a multifactorial disease; the environment, genetic background, job, gender, smoking, and many other

factors can affect RA susceptibility (Anaya et al., 2016; Arleevskaya et al., 2016; Chung et al., 2016) (Fig. 1).

Early diagnosis and prognosis are important elements in RA management. A current challenge in many diseases is personalizing therapeutic approaches by using genetic biomarkers and SNPs. However, the application of genetic biomarkers and SNPs in RA is limited because RA development depends on the presence of SNPs in the majority of people, not an exact mutation in the genome (Tedesco et al., 2009; Zengin et al., 2016). HLA subtypes may just increase the risk of change in DNA methylation, which can lead to disease development and relate to RA risk (Viatte et al., 2013; Glant et al., 2014). Environmental factors can cause genetic predispositions to RA and SNPs can be early predictors of RA development.

Role of epigenetics in RA

RA onset seems to be a result of complex interactions between genetic susceptibility and epigenetics (Angiolilli et al., 2017). Epigenetics covers DNA methylation, various histone modifications, and non-coding RNAs (Angiolilli et al., 2014). Epigenetics works as a backup of cellular reprogramming; when reprogramming fails, epigenetics can be transmitted to the next generation. Epigenetic mutations, whether they are natural or deleterious, frequently involve transposable elements and are inherited adaptively or even in response to environmental changes (Heard and Martienssen, 2014). Recent studies revealed that errors in epigenetic mechanisms can lead to inflammatory disorders (Glant et al., 2014). Several studies suggest that epigenetic changes can cause permanent gene expression changes and can also be heritable (Glant et al., 2014). Histone acetylation and deacetylation changes by histone acetyl transferase (HAT) and histone deacetylase (HDAC), respectively, are epigenetic changes that can affect inflammatory cytokine production. In other words, the balance between HATs and HDACs can be useful in controlling inflammation by interfering with inflammatory signaling pathways in a number of diseases like (Toussirot et al., 2013). HDAC4 is a distinguishing member of the HDACs family because HDAC4 may play a protective role by preserving cartilage integrity (Angiolilli et al., 2017). HDAC7 may be able to suppress Runx2 activity and osteoblast differentiation (Angiolilli et al., 2017). HDAC5 is associated with disease severity in RA; it can be suppressed by tumor necrosis factor (TNF). HDAC9 can suppress FOXP3 in Treg cells (Parra, 2015). HDACs may play a specific role in normal and pathological circumstances, and HDAC inhibitor (HDACi) usage may emerge as a beneficial therapy in RA treatment, and acetyl code aberrations can be used as prognostic markers in RA (Parra, 2015).

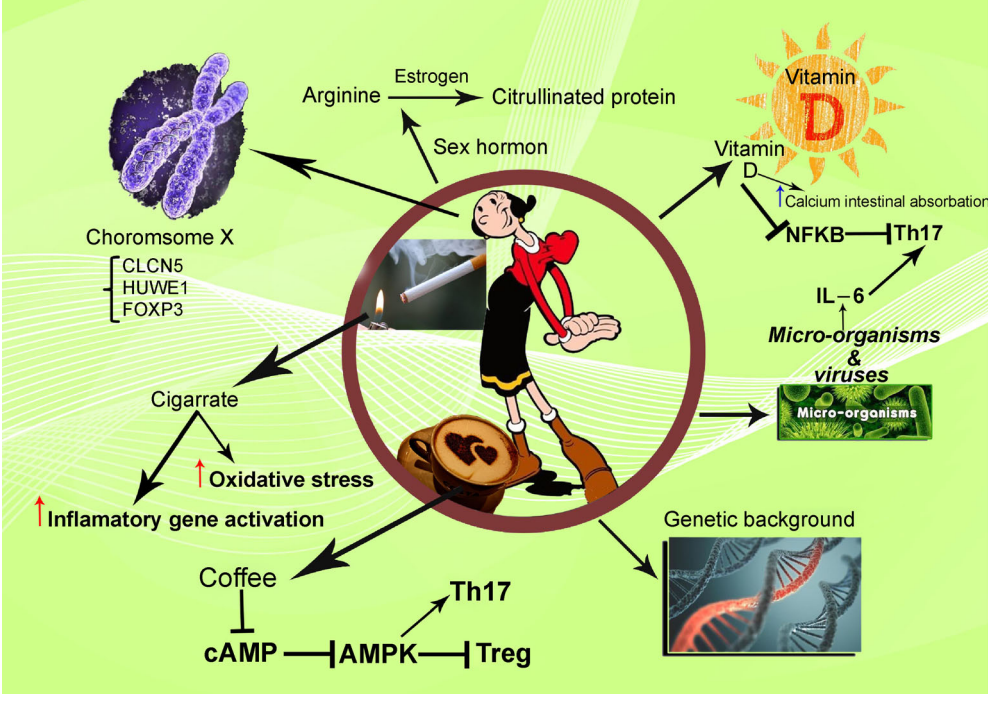

Figure 1 Many agents render people susceptible to RA. Genetic bases, different polymorphisms, and environmental agents such as viruses and microorganisms can induce RA. Usage of coffee can also increase risk of RA. Smocking can increase IL-6 levels and modify T-effector balance, acting as a triggering agent in RA. Decrease in Vit-D and estrogen can affect RA susceptibility add to chromosome X itself got number of genes which make more susceptibility to RA.

Biomarkers in RA diagnosis

RF, anti-CCP, CRP, and ESR

Rheumatoid Factor (RF) and anti-CCP are RA-related biomarkers that are associated with disease (Sharma and Bhar, 2017). Interestingly, anti-CCP can be detectable in the serum of patients with RA, years before pathological symptoms of disease emerge (Mc Ardle et al., 2015). CRP and ESR are not RA-specific and they remain normal while RA progresses; hence, CRP and ESR are not sensitive predictors. On the other hand, acute phase serum amylase-A (A-SAA) levels can reflect local and systemic inflammation in RA (Connolly et al., 2012), and A-SAA can be a good biomarker for therapeutic response to disease-modifying antirheumatic drugs (DAMARs) (Hwang et al., 2016). RF is disease-specific and it is useful in early diagnosis but not for estimating disease progress, while anti-CCP is predictive in early and progressive stages of the disease (Nell et al., 2005; Syversen et al., 2008). RF is an Immunoglobulin M (IgM) but anti-CCP is an Immunoglobulin G (IgG); RF affects the complementary system stronger and leads to a stronger inflammatory response (Aletaha et al., 2015).

Biomarkers for joint damage and cartilage destruction

Finding a reliable predictive biomarker for joint damage would be revolutionary. Some inflammatory biomarkers such as IL-6 and IL-33 are associated with joint damage (Chimenti et al., 2015). Additionally, products of collagen damage such as C-terminal telopeptides of collagen CTX \ and CTX II are diagnostic and prognostic (Siebuhr et al., 2012; Henrotin et al., 2015). Enzyme mediators of destruction, such as matrix metalloproteinases (MMPs) like trapeze, might be involved in pathogenesis and increased cartilage damage (Kim et al., 2011). COMP is a valuable biomarker when evaluating cartilage damage (Gavrilă et al., 2016). S100A8/9 is associated with joint damage in RA, and may represent a good prognostic biomarker (Kang et al., 2014). Matrix metalloproteinase-3 (MMP-3) is one of the most important biomarkers in bone destruction and cartilage damage (Zhai et al., 2016).

miRs as novel inflammatory biomarkers

Micro-RNAs (miRs) are tissue- and disease-specific, "inflammaMiRs" like miR-155 and MiR-146a showed differential expression in RA but sufficient expression level sensitivity and specificity have not been determined yet (Elmesmari et al., 2016; Ospelt, 2016). miR-146a expression can be a negative regulator of interferon (INF) pathways (Picascia et al., 2015). miR-146a and miR-155 are highly expressed in synovial fibroblasts of patients with RA (Picascia et al., 2015). miR-146a can be used as a biomarker for disease severity (Castro-Santos et al., 2015). miR-16 and miR-223 also can be used as biomarkers in joint destruction diagnosis (Castro-Santos et al., 2015). Several studies suggest that miR-19 may be involved in RA pathology by inducing inflammatory cytokine release (Li et al., 2016). For example, miR-23a directly targets IKKa and decreases IL-17 mediators' expression (Hu et al., 2017). The miR-17-92 cluster is a useful factor in osteoblastogenesis, and it can be used as a biomarker to evaluate bone formation (Ibrahim et al., 2016). miR-22 significantly suppresses NF-κB activity and miR-340-5p can be a potentiated biomarker for osteoclastogenesis (Ma et al., 2016). Another recent use of miRs, like using miR-222 and miR-29a, as HDACi have been suggested as an RA therapy (Desiderio et al., 2014; Song et al., 2014). Therefore, miRs have gained significant value in the recent century.

Changes in cytokine and other protein profiles in RA

Imbalanced cytokine production plays an important role in RA pathogenesis. Tumor necrosis factor α (TNFα) is responsible for inflammation in RA and IL-1 is mostly responsible for cartilage damage and bone destruction. Pro-inflammatory cytokines induce gene expression of inflammatory mediators (Brzustewicz and Bryl, 2015). Cytokines can increase synovial membrane inflammation and cartilage damage; IL-12 is associated with disease activity and IL-23 stimulates RANK/RANKL to induce osteoclastogenesis (Niu and Chen, 2014). IL-23 increases Th17 proliferation and inflammation. Therefore, IL-17 and IL-23 play roles in disease severity, and IL-23 can be an especially good target for knockout strategies as a new emerging therapy (Guo et al., 2016). Anti-CCP, TNFα, and IL-6 act as triggers for RA and increase inflammation; IL-6 and TNFα also cause bone erosion and osteoclastogenesis (Wei et al., 2015). TNFα inhibits Treg function too; hence, TNFα, IL-6 and IL-17 are potential biomarkers for inflammation (Zhang et al., 2013). IL-33 signals to the IL-1RL1/STs receptor, which activates MAPK pathways and finally NF-κβ as well (Martin NT and Martin MU, 2016). IL-33 induces Auto-antibody Induced Arthritis (AIA); therefore, blocking IL-33 can reduce the effects of RA (Palmer et al., 2009) (Table 1).

Using SNPs as biomarkers

Genetics affects RA severity and therapeutic response. Genes and SNPs can be good prognostic biomarkers for RA management.

6q23 is one of the important loci associated with RA, after HLA-DRB1 and PTPN22 (McGovern et al., 2016). Genes *PADI4* and *CTLA-4* are RA susceptibility factors (61). Several studies revealed that the rs247660 SNP in *PTPN22* is a loss-of-function allele that destabilizes the gene and is associated with RA susceptibility (Viatte et al., 2013). STAT3 over-expression increases IL-6 production in anti-CCP-negative RA in undifferentiated Arthritis (UA), and can be a prognostic biomarker in Early Arthritis (EA) (Anderson et

Table 1 Categories of potential biomarkers in RA

Prognostic	Ref.	Diagnostic	Ref.	Inflammatory	Ref.	Bone& cartilage damage	Ref.	Response to treatment	Ref.
TNF-α, IL-6, IL-33	Wei et al., 2015	ESR, CRP	Lavric et al., 2016	A-SAA	Smolenska et al., 2016	HA	Watanabe et al., 2016	Uric Acid	Choe and Kim, 2015
RF, anti-CCP	Smolenska et al., 2016	RF, anti-CCP	Smolenska et al., 2016	TNF-a	Wei et al., 2015	IL-17	Hwang et al., 2016	IL-8, IL-33 A-SAA	Visvanathan et al., 2009 Sellam et al., 2016 Hwang et al., 2016
MiR-155 MiR-146a	Robinson et al., 2013	A-SAA	Hwang et al., 2016	IL-6, IL-17	Wei et al., 2015 Barbi et al., 2013	CTX \,	Niki et al., 2012	S100A8 S100A9	Lavric et al., 2016
HSPs, Uric Acid	Lavric et al., 2016	IL-17	Mc Ardle et al., 2015	IL-33	Wei et al., 2015	COMP	Liu et al., 2016	Apo-B100	Ortea et al., 2016
(S100A8/ S100A9 S100A12)	Lavric et al., 2016	IL-6 TNF-a	Wei et al., 2015	ESR, CRP	Zengin et al., 2016	MMPs	Uemura et al., 2015	A2M Complement-C3	Ortea et al., 2016

HA: hyaluronan; HSPs: heat shock proteins; S100A: phagocyte specific-S100 proteins; Apo-B100: Apo-Lipoprotein B100; A2M: Alfa 2 Macroglobulin.

Table 2 Categories of potential gene biomarkers and SNPs in RA

Gene	Location	Function	Associate	Gold SNP	Therapeutic response	Prognosis	Ref.
TNFAIP3	6q23.3	Encodes a protein that inhibits NF-κβ activation	RA Increasing IL20 Therapy Therapy	rs6920220 rs6927172 rs610604 rs2230926	_ _ anti-TNF anti-TNF	_ _ Good Good	McGovern et al., 2016 McGovern et al., 2016 Tejasvi et al., 2012 Tejasvi et al., 2012
HLA-DRB1	6p21.3	Encodes the β-chain protein of HLA-	Joint distraction RA risk factor in Asian population	_ _	NEG to TNFi	Val&Leu at position 11 Bad Ser at position 11 Good	van Steenbergen et al., 2015 Chung et al., 2016 van Steenbergen et al., 2015 Jiang et al., 2016
*HLA-DRB1*04*	6P21.32	Belongs to HLA- gene	Development of anti-CCP	_	_	_	Snir et al., 2014
*HLA-DRB1*11*	6	Belongs to HLA- gene	Risk factor for sJIA	rs151043342	_	_	Ombrello et al., 2015
PAD14	6	Encodes peptidyl Arginine Deiminase	RA risk factor in Japanese population	_	_	_	Snir et al., 2014
Ptpn22	1p13.2	Encodes LYP	CEP-1 in HLA-DRB1*04 carriers in Japanese population	rs2317230 rs2476601	Rituxan (anti-CD20) _	Good _	Walsh et al., 2016 Snir et al., 2014
CDK6	7q21.2	Encodes a cyclin-dependent protein	Joint distraction	rs42041	_	_	Sniret al., 2014
GPSM3	6p21.3	Encodes GPSM3	Protection from RA	rs204989 rs204991	_	Good	Gall et al., 2016
RANK	18q21.33	Encodes a protein involved in T cell activation& DC survival	RA risk	rs8086340	_	Bad	Ruyssen-Witrand et al., 2016
RANKL	13q14.11	Encodes a member of the TN family, which is a ligand of osteoprotegerin	Erosion in RA	rs7984870 rs7325635 rs1054016	_	Bad	Ruyssen-Witrand et al., 2016

(*Continued*)

Gene	Location	Function	Associate	Gold SNP	Therapeutic response	Prognosis	Ref.
OPG	8q24.12	Encodes a member of the TNF-receptor superfamily	Erosion in RA	rs2073618	_	Bad	Ruyssen-Witrand et al., 2016
TLR10	4p14	Encodes a member of the TLR family	_	_	Reduced response to infliximab	Bad	Torices et al., 2016
HLA-G	6p	Belongs to HLA-\ heavy chain paralogs	Decrease risk of RA in Iranian population	rs1063320	_	Good	Hashemi et al., 2016
LRPAP1	4p16.3	Encodes a protein that interacts with LDL receptor	Higher DNA methylation	rs3468	TNFi	Good	Plant et al., 2016
CD48	1q23.3	Encodes a member of CD2 sub forming of Ig like receptors	_	rs6427528	Etanercept in European population	Good	Plant et al., 2016
miR-155	21q21.3	Involved in TCR & BCR signaling pathway	RA inflammation	_	_	Bad	Elmesmari et al., 2016
FOXP3	Xp11.35	Encodes miR-221	RA pathogenesis	rs3761548 rs2232365	_	_	Khalifa et al., 2016
FOXP3	Xp11.3	Encodes miR-222	Cartilage distraction	rs3761548 rs2232365	_	Bad	Khalifa et al., 2016
CLCN5	Xp11.2	Encodes miR-532	Decrease inflammation and disease activity	rs12212067	_	Good	Viatte et al., 2016
HUWE1	Xp11.2	Encodes miR-98	Inflammation in OA	_	_	Bad	Khalifa et al., 2016
VEGF	6p21.1	Encodes protein induce pro inflammatory change	Severity & joint damage in RA	rs833070 rs3025030	_	Bad	Yi et al., 2016
MAP3K7	6q15	Encodes ser/thr protein kinase family	Therapeutic response	rs284515	TNF among Japanese population	Good	Honne et al., 2016
WDR27	6q27	Encodes a protein that plays a role in cell signaling	Therapeutic response	rs75908454	TNF among Japanese population	Good	Honne et al., 2016
GFRA1	10q25	Encodes a receptor	Therapeutic response	rs1679568	TNF among Japanese population	Good	Honne et al., 2016
IL-17	6p12.2	Encodes a cytokine produced by activated T cells	Radiographic progress	rs3804513	IL-17 antagonist	_	Pawlik et al., 2016
IL-17F	6p12.2	Encode cytokine share sequence similarity	Polish RA longer disease duration	rs763780 rs2397084	_	Bad	Pawlik et al., 2016
STAT3	17q21.2	Encodes a protein involved in cell signaling	IL-6 production in RA	_	_	Bad in EA	Anderson et al., 2016
LEPR	1p31.3	Encodes a leptin receptor	Susceptibility to knee OA & higher risk of RA in Chinese populations	rs1137101	_	Bad	Yang et al., 2016
FCGR	1q23.3	Encodes a protein with low affinity receptor for the FC region of IgG	Increase RA risk	rs72717009	_	_	Walsh et al., 2016
TAGAP	6q25.3	Encodes a member of the Rho GTPase activator superfamily	Increase RA risk	rs182429	_	_	Walsh et al., 2016

(*Continued*)

Gene	Location	Function	Associate	Gold SNP	Therapeutic response	Prognosis	Ref.
IRAK3	12q14.3	Encodes a member of the interleukin-1 receptor-associated kinase protein family	Therapeutic response	rs11541076	Anti-TNF	Good	Sode et al., 2016

Ig: Immunoglobulin; IL: interleukin; NEG: Negative; TNFi: Tumor necrosis factor inhibitor; Val: valine; Leu: Leucine; Ser: Serine; sJiA: systemic juvenile idiopathic Arthritis; LYP: lymphoid tyrosine phosphatase of non-receptor type signaling pathway; CEP-1: anti-citrullinated enolase peptide antibodies; GPSM3: G protein signaling modulator 3; EA: early arthritis

al., 2016). RA patients that are anti-CCP-negative have different signals in HLA-B products, and this difference depends on the gene *DRB1* that encodes serine11, and HLA-B8 which produces aspartate9 (Yamamoto et al., 2015). RA patients with HLA-DRB1, that shares an epitope with RANK, RANK Ligand (RANKL), Osteoprotegrin (OPG), and IL-17 have been associated with the age of RA onset and radiographic progression in Japanese patients (Paradowska-Gorycka et al., 2010). Current studies suggest that the G2677A/T SNP was significantly associated with a glucocorticoid-resistant response (Cuppen et al., 2017). According to new findings, the *VAV1* gene plays a role in T cell signaling and is associated with RA. Vav1 SNPs such as rs682626, rs2546133, rs2617822, and rs12979659 are associated with anti-CCP-negative RA (Guerreiro-Cacais et al., 2017).

Conclusions and future perspectives

RA is a multifactorial autoimmune disease associated with genetic and epigenetic factors. Genes and epigenetic factors such as HDACs and miRs can be used as prognostic markers in early RA diagnosis, and can be targeted in future therapeutic approaches.

RA SNPs and classic biomarkers can work synergistically for early RA diagnosis, to provide significant insights into RA management. *HLA-DR*, *PTPN22*, genes in the 6q23 region and Xp11 region, respectively, are relevant for RA susceptibility. Other SNPs categorized in the tables presented herein possess good potential for developing RA guidelines. SNPs are touted as a new type of RA biomarker but their effects are not well-understood by rheumatologists yet. Classic biomarkers work stronger beside SNPs and can offer a meaningful overview in prognosis and early diagnosis of RA. Additionally, SNPs can be useful for predicting a therapeutic response. Finally, choosing good prognostic and diagnostic biomarkers can be helpful in early treatment and disease management and can decrease the treatment costs involved.

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Compliance with ethics guidelines

This article does not contain any studies with human participants or animals performed by any of the authors.

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