Soluble RECEPTORS of advanced Glycated End Products (sRAGE) and Glycine 82 Serine (G82S) Polymorphism in Rheumatoid Arthritis

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Abstract

The receptor for advanced glycation end-products (RAGE) is a cell surface transmembrane multiligand receptor, encoded by the *AGER* gene. RAGE presents many transcripts, is expressed mainly in the lung, and involves multiple pathways (such as NFκB, Akt, p38, and MAP kinases) that initiate and perpetuate an unfavorable proinflammatory state. Due to these numerous functional activities, RAGE is implicated in multiple diseases. *AGER* is a highly polymorphic gene, with polymorphisms or SNP (single-nucleotide polymorphism) that could be responsible or co-responsible for disease development. This review was designed to shed light on the pathological implications of *AGER* polymorphisms. Five polymorphisms are described: rs2070600, rs1800624, rs1800625, rs184003, and a 63 bp deletion. The rs2070600 SNP may be associated with the development of human autoimmune disease, diabetes complications, cancer, and lung diseases such as chronic obstructive pulmonary disease and acute respiratory distress syndrome. The rs1800624 SNP involves *AGER* gene regulation and may be related to reduced risk of heart disease, cancer, Crohn's disease, and type 1 diabetes complications. The rs1800625 SNP may be associated with the development of diabetic retinopathy, cancer, and lupus but may be protective against cardiovascular risk. The rs184003 SNP seems related to coronary artery disease, breast cancer, and diabetes. The 63 bp deletion may be associated with reduced survival from heart diseases during diabetic nephropathy. Here, these potential associations between *AGER* polymorphisms and the development of diseases are discussed, as there have been conflicting findings on the pathological impact of *AGER* SNPs in the rheumatoid arthritis.

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Introduction:

This SNP (single-nucleotide polymorphism), often referred to as Gly82Ser or G82S, is the most described SNP within the AGER gene. It is reported in the Human Gene Mutation Database (HGMD) as being associated with microangiopathy in type 2 diabetes (**1).**

In the general population, the G allele frequency is 92.8% and the A allele frequency is 7.2%. In the CEU population, the G and A allele frequencies are 92.4% and 7.6%, respectively; in the EAS population, they are 78.1% and 21.9%, respectively (1000 Genome data). The rs2070600 SNP or Gly82Ser polymorphism is located in exon 3 of the AGER gene. The rs2070600 SNP probably emerged after migrations from Africa, reaching the highest frequencies in Asia **(2).**

It is a missense variation inducing the substitution of glycine by serine at codon 82 within the RAGE protein. It involves the formation of an AluI restriction site that has facilitated its exploration. Exon 3 is a putative site of ligand binding. The rs2070600 SNP is located in the ligand-binding V domain of AGER,

suggesting a possible influence of this variant on AGER function **(3).**

To be more specific, rs2070600 is located in the second N-glycosylation motif and promotes glycosylation of RAGE, which modifies the RAGE ligand-binding structure and induces an increase in RAGE affinity for ligand AGEs **(4).**

Functional studies of rs2070600 have found that it affects the structure of the receptor protein, influencing its cleavage by some proteases. The rs2070600 SNP has been reported to decrease proteolysis of RAGE **(5).**

The rs2070600 SNP is associated with changes in blood AGEs and sRAGE levels. The 82Gly/Gly genotype was reported as strongly associated with higher plasma levels of sRAGE than 82Gly/Ser or 82Ser/Ser genotypes. Heterozygote carriers of rs2070600 had lower sRAGE levels than wild-type carriers. The homozygote carriers of rs2070600 are rare and exhibit lower sRAGE levels as well. These results were observed in different studies, in particular in those of German and Korean cohorts. This association may be explained by a decrease in RAGE proteolysis **(6).**

In addition, healthy homozygote carriers of rs2070600 showed higher AGE serum levels, insulin resistance, plasma TNF-alpha, serum CRP, and 8-epi-prostaglandin F (2alpha) blood concentrations than did heterozygote carriers or wild-type carriers **(7).**

Homozygotes for the minor allele had higher risk factors for cardiovascular disease, such as low sRAGE levels, inflammation, oxidative stress, and insulin resistance, compared with those bearing at least one G allele. The rs2070600 SNP enhances the stimulation of RAGE by its ligands and induces a proinflammatory signal that stimulates mechanisms underlying inflammatory diseases **(8).**

Many studies have focused on the implications of rs2070600 in different diseases such as inflammatory diseases, cancer, coronary artery disease, lung diseases, or myocardial infarction, with some conflicting results. The rs2070600 SNP could be relevant in human autoimmune diseases. rs2070600 has been shown to be more frequent in rheumatoid arthritis patients **(9).**

In autoimmune diseases:

A decrease in circulating sRAGE has also been shown in children during active autoimmune diseases, such as Kawasaki disease or systemic onset juvenile idiopathic arthritis **(10).**

A) In diabetes:

The rs2070600 SNP was assessed in diabetic patients with controversial results. An Indian study on type 2 diabetes has shown significant associations between rs2070600 and diabetic retinopathy **(11).** Significant associations between rs2070600 with diabetic retinopathy were also reported in Asian Indians and Asian Chinese with type 2 diabetes **(12).** A study in Ashkenazi or Sephardic Jewish patients with type 1 or type 2 diabetes established that rs2070600 was associated with the risk of developing diabetic nephropathy **(13).** However, this association also seems true in an Asian population **(14).**

Another meta-analysis has highlighted a significant association of rs2070600 with the risk of diabetic nephropathy development. The rs2070600 SNP was associated with skin manifestations of microangiopathy and with psoriasis vulgaris in Czech type 2 diabetic patients, compared to the control. The development of dermatoses in subjects with a predisposition to glucose intolerance could be influenced by rs2070600 **(15).**

An analysis of patients with type 1 diabetes from the Finn Diane cohort has found that rs2070600 could predict an increased risk of type 1 diabetes, with an association with decreased circulating sRAGElevels**(10).**

Another study showed the same result, although carriers with type 1 diabetes were younger at the time they were diagnosed. These studies have reported that AGER polymorphisms were associated with diabetes complications. However, other studies did not find any association with diabetes **(16).** A study in a Boston cohort did not find any association between type 2 diabetes, insulin resistance, and AGER polymorphisms including rs2070600, even with haplotype analysis **(17).**

B) In cancer:

The association of SNP rs2070600 with an increased risk of cancer development has been evaluated. Some studies have confirmed such an association, such as a study on gastric cancer in a Chinese population, another on epithelial ovarian cancer also in a Chinese population, and another on nonsmall cell lung cancer in which rs2070600 was associated with a decreased response to chemotherapy and worse prognosis in non-small cell lung cancer **(4).**

A meta-analysis has shown that rs2070600 frequency was positively related with risk of lung cancer but not with breast cancer **(18).** Two meta-analyses confirmed that rs2070600 was significantly associated with cancer risk, especially lung cancer, and with variations of sRAGE levels **(19).**

Another meta-analysis has revealed that rs2070600 was significantly associated with increased risk of cancer **(20),** albeit a Czech study established that rs2070600 was associated with lower sRAGE levels. RAGE was implicated in the pathogenesis of pancreatic cancer and its metastatic process, revealed by an in vitro experiment. In addition, sRAGE was associated with autoimmune pancreatitis, chronic pancreatitis, pancreatic cancer, and intraductal papillary mucinous cancer of the pancreas. But they did not find any significant differences in allelic and genotype rs2070600 frequencies among patients with pancreatic cancer, diabetes mellitus, and healthy controls, even if rs2070600 was associated with sRAGE levels **(21).**

Furthermore, a Czech study did not find any association between the presence of rs2070600 and clear cell renal cancer. But RAGE is one of the key factors accelerating tumor progression and metastasis in various types of cancers, including clear cell renal cancer **(4).**

C) In lung diseases:

RAGE is abundantly expressed in the lung. To characterize RAGE expression in the lung, some authors assessed fetal lung samples and found that the mRNA of AGER increased with increasing gestational age during human lung development **(22).**

RAGE expression is most abundant in the lung, and its expression in respiratory epithelial cells varies during lung morphogenesis. RAGE has been shown to play a critical role in this process to obtain a mature, functional lung **(23).**

RAGE might have physiological roles in the lung, and polymorphisms in AGER can be associated with lung diseases **(24).** A study reported that SNP in AGER was associated with pulmonary function in a Chinese Han population **(25).** Many GWA studies had associated this locus with lung function and with COPD susceptibility **(26).**

rs2070600 was found more frequently in COPD patients than in healthy controls and homozygous carriers developed COPD more frequently. rs2070600 was associated with severe COPD in a study of Caucasian smokers from Poland **(27).**

Moreover, rs2070600 was also associated with COPD in a Chinese population. The rs2070600 SNP associated with COPD-related pulmonary function might involve an exacerbated inflammatory response in the lung **(25).**

The rs2070600 SNP was also associated with circulating sRAGE levels. Lower circulating sRAGE levels were associated with emphysema and COPD severity. In a study, rs2070600 was also significantly associated with the amount of emphysema among European Americans and African Americans **(28).**

D) In cardiovascular diseases.

Only a few studies have explored the links between rs2070600 and cardiovascular diseases. A meta-analysis reported that rs2070600 was not associated with cardiovascular diseases **(29).** Two other meta-analyses did not highlight any association between rs2070600 and coronary heart diseases **(30).**

In the Atherosclerosis Risk in Communities study, rs2070600 was not significantly associated with death, coronary heart disease, diabetes, heart failure, or chronic kidney disease even if rs2070600 was associated with an approximate 50% reduction in sRAGE levels **(31).**

Moreover, a meta-analysis assessed the relationship between the risk of cardiovascular disease, various RAGE isoforms, and rs2070600; sRAGE levels were non significantly lower in patients with coronary artery disease than in controls but were lower in patients with coronary artery disease who had Caucasian ancestry. Circulating esRAGE levels were remarkably lower in coronary artery disease patients, as well as in subgroups with or without diabetes mellitus and without renal disease. Circulating esRAGE might therefore be considered as a powerful negative predictor for the development of coronary artery disease. The rs2070600 SNP may contribute to coronary artery disease development in patients with diabetes mellitus or renal disease, but this contribution is probably dependent on the ethnicity. The risk of cardiovascular disease was associated with rs2070600 in Eastern Asians but not in Caucasians. It has therefore been hypothesized that diabetes mellitus and/or renal disease might favor the occurrence of coronary artery disease through the inheritance of genetic defects leading to the transcriptional activation of AGER **(32).**

For example, a meta-analysis has suggested an association between rs2070600 and the risk of coronary artery disease and ischemic stroke only in the Chinese population **(33).**

E) In CNS diseases:

In a Chinese cohort, rs2070600 was associated with Alzheimer's disease and with its early onset. Moreover, plasma sRAGE levels were lower in Alzheimer's disease patients than in controls. The rs2070600 SNP was associated with lower sRAGE levels and with faster cognitive deterioration. These findings suggest that rs2070600 is probably a risk factor for the early onset of Alzheimer's disease **(34).**

Another analysis from a Chinese cohort showed a higher prevalence of rs2070600 in early-onset Alzheimer's disease patients **(35).** Moreover, this result was also found in another study in which rs2070600 was associated with increased risk of Alzheimer's disease **(36).** Finally, in a cohort of schizophrenic patients, rs2070600 was associated with decreased esRAGE levels. Patients with schizophrenia have lower esRAGE and sRAGE levels than those without schizophrenia, but no association was found between rs2070600 and schizophrenia itself **(37).**

However, in another study, the presence of rs2070600 was associated with higher psychoticism factors. In addition, rs2070600 was associated with an increased risk of schizophrenia and was possibly associated with earlier onset. It has therefore been hypothesized that rs2070600 increased RAGE signaling, leading to increased secretion of inflammatory mediators, which in turn might influence mental brain

functions through developmental processes and/or neurotoxicity **(5).**

Soluble RECEPTORS of advanced Glycated End Products (sRAGE) and Glycine 82 Serine (G82S) Polymorphism in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that leads to bone and cartilage destruction and extra-articular complications, including atherosclerotic vascular disease and premature mortality **(38).**

The receptor for advanced glycation end products (RAGE) has been implicated in the pathogenesis of RA through its ability to amplify inflammatory pathways**(39).**

RAGE, is a member of the immunoglobulin super family, encoded in the Class III region of the major histocompatibility complex. This multiligand receptor has one V type domain, two C type domains, a transmembrane domain, and a cytoplasmic tail. The V domain has two N-glycosylation sites and is responsible for most (but not all) extracellular ligand binding. The cytoplasmic tails are believed to be essential for intracellular signaling **(7).**

Although first described as a receptor for AGEs, the products of non-enzymatic glycation and oxidation of proteins/lipids, later studies indicated that RAGE was also a signal transduction receptor for pro-inflammatory S100/ calgranulins , amphoterin [or high mobility group box 1 (HMGB1)], amyloid peptide and sheet fibrils. Additionally, RAGE is a counter-receptor for Mac-1. These ligands may be generated and accumulate in diverse settings such as diabetes, renal failure, neurodegeneration, autoimmunity/inflammatory milieu, and aging **(40)**

RAGE, functions as a master switch that induces sustained activation of nuclear factor-kappaB (NF-κB), suppresses a series of endogenous auto regulatory functions and converts long-lasting pro-inflammatory signals into sustained cellular dysfunction and disease. Its activation is associated with high levels of dysfunctioning proteins in body fluids and tissues, and strongly associated with a series of diseases from allergy and Alzheimer to rheumatoid arthritis and urogenital disorders **(41).**

As regards RA, RAGE is expressed by many of the cells that participate in the development of RA, including macrophages, neutrophils and T cells. RAGE is expressed on macrophages and T cells within synovial tissues of RA patients as well as on synovial fluid macrophages **(42).**

Synovial fibroblasts that account for about 50% of the cellular constituents of the synovial lining layer constitutively also express RAGE **(43).**

Not only the RAGE but also its ligands have been investigated in arthritis. One of the RAGE ligand HMGB1 is over expressed in inflammatory arthritis with a consequence of RAGE binding resulting in macrophage stimulation, induction of TNF-α and IL-6, maturation of DCs, Th1 cell responses, stimulation of CD4+ and CD8+ cells, and amplification of response to local cytokines occurs **(44).**

Several RAGE ligands are characteristically overexpressed in RA. High concentrations of three of its putative pro-inflammatory ligands, S100A8/A9 complex (calprotectin), S100A8, and S100A12, are found in rheumatoid arthritis (RA) serum and synovial fluid **(45).**

RAGE binding to pro-inflammatory ligands, including members of the S100/calgranulin family, and high mobility group box chromosomal protein 1 (HMGB1), is implicated in cell signaling by synergizing with DNA CpG motifs **(46).**

Soluble C-truncated RAGE (sRAGE) lacks the transmembrane and cytosolic domains of the full-length receptor, is a secretory splice isoform which can prevent pro-inflammatory effects of RAGE signaling by

acting as a decoy by removal/neutralization of circulating ligands **(47).**

Increasing the production of plasma sRAGE is therefore considered to be a promising therapeutic target that has the potential to prevent multiple diseases **(48).**

Clinical studies have shown that higher plasma levels of sRAGE are associated with a reduced risk of coronary artery disease, hypertension, arthritis and Alzheimer's disease **(49).**

In a collagen-induced arthritis (CIA) murine model, treatment with murine sRAGE significantly reduced joint inflammation and destruction. It has previously been shown that a polymorphism of the gene encoding RAGE located within the V-type immunoglobulin domain ofRAGE,whichresultsin
a glycine to serinesubstitution at amino acid position 82, is in linkage disequilibrium with HLA-DR4, it was therefore not surprising that the Ser82 allele was increased in RA subjects **(47).**

It is conceivable that this, or other linked polymorphisms in the RAGE gene affect splicing of the C-truncated, endogenously secreted form of the receptor, or susceptibility to cell surface RAGE cleavage by matrix metalloproteinasethus altering the ratio of soluble to membrane RAGE**(45)**.

References:

1. **Kankova K., A. Vasku, D. Hajek, J. et al., (1999):** "Association of G82S polymorphism in the RAGE gene with skin complications in type 2 diabetes," Diabetes Care, vol. 22, no. 10, p. 1745.
2. **Torres M.C., M.H. Beltrame, I.C.R. Santos, et al., (2012):** Polymorphisms of the promoter and exon 3 of the receptor for advanced glycation end products (RAGE) in Euro- and Afro-Brazilians, International Journal of Immunogenetics, vol. 39, no. 2, pp. 155–160.
3. **Lu, B. Feng, G. Xie, et al. (2011):** Association of AGER gene G82S polymorphism with the severity of coronary artery disease in Chinese Han population, Clinical Endocrinology, vol. 75, no. 4, pp. 470–474.
4. **Chocholatý M., M. Jáchymová, M. Schmidt et al., (2015):** Polymorphisms of the receptor for advanced glycation end-products and glyoxalase I in patients with renal cancer, Tumour Biology, vol. 36, no. 3, pp. 2121–2126.
5. **Suchankova, P., J. Klang, C. Cavanna, et al., (2012):** Is the Gly82Ser polymorphism in the RAGE gene relevant to schizophrenia and the personality trait psychoticism?, Journal of Psychiatry & Neuroscience, vol. 37, no. 2, pp. 122–128.
6. **Gaens K.H.J., I. Ferreira, C.J.H. van der Kallen et al., (2009):** "Association of polymorphism in the receptor for advanced glycation end products (RAGE) gene with circulating RAGE levels," The Journal of Clinical Endocrinology and Metabolism, vol. 94, no. 12, pp. 5174–5180.
7. **Serveaux-Dancer, M., Jabaudon, M., Creveaux, I., et al., (2019)**: Pathological Implications of Receptor for Advanced Glycation End-Product (AGER) Gene Polymorphism. Disease markers, 2019.
8. **Adams J. N., L. M. Raffield, S.E. Martelle et al., (2016):** "Genetic analysis of advanced glycation end products in the DHS MIND study," Gene, vol. 584, no. 2, pp. 173–179.
9. **Lindholm, E., E. Bakhtadze, M. Sjögren, et al., (2006):** The -374 T/A polymorphism in the gene encoding RAGE is associated with diabetic nephropathy and retinopathy in type 1 diabetic patients, Diabetologia, vol. 49, no. 11, pp. 2745–2755.
10. **Forbes, J.M., J. Söderlund, F.Y.T. Yap et al., (2011):** "Receptor for advanced glycation end-products (RAGE) provides a link between genetic

susceptibility and environmental factors in type 1 diabetes," Diabetologia, vol. 54, no. 5, pp. 1032–1042.

11. **Balasubbu S., P. Sundaresan, A. Rajendran et al., (2010):** "Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy," BMC Medical Genetics, vol. 11, no. 1, p. 158.
12. **Li, J., W. Cai, W. Zhang, et al., (2016):** Polymorphism 2184A/G in the AGER gene is not associated with diabetic retinopathy in Han Chinese patients with type 2 diabetes, The Journal of International Medical Research, vol. 44, no. 3, pp. 520–528.
13. **Blech I., M. Katzenellenbogen, A. Katzenellenbogen et al., (2011):** Predicting diabetic nephropathy using a multifactorial genetic model, PLoS One, vol. 6, no. 4, article e18743.
14. **Yuan D., D. Yuan, and Q. Liu, (2012):** Association of the receptor for advanced glycation end products gene polymorphisms with diabetic retinopathy in type 2 diabetes: a meta-analysis, Ophthalmologica, vol. 227, no. 4, pp. 223–232.
15. **Yu W., J. Yang, W. Sui, B. et al., (2016):** Association of genetic variants in the receptor for advanced glycation end products gene with diabetic retinopathy: a meta-analysis, Medicine, vol. 95, no. 39, article e4463.
16. **Simó-Servat O., C. Hernández, and R. Simó, (2013):** Genetics in diabetic retinopathy: current concepts and new insights, Current Genomics, vol. 14, no. 5, pp. 289–299.
17. **Goulart, A.C., S. Germer, K.M. Rexrode, M. et al., (2008):** "Polymorphisms in advanced glycosylation end product-specific receptor (AGER) gene, insulin resistance, and type 2 diabetes mellitus," ClinicaChimicaActa, vol. 398, no. 1-2, pp. 95–98.
18. **Yin N.C., X.P. Lang, X.D. Wang, et al., (2015):** AGER genetic polymorphisms increase risks of breast and lung cancers, Genetics and Molecular Research, vol. 14, no. 4, pp. 17776–17787.
19. **Huang,Q., J. Mi, X. Wang, et al. (2016):** Genetically lowered concentrations of circulating sRAGE might cause an increased risk of cancer: meta-analysis using Mendelian randomization, The Journal of International Medical Research, vol. 44, no. 2, pp. 179–191.
20. **Xia W., Y. Xu, Q. Mao, et al., (2015):** Association of RAGE polymorphisms and cancer risk: a meta-analysis of 27 studies, Medical Oncology, vol. 32, no. 2, p. 33.
21. **Krechler, T., Jachymova, M., Mestek, O., et al., (2010):** Soluble receptor for advanced glycation end-products (sRAGE) and polymorphisms of RAGE and glyoxalase I genes in patients with pancreas cancer. *Clin. Biochem.; 43: 882-886.*
22. **Miller S., A.P. Henry, E. Hodge, et al., (2016):** The Ser82 RAGE variant affects lung function and serum RAGE in smokers and sRAGE production in vitro," PLoS One, vol. 11, no. 10, article e0164041.
23. **Kerkhof, M., H. M. Boezen, R. Granell, et al., (2014):** Transient early wheeze and lung function in early childhood associated with chronic obstructive pulmonary disease genes, The Journal of Allergy and Clinical Immunology, vol. 133, no. 1, pp. 68–76.e4.
24. **Yamaguchi, K., H. Iwamoto, Y. Horimasu et al., (2017):** AGER gene polymorphisms and soluble receptor for advanced glycation end product in patients with idiopathic pulmonary fibrosis, Respirology, vol. 22, no. 5, pp. 965–971, 2017.
25. **Yang J., H. Zhou, B. Liang, et al., (2014):** Association of five genetic variants with chronic obstructive pulmonary disease susceptibility and spirometric phenotypes in a Chinese Han

population, Respirology, vol. 19, no. 2, pp. 262–268.

26. **Castaldi P.J., M.H. Cho, A. A. Litonjua et al., (2011):** The association of genome-wide significant spirometric loci with chronic obstructive pulmonary disease susceptibility, American Journal of Respiratory Cell and Molecular Biology, vol. 45, no. 6, pp. 1147–1153.
27. **Guo Y., Y. Gong, C. Pan, et al., (2012):** Association of genetic polymorphisms with chronic obstructive pulmonary disease in the Chinese Han population: a case-control study, BMC Med Genomics, vol. 5, no. 1, p. 64.
28. **Burkart K. M., A. Manichaikul, J. B. Wilk et al., (2014):** APOM and high-density lipoprotein cholesterol are associated with lung function and per cent emphysema, European Respiratory Journal, vol. 43, no. 4, pp. 1003–1017.
29. **Biros, E., C. S. Moran, Norman, P. E. (2015):** Association between the advanced glycosylation end product-specific receptor gene and cardiovascular death in older men, PLoS One, vol. 10, no. 7, article e0134475.
30. **Liu, L. and Qiu, X. (2013):** Association between the receptor for advanced glycation end products gene polymorphisms and coronary artery disease, Molecular Biology Reports, vol. 40, no. 11, pp. 6097–6105.
31. **Maruthur N.M., M. Li, M.K. Halushka et al., (2015):** Genetics of plasma soluble receptor for advanced glycation endproducts and cardiovascular outcomes in a communitybased population: results from the atherosclerosis risk in communities study, PLoS One, vol. 10, no. 6, article e0128452.
32. **Peng F., D. Hu, N. Jia et al., (2013):** Association of four genetic polymorphisms of AGER and its circulating forms with coronary artery disease: a meta-analysis, PLoS One, vol. 8, no. 7, article e70834.
33. **Ma, W.Q., Q.R. Qu, Y. Zhao, et al., (2016):** Association of RAGE gene Gly82Ser polymorphism with coronary artery disease and ischemic stroke: a systematic review and metaanalysis, Medicine, vol. 95, no. 49, article e5593.
34. **Li, K., D. Dai, B. Zhao, et al., (2010):** Association between the RAGE G82S polymorphism and Alzheimer's disease, Journal of Neural Transmission, vol. 117, no. 1, pp. 97–104.
35. **Cacabelos R., R. Martínez, L. Fernández-Novoa et al., (2012):** Genomics of dementia: APOE- and CYP2D6-related pharmacogenetics, International Journal of Alzheimer's Disease, vol. 2012, Article ID 518901, 37 pages.
36. **Daborg J., M. von Otter, A. Sjölander et al., (2010):** Association of the RAGE G82S polymorphism with Alzheimer's disease, Journal of Neural Transmission, vol. 117, no. 7, pp. 861– 867.
37. **Miyashita M., T. Watanabe, T. Ichikawa et al., (2016):** The regulation of soluble receptor for AGEs contributes to carbonyl stress in schizophrenia, Biochemical and Biophysical Research Communications, vol. 479, no. 3, pp. 447–452.
38. **Picerno, V., Ferro, F., Adinolfi, A., et al., (2015)**: One year in review: the pathogenesis of rheumatoid arthritis. ClinExpRheumatol, 33(4), 551-8.
39. **Oczypok, E. A., Perkins, T. N., &Oury, T. D. (2017):** All the "RAGE" in lung disease: the receptor for advanced glycation endproducts (RAGE) is a major mediator of pulmonary inflammatory responses. Paediatric respiratory reviews, 23, 40-49.
40. **Khan, M.N., &Gothawal, R. (2018)**: Advanced Glycation Endproducts, (AGEs): Formation, Complication and Pharmacological Evaluation to Its

Inhibition. Asian Journal of Research in Medical and Pharmaceutical Sciences, 1-18.

41. **Bengmark, S., Hajdu, N. (2008).**Endproducts and receptor of advanced glycation and lipoxidation (AGE, ALE, RAGE) and chronic diseases – a food perspective. Orv Hetil;149(17):771–8.
42. **Drinda, S. Franke, M. Ruster, P. et al., (2005):** Identification of the receptor for advanced glycation end products in synovial tissue of patients with rheumatoid arthritis RheumatolInt, 25 (6), pp. 411-413.
43. **Chen, Y.J., Chan, D. C., Chiang, C. K., et al., (2016):** Advanced glycation end-products induced VEGF production and inflammatory responses in human synoviocytes via RAGE-NF-κB pathway activation. Journal of Orthopaedic Research, 34(5), 791-800
44. **Sparvero L., D. Asafu-Adjei, R. Kang, D. et al., (2009):** RAGE (receptor for advanced glycation endproducts), RAGELigands, and their role in cancer and inflammation J Trans Med, 7, p. 17.
45. **Chen Y.S., Yan W., Geczy C.L, et al., (2009):** Serum levels of soluble receptor for advanced glycation end products and of 100 proteins are associated with inflammatory, autoantibody, and classical risk markers of joint and vascular damage in rheumatoid arthritis. Arthritis Res Ther.; 11(2):R39.
46. **Taniguchi, K. Kawahara, K. Yone, T. et al., (2003):** High mobility group box chromosomal protein 1 plays a role in the pathogenesis of rheumatoid arthritis as a novel cytokine Arthritis Rheum, 48, pp. 971-981.
47. **Mokbel, A., Rashid, L., & Al-Harizy, R. (2011):** Decreased level of soluble receptors of advanced glycated end products (sRAGE) and glycine82serine (G82S) polymorphism in Egyptian patients with RA. The Egyptian Rheumatologist, 33(1), 53-60.
48. **Falcone. C., E. Emanuele (2006):** Soluble receptor for advanced glycation end products: from disease marker to potential therapeutic target Curr Med Chem, 13 (17), pp. 1971-1978.
49. **Pullerits R., M. Bokarewa, L. Dahlberg, A. et al., (2005):** Decreased levels of soluble receptor for advanced glycation end products in patients with rheumatoid arthritis indicating deficient inflammatory control Arthritis Res Ther, 7 (4), pp. R817-R824.