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Review Article

GENE VARIANTS OF INTERLEUKIN-1 (IL-1) AND THEIR ROLE IN DEVELOPMENT OF OSTEOARTHRITIS

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ABSTRACT

Osteoarthritis (OA) is considered as a degenerative disorder that affects millions of people across the world and impairs quality of life. Numerous risk factors include obesity, aging, joint overuse, trauma, systemic diseases and cytokine gene variants. Several consequences are reported during progression of the disease that includes degeneration of articular cartilage, joint space narrowing, subchondral bone remodelling and internal synovial inflammation which reduces joint function progressively as a person gets older. One of the key cytokine is IL-1, involved in pathogenesis of OA. Genetic variants of IL-1 have been recognised as catabolic mediators that cause disorganization of joint homeostasis. Previous studies have revealed the association of IL-1 gene polymorphism with OA, in particular IL-1α (-889), IL-1β (+3953), IL-1β (-511) andIL1RN (VNTR).This study explores different gene variants of IL-1 associated with OA and the understanding about future potential therapies to overcome the effect of cartilage destruction caused.

INTRODUCTION

Osteoarthritis (OA) is the most frequent multifactorial joint disorder characterized by progressive loss of articular cartilage, joint inflammation (Swellam *et al.,* 2010) and subchondral bone remodelling (Choi *et al.,* 2013). It causes adverse effect on daily life activities. In United States, an average of 27 million people (Lawrence *et al.,* 2008) have been found with various forms of arthritis who have subsequently created economic load on society for middle and older age people (Arliani *et al.,* 2014). The constantly increasing risk factors influence the progression of OA (Richette *et al.,* 2003). OA is considered as potentially irreversible disease (Wojdasiewicz *et al.,* 2014, Madryand Cucchiarini, 2013) that reduces range of motion of joints. Joint disability is the result of change in musculoskeletal system of knee, hip, hand and spine whereas healthy joints keep their balance between production and destruction of articular cartilage (Helmick *et al.,* 2008; Fu *et al.,* 2015). Popularly known proinflammatory cytokine viz IL-1, IL-6, IL-15, IL-17 and IL-18 are involved in development of the OA. Among them IL-1 has a pivotal role in destruction of joint supportive tissues. Strong association of genetic components in progression of the disease has been reported by Lanyon *et al.,* 2000. Variants of IL-1 gene are involved in late onset of the OA (Bijkerk *et al.*, 1999). Leppavuori *et al.,* 1999 reported the association of IL-1 gene cluster present on 2q12 to 2q21 with distal interphalangeal joints.

Classification of IL-1 family

IL-1 family is a large group of cytokines which consists of eleven members including IL-1α (IL-1F1), IL-1β(IL-1F2),IL-1Ra (IL-1F3), IL-18 (IL-1F4), IL-36Ra (IL-1F5), IL-36α (IL-1F6), IL-37 (IL-1F7), IL-36β(IL-1F8), IL-36γ (IL-1F9), IL-38 (IL-1F10), and IL-33 (IL-1F11) (Dinarello, 2011; 2010) that are encoded by eleven individual genes (Weber *et al.,* 2010). Among these cytokines some are having proinflammatory properties (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, andIL-36 γ), some are known for receptor antagonistic properties (IL-1Ra, IL-36Ra and IL-38) while only IL-37 has anti-inflammatory role (Garlanda *et al.,* 2013). These members are

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involved in immune response defence mechanism against exposure to various microscopic organisms.

It has been reported that active form of IL-18 is involved in OA development. Elevated level of a particular proteinase enzyme referred as *Caspase-1* found in articular cartilage and synovium in OA patients is responsible for activation of IL-18 as well as IL-1β and subsequently promotes the OA progression. (Wojdasiewicz *et al.,* 2014). IL-18 considered as a pro-inflammatory cytokine causes expression of IL-18Rα on the non-cytosolic surface of chondrocyte and induces signal for production of Matrix Metalloproteinases (MMPs) such as MMP-1, MMP-2 and MMP-13 (Dai *et al.,* 2005).

Role of IL-1 in evolution of Osteoarthritis

OA is marked by elevated levels of circulating inflammatory cytokines such as IL-1 that is primarily synthesized by chondrocyte cells (Loughlin *et al.,* 2002). IL-1 super family consist of three key classes of interrelated cytokines viz IL-1α, IL-1β, and Interleukin-1 receptor natural antagonist (IL-1RN) involved in pathophysiology of OA. Both the ligands IL-1α and IL-1β are recognised by same receptor, IL-1RI induces signal transduction whereas binding of IL-1β to receptor IL-1RII inhibits further signal induction. (Boraschi and Tagliabue 2013). IL-RN gene counteracts the inflammatory influence of IL-1 without inducing signal cascade (Grover *et al.,* 2006). It contains specific sequences repeats called variable numbers of tandem repeats (VNTR) of 86 bp in its polymorphic region of intron-2. Three potential transcription factor binding sites located on 86 bp in VNTR region may increase the level of expression of gene transcription and translation (Arnalich *et al.,* 2002).

It has been demonstrated that IL-1β induces the biosynthesis of various extra cellular matrix (ECM) degradative enzymes such as MMPs, Aggrecanases (ADAMTS-4) and Hyaluronidase (Fig 1). It also induces the production of other catabolic mediators like IL-6, IL-18 etc (Guerne *et al*., 1990 and Lotz *et al.,* 1992). Both IL-1β and TNF-α are responsible for induction of biosynthesis of ADAMTS-4 whereas ADAMTS-5 express constitutively (Koshy *et al.,* 2002; Verma and Dalal 2011). According to Lark *et al* 1997 and Bau *et al* 2002 MMPs play predominant role in degradation of articular cartilage. Moreover, aggrecanases are also responsible for destruction of articular cartilage, especially during onset of the OA (Nagaseand Kashiwagi 2003). Excessive loss of ECM increases the space between joints of two bones and reduces their normal functioning. In articular cartilage two major components are collagen type-II and aggrecans (Lee *et al.,* 2013) where excessive losses of these components result in OA.IL-1β enhances miRNAs levels in the ECM (Miyaki *et al.,* 2009) that are known to be associated with destruction of articular cartilage (Akhtar*et al.,* 2010).

IL-1 gene polymorphism and OA

The IL-1 gene cluster on chromosome 2 is a genetic locus that contributes to the risk of OA. Several family studies and genetic linkages suggested that the complex inheritance pattern of cytokine gene may cause susceptibility to OA (Sandell, 2012). Different levels of cytokine production in inter-individual may have genetic influences and proinflammatory effect of cytokines is involved in number of infectious diseases (Witkin *et al.,* 2002). The IL-1 gene has cluster spanning of 10.9Mb on chromosome 2q13-14. Single nucleotide polymorphisms (SNPs) for IL-1 gene on chromosome number 2 are IL-1α (-889C>T), IL-1β (+3953C>T), IL-1β (-511G>A), IL-1β (-31T>C), IL-RN (8006T>A), IL-1RN (VNTR), IL-1RN (11100T>C).They are associated with OA (Loughlin *et al.,* 2002) (Fig 2)

Several genetic variants of IL-1 have been involved in different forms of OA, whereas meta-analyses revealed that no kind of IL-1 gene is involved in susceptibility to knee OA (Kerkhof *et al.,* 2011). In clinical population of symptomatic knee OA, it has been demonstrated that the haplotypes of IL-1RNare associated with radiographic severity (Attur *et al.,* 2010). Moreover, a single study in a cohort of Caucasians has also demonstrated that some specific IL-1RN haplotypes are associated with radiographic progression of knee OA (Wu *et al.,* 2013).

It has been reported that *IL-1RN* C-T-A haplotype may be involved in severe knee OA with a negative regulation on cartilage breakdown induced by IL-1β (Kerkhof *et al.,* 2011). Other possibilities that increase the production of IL-1 are the methylation of regulatory promoter elements or acetylation of histone proteins (Zdravko *et al.,* 2011). Meulenbelt *et al.,* 2004 in their study indicated independent predisposition for signs of radiographic OA in carriers of IL-1β (-511T) allele and IL-1RN (VNTR) allele-2. These allelic carriers may enhance the breakdown of cartilage matrix and induce inflammation.

The ambiguity in the role of IL-1 gene cluster that causes genetic risk of OA was investigated by different studies (Table 1). A number of previous studies revealed the association of *IL-1* gene polymorphism in development of OA, whereas some studies also find insignificant association of *IL-1* gene polymorphism in OA. Smith *et al* (2005) studied 44 hip OA patients from United Kingdom and found significant association of *IL-1* gene variants with OA. However Chapman and Loughlin, (2006) in the same population found insignificant association of the IL-1 gene variants with OA. Swellam *et al.,* 2010 in their study found that IL-1RN allele 2 represents a strong factor inducing the progression and severity of the knee OA, thereby their studies supported the association of IL-1 in pathogenesis of the OA.

Meta-analysis data have not shown fully significant evidence of association of IL-1 gene variants to risk of OA but it has been suggested that IL-1β gene could be associated in some hip and hand OA risk (Moxley *et al*., 2010). A recent study on Croatian population (259 hip OA patients) found significant association of IL-1β (-511 G>A) in protection of hip OA, whereas in case of haplotypic frequencies, no significant association was found with hip OA (Jotanovic *et al.,* 2011). Previous publications demonstrated that C-G-C haplotype was strongly associated with risk to develop hip OA (Chapman and Loughlin, 2006). However this study was not further revised by another larger study. Nakki *et al.,* 2010 did a case-control study which revealed that SNP rs2287047 (*IL-1R1gene*) is strongly associated with hand OA.

Recently a significant association of IL-33 has been described during inflammation and the arthritis (Kearley *et al.,* 2009).

Table 1 Variants of IL- gene cluster and their association with hip OA

S.No.	Variants	Position	OA cases	Population	Association	References
1	IL1R1	-1028	298	Chinese	S	Yuyan *et al* (2017)
2	IL-1α	3'UTR	931	Chinese	S	Yang *et al* (2015)
3	IL-1RN	VNTR	154	Caucasians	s	Wu *et al* (2013)
4	IL1-β	-551	259	Croation	S	Jotanovic *et al*(2011)
	IL-1RN	VNTR				
5	IL-1α	-889	252	United Kingdom	S*	Moxley *et al* (2010)
	IL1-β	3958		and Ductch		
	IL-1RN	VNTR				
6	IL1-β	3953	370	United Kingdom	NS	Chapman *et al* (2006)
	IL1-β	-551				
	IL-1RN	9589				
7	IL1-β	3953	70	Dutch	S	Meulenbelt *et al* (2005)
	IL1-β	-511				
	IL-1RN	VNTR				
8	IL-1α	-889	44	United Kingdom		Smith *et al* (2005)
	IL1-β	-31				
	IL1-β	-511				
	IL1-β	3953				
	IL-1RN	8006				
	IL-1RN	11100				
	IL-1RN	VNTR				
9	IL-1α	-889	390	United Kingdom	NS	Loughlin *et al* (2002)
	IL1-β	5810				
	IL1-β	-31				
	IL1-β	-511				
	IL-1RN	VNTR				
	IL-1RN	9589				
	IL-1RN	11100				
10	IL1-β	3953	61	German	S	Moos *et al* (2000)
	IL-1RN	VNTR				

S: Significant; NS: Non-Significant; *: Some hip OA associated with IL-1 gene polymorphism.

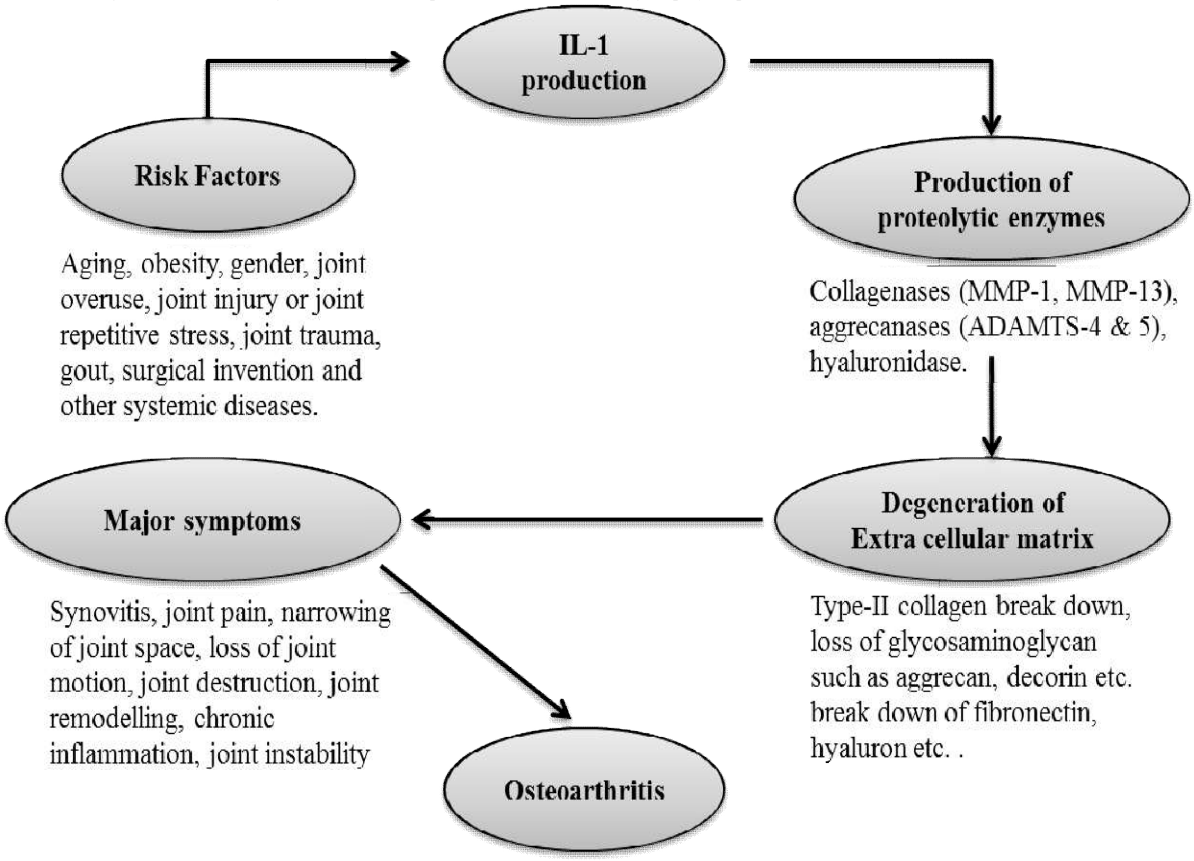

Figure 1 Schematic representation of overall progression of disease

Further enhancing the knowledge that inhibitory effect of IL-33 on signaling through IL1RL1 receptor could cease the arthritis progression (Iikura *et al.,* 2007).

Summary

OA is joint destructive and irreversible disease affecting normal daily life activities and causes negative impact on

economics of society. It has been found positive association of both IL-1β (3953) and IL-1RN (VNTR) gene polymorphismin development of OA (Moos *et al.,* 2000).

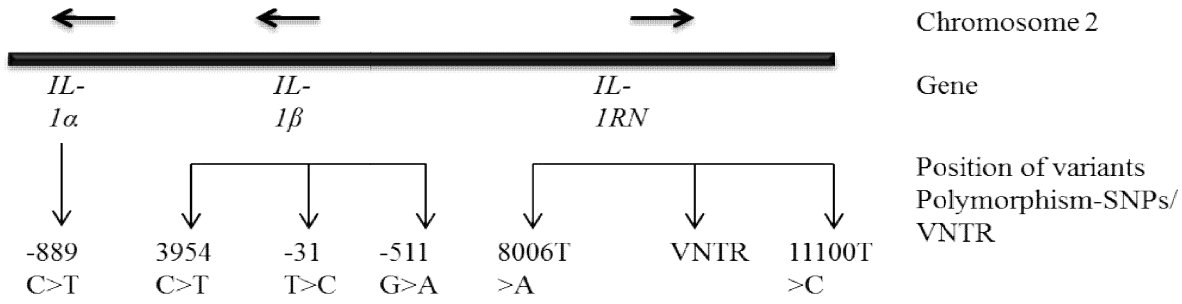

Figure 2 IL-1 gene locus with different variants on chromosome 2. Inteleukin-1alpha (IL-1α); Inteleukin-1alpha (IL-1β); Inteleukin-1receptor antagonist (IL-1RN); Variable number of tandem repeat (VNTR).

Another study suggested that IL-1β may have strong association than TNF-α in regulation of cytokine and expression of different growth factor in chondrocyte (Moos *et al.,* 1999). It has also been suggested that the deregulation for IL-1 gene expression may enhance the over expression of MMPs and down regulate the production of collagen and aggrecan (extra cellular matrix), and thereby promote the development of OA (Westacott and Sharif, 1996). Previous studies have demonstrated the effect of IL-1 gene polymorphism in OA but it is not much clear to distinguish whether the association of selected gene is significant or not. Therefore, further study is needed to find out the exact role of IL-1 gene polymorphism in OA. There is further need of relative account of impact of IL-1 gene variants and prediction of individuals at risk of developing Osteoarthritis.

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