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Genetic and Epidemiological Risk Factors in the Etiology of Arthritides

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ABSTRACT Arthritis is a multifactorial disease that results from interactions between genetic and environmental factors. Three types of arthritis have been considered in our study – juvenile rheumatoid arthritis, rheumatoid arthritis, and osteo arthritis. The present study was envisaged to investigate the genetic and epidemiological risk factors predisposing to arthritides in Indian subjects. Arthritis patients and healthy individuals matched for age and sex were considered for the study. A significant deviation from 1:1 sex ratio was observed in all the three types of arthritis with preponderance of female arthritis patients. Predominance of arthritis in females suggests the role of hormonal factors. Frequency distribution of age at onset in familial cases showed that arthritis had an early onset of the condition. The segregational analysis and Penrose relative frequency analysis were found to follow a multifactorial mode of inheritance. The observations could pinpoint that sex variation, age at onset and familial history are some of the epidemiological factors in the pathogenesis of arthritides. However, arthritis presents an epidemiological challenge and several risk factors have been suggested during the development or progression of arthritides. Despite extensive epidemiologic research, the etiology of arthritis is still unknown. Hence, identification of epidemiologic and genetic factors associated with susceptibility/protection from autoimmune disease is essential as it could lead to our understanding of disease pathogenesis for better diagnosis.

INTRODUCTION

Arthritis is a complex genetic disorder with interplay of both genetic and environmental factors in the aetiopathogenesis of the disease. It is a chronic disease, mainly characterized by inflammation of the lining or synovium, of the joints. Further, it can lead to long-term joint damage, resulting in pain, loss of function and disability. Arthritides are a heterogenous group of disorders affecting the joints in which heredity and environment factors in combination with immune response like, human leucocyte antigens (HLA) appear to play a causative and pathogenic role.

Juvenile rheumatoid arthritis (JRA) designates a group of diseases that have in common chronic idiopathic inflammation of one or more joints in children (Miterski et al. 2004). Juvenile rheumatoid arthritis (JRA) is particularly an unpredictable and heterogeneous disease group (Ki and Dong 2010). Epidemiologic studies have noted a relatively wide incidence of juvenile arthritis ranging between approximately 10 and 23 per 100,000 persons, with female predominance (Debbie et al. 2009). Immune dysfunction in juvenile idiopathic arthritis (JIA) is evident with the presence of autoantibodies, such as antinuclear antibodies (ANAs)-present in 40 percent of patients—and rheumatoid factor (RF)—present in 5 to 10 percent of patients (James and Rose 2005; Jennifer and Norman 2007). Reduced bone mineral density is now well recognized in children and young adults with juvenile idiopathic arthritis which is reported to be multifactorial in origin (Janet 2001). Although undoubtedly there are genetic predispositions to juvenile idiopathic arthritis, other contributing factors have been suggested, such as environmental agents, infectious vectors, trauma, psychological stress, and hormonal abnormalities (James and Rose 2005; Jennifer and Norman 2007). The etiology is largely unknown (Ki and Dong 2010), and the genetic component is complex. Although juvenile idiopathic arthritis is believed to be influenced by genetic and environmental factors, twin and family studies strongly support a substantial role for genetic factors in juvenile arthritis susceptibility (Sheila and Prahalad 2010). Higher preva-

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lence of autoimmunity was observed in relatives of juvenile rheumatoid arthritis affected sibling pairs than the control group (Prahalad and Glass 2002). Juvenile idiopathic arthritis has often been described as a complex genetic trait wherein multiple genes interact to result in a specific phenotype (Sheila and Prahalad 2010). Association of inflammatory arthritis and a chromosome deletion disorder (22q 11 deletions) provides evidence of important genetic factors in the pathogenesis of juvenile idiopathic arthritis (Karen et al. 2001).

Rheumatoid arthritis is a progressive, debilitating autoimmune disease of joints (Roth and Finckh 2009). Rheumatoid arthritis is triggered by a combination of factors like genetic susceptibility, and some environmental or biologic trigger, such as a viral infection or hormonal changes. It also shows a wide variation in its incidence and prevalence worldwide (Oliver and Silman 2009) and affects up to 1 percent of the world population and is a disease with a clear gender bias wherein, women are affected 2.5-fold as often as men (Jirholt et al. 2001). Rheumatoid arthritis (RA) is a complex mutifactorial autoimmune disease (Kochi 2010) and its occurrence and severity are related to both genetic and environmental factors (Yannis et al. 2005) which is associated with increased mortality and may reduce life expectancy by 3 to 18 years (Theodore et al. 2004).

Genetic susceptibility to rheumatoid arthritis has been clearly demonstrated, with familial clustering and the concordance of monozygotic (30 percent) to dizygotic (5 percent) twins being high (Ghodke et al. 2005). A major whole genome screen found that while the single nucleotide polymorphism marker rs11761231 (on chromosome 7) had no effect on rheumatoid arthritis in males, but, it had a strong and apparently additive effect in females – which may represent one of the first sex-differentiated effects in human diseases (Oliver and Silman 2009). The major genetic risk factor continues to be shared epitope-expressing HLA-DRB1 alleles, which function in triggering the T-cell receptor (TCR) (Goronzy and Weyand 2009). A novel finding has been the transfer, through microchimerism, of the shared epitope – a strong risk factor associated with rheumatoid arthritis – in women (Rak et al. 2008). Studies provide evidence that HLA susceptibility alleles can contribute to the risk of an autoimmune disease through microchimerism (Oliver and Silman 2009). However, some studies suggest a possible role of specific genetic, lifestyle, and environmental factors in the geographical variations of the diseases (Yannis et al. 2005).

Osteoarthritis is a degenerative joint disease that typically affects joints in the knees, hip, hand, feet, and spine. Osteoarthritis is the most common form of arthritis in the elderly and is influenced by both genetic and environmental risk factors (Valdes and Spector 2010). The number of persons in the United States affected by arthritis was estimated at 40 million (15 percent of the population) in 1995 and is expected to increase to 59.4 million (18.2 percent of the population) by 2020 (Issa and Sharma 2006). Symptomatic knee osteoarthritis occurs in 10 percent men and 13 percent in women aged 60 years or older (Zhang and Jordan 2010), making it more prevalent than any other form of arthritis (Lawrence et al. 2008). Genetic risk factors can influence the risk of osteoarthritis and can also affect the outcomes of osteoarthritis at various stages during the course of the disease (Valdes and Spector 2011). The etiology of osteoarthritis is multifactorial, and differences in the prevalence of osteoarthritis may be attributable to both genetic and life-style factors (Corti and Rigon 2003). The identification of a high number of candidate genes to confer susceptibility to the development of the osteoarthritis shows the complex nature of this disease (Fernández-Moreno et al. 2008). Studies suggest that multiple genes are likely to be involved in osteoarthritis susceptibility, and that environmental factors also have an important influence on disease expression (Arden and Nevitt 2006).

Hence, the need for an intense study in this area is, therefore, necessitated at the epidemiological and genetic levels as this genetic diseases cause great morbidity not only to the family of the affected individual but also to the society at large. Therefore, the present study was envisaged to investigate the epidemiological and genetic risk factors predisposing to arthritides.

MATERIALS AND METHODS

The present study includes arthritides patients referred to the unit of orthopedic department at Andhra Vaidya Vidhan Parishad (AVVP) Hospital, Hyderabad, Andhra Pradesh,

India. Cases of juvenile rheumatoid arthritis, rheumatoid arthritis and osteo arthritis referred and confirmed radiologically based on small and large joint involvement, were considered for which the hospital was visited during the period 1998-2006. Information like age, gender, family history and parental consanguinity was collected and analyzed from 41 juvenile rheumatoid arthritis, 101 rheumatoid arthritis, 100 osteo arthritis patients. For comparative purposes, 25 juveniles from various schools of Hyderabad and 125 adult healthy individuals matched for age and sex were considered.

The juvenile rheumatoid arthritis patients were inpatient at pediatric division of AVVP hospital. All patients met American College of Rheumatology (ACR) criteria for the diagnosis of juvenile rheumatoid arthritis (James et al. 1986). The diagnosis of rheumatoid arthritis was established using the classification criteria of the American College of Rheumatology (Arnett et al. 1988). Osteoarthritis was diagnosed from clinical symptoms, examinations and radiographic findings. All patients fulfilled the ACR criteria for knee osteoarthritis (Altman 1991). All the subjects both patients and healthy individuals were informed and their consent was taken prior to the inclusion in the study.

Statistical Analysis

The data obtained on epidemiological variables were compiled by appropriate statistical/ genetic analysis such as Chi-square test of association for autosomal dominant mode of inheritance and Penrose's relative frequency estimates were calculated. Segregation analysis was carried out to find the possible mode of inheritance, depending upon the sibship size and the proportion of affected individuals. The mode of inheritance was identified based on the comparison of the observed relative frequencies with those of the expected values. The calculated observed probability was examined for its close agreement to that of expected probability estimates of the dominant, recessive or multifactorial modes of inheritance.

RESULTS

Table 1 gives the frequency distribution of arthritides with respect to gender, 31.7 percent of males and 68.3 percent of females constituted the juvenile arthritis group, while in rheumatoid arthritis, 29.3 percent were males and 70.7 percent were females. Osteoarthritis comprised of 29.0 percent males and 71.0 percent females. A significant deviation from 1:1 sex ratio was observed with respect to JRA 1:2.2 (χ^2:5.845); while in rheumatoid arthritis and osteoarthritis it is reported to be 1:2.4, with the chi square analysis being (χ^2: 7.712) in rheumatoid arthritis and (χ^2: 6.304) in osteoarthritis, with female preponderance in different types of arthritides.

Table 2 gives the age distribution in control and disease groups. In the present study, 12.2 percent of juvenile rheumatoid arthritis patients exhibited symptoms at less than 10 years of age, while 87.8 percent between 10-20 years. Thus it is observed that juvenile rheumatoid arthritis is significantly exhibited in individuals between 10-20 years, (χ^2: 5.736) when compared to the juvenile control group. With respect to rheumatoid arthritis, 54.0 percent of the patients exhibited symptoms between 30-50 years with significant association of the condition with this age group (χ^2: 25.365). Similarly, in osteoarthritis 55.0percent of patients belonged to the age group of 30-50 years of age which was found to be highly significant (χ^2: 84.044).

Table 3 gives the mean age at onset in simplex and multiplex families based on parental phenotypes and consanguinity of the condition. In juvenile arthritis NXA (one parent affected) parental type without consaguinity, mean age at onset was 15 ± 3.0 years and 10.8 ± 1.79 in

Table 1: Distribution of arthritides in comparision with male and female

Condition	*Male*		*Female*		*Total*	*χ^2 value*
	n	*%*	*n*	*%*		
Juvenile control	16	64.0	9	36.0	25	-
Juvenile arthritis	13	31.7	28	68.3	41	5.85*
Control	19	15.2	106	84.8	125	-
Rheumatoid arthritis	44	29.3	106	70.7	150	7.71*
Osteo arthritis	29	29.0	71	71.0	100	6.30*

Ratio: JA- 1:2.2, RA and OA- 1:2.4

Table 2: Age frequency distribution in control and disease groups

Condition	*< 10 yrs*		*10-20 yrs*		*20-30 yrs*		*30-50 yrs*		*>50 yrs*		χ^2 *value*
	n	*%*	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*	
Juvenile control	10	40.0	15	60.0	-	-	-	-	-	-	-
Juvenile arthritis	5	12.2	36	87.8	-	-	-	-	-	-	5.73*
Control	-	-	-	-	61	48.8	61	48.8	3	2.4	-
Rheumatoid arthritis	-	-	-	-	45	30.0	81	54.0	24	16.0	25.36*
Osteo arthritis	-	-	-	-	8	8.0	55	55.0	37	37.0	84.04*

multiplex and simplex families respectively. In NXA parental type families with consanguinity the mean age at onset was 10.6 ± 0.67 in simplex cases. Thus, it is observed that in consanguinous family with already one parent affected, the mean age at onset was found to be early compared to patients with both parents being normal. With respect to rheumatoid arthritis an interesting observation made in the simplex families of NXN and NXA parental types with consanguinity the mean age at onset was 37.0 ± 6.02 years and 31.3 ± 6.17 years respectively, compared to families of NXN and NXA parental phenotypes without parental consanguinity. Thus, it is observed that the onset of the disease in juvenile rheumatoid arthritis and rheumatoid arthritis was early in patients with parental consanguinity in simplex families. In osteoarthritis, irrespective of parental types (NXN, NXA) all patients of multiplex families exhibited an early age at onset of the condition. Thus, the mean age at onset could help in partially delineating heterogeneity in the inheritance of arthritides.

Table 4 gives the familial segregation of arthritides with respect to parental phenotypes and parental consanguinity. Predominance of familial clustering was observed in patients whose parents were of NXN (both parents normal) and NXA (one parent affected) phenotypes, with no history of consanguinity. The probability of being affected was found to be 0.153 in juvenile rheumatoid arthritis confirming the multifactorial mode of inheritance. A similar observation was made in rheumatoid arthritis and osteoarthritis cases, wherein the mode of inheritance was reported to be multifactorial with the probability of being affected to be 0.065 and 0.176 respectively. The probability estimates thus could reveal the multifactorial mode of inheritance with the observed value being in close agreement with the expected value.

The segregational analysis to identify the mode of inheritance in disease condition (Table 5) was based on the single incomplete ascertainment method by Fischer (1934). Total sibship size and number of affected in a sibship was calculated in juvenile rheumatoid arthritis, rheumatoid arthritis and osteoarthritis, it is observed from the pedigree data, that the probability of being affected was 0.038 ± 0.012 in juvenile rheumatoid arthritis, 0.025 ± 0.005 in rheumatoid arthritis and 0.061 ± 0.11 in osteoarthritis cases, highlighting that arthritides, irre-

Table 3: Mean age at onset based on parental consanguinity

Diseases	*Parental phenotype*	*Parental consanguinity*	*Simplex families*			*Multiplex families*		
			X	*±SD*	*n*	*X*	*±SD*	*n*
Juvenile	NXN	Absent	11.2	1.28	5	10.5	1.50	2
Arthritis	NXN	Present	11.5	0.50	2	-	-	-
	NXA	Absent	10.8	1.79	4	15	3.00	3
	NXA	Present	10.6	0.67	3	-	-	-
Rheumatoid	NXN	Absent	40.4	3.41	10	38	4.90	5
Arthritis	NXN	Present	37.0	6.02	2	-	-	-
	NXA	Absent	33.5	1.83	35	40	4.75	4
	NXA	Present	31.3	6.17	4	-	-	-
	AXA	Absent	33.3	11.41	3	-	-	-
Osteo	NXN	Absent	44.5	0.5	2	42	10.13	3
Arthritis	NXN	Present	-	-	-	-	-	-
	NXA	Absent	43.3	4.78	10	40.9	5.58	72
	NXA	Present	51	3.00	2	42.5	0.50	-
	AXA	Absent	35.5	5.52	2	-	-	

Table 4: Familial segregation of arthritides conditions (Pooled Data)

Diseases	*No. of pedigrees*	*Parental phenotype*	*Parental consanguinity*	*Total progeny living*	*No. of progeny affected*	*Affected relatives*	*Probability of being affected*
Juvenile Arthritis	7	NXN	Absent	20	9	7	0.153
	2	NXN	Present	11	2	2	-
	7	NXA	Absent	23	7	6	-
	4	NXA	Present	14	4	3	-
Rheumatoid Arthritis	15	NXN	Absent	91	20	16	0.065
	2	NXN	Present	6	2	2	0.038
	39	NXA	Absent	193	45	5	0.074
	5	NXA	Present	32	7	1	-
	3	AXA	Absent	10	3	-	-
	1	AXA	Present	5	1	1	-
Osteo Arthritis	5	NXN	Absent	22	8	5	0.176
	1	NXN	Present	4	1	2	-
	17	NXA	Absent	80	26	5	0.142
	4	NXA	Present	21	5	2	0.058
	2	AXA	Absent	8	2	-	-

spective of the type, was found to follow a multifactorial mode of inheritance with gene-gene or gene-environment interactions, thus strengthening the Penrose relative frequency estimates in arthritis as multifactorial mode of inheritance.

Table 6 gives the relative frequency estimates in arthritides based on the general population frequency reported from India. The prevalence was reported to be 0.005 in juvenile rheumatoid arthritis, 0.007 in rheumatoid arthritis and 0.036 in osteoarthritis. Hence, based on the prevalence data and pedigree information, Penrose's corrected frequency method was adopted to identify the modes of inheritance in arthritides. It was observed that relative frequency was 7.6 in juvenile rheumatoid arthritis, 3.33 in rheumatoid arthritis and 1.69 in osteoarthritis, which is in agreement with the expected relative frequency of the multifactorial mode. Thus the study highlights that arthritides in general is found to follow the multifactorial mode of inheritance confirming the earlier reports (Janet McDonagh 2001; Kochi 2010; Corti and Rigon 2003).

DISCUSSION

Epidemiological factors like sex, early age at onset and familial history are the three identifiable risk factors in the etiopathogenesis of the condition. The present study revealed the sex ratio in juvenile rheumatoid arthritis as 1:2.2, while in rheumatoid arthritis and osteoarthritis it was found to be 1:2.4 with female preponderance in all the three types of arthritis indicating hormone level variation, wherein lowered estrogen and progesterone hormone ob-

Table 5: Segregational analysis for identification of mode of Inheritance in Disease condition.

Complete Pedigree	*Total number of individuals in Sibship*	*Sibship size*	*Number of affected children*	*Probability of affected p*	*Probability of unaffected q*
Juvenile Arthritis	311	73	82	0.038	0.962
Rheumatoid Arthritis	1131	229	252	0.025	0.975
Osteo Arthritis	625	135	165	0.061	0.931

Table 6: Penrose's relative frequency estimates in disease condition

Condition	*General population*	*Sibs*	*Observed*	*Expected*		
			(S/q)	*Dominant*	*Recessive*	*Multifactorial*
Juvenile arthritis	0.005	0.038	7.6	100	50	14.08
Rheumatoid arthritis	0.007	0.025	3.33	66.67	33.33	11.54
Osteo arthritis	0.036	0.061	1.69	13.89	6.94	5.29

served in post menopausal women conferring decreased protection (Samanta et al. 1993). Similarly, in male patients presence of weak and lowered testosterone levels may confer decreased protection (Silman 2001). Studies indicate that females have enhanced immunoreactivity, compared with males, with higher immunoglobulin levels and enhanced antibody production to antigen stimulation (Zandman-Goddard et al. 2007). The immune response in women is more T-helper type 2 predominant compared with men, who have a T-helper type 1 response (Fairweather et al. 2008). The sex hormones estrogen, androgen and prolactin hormones all modulate the immune response via androgen and estrogen receptors and a complex interaction between the hormones may influence disease susceptibility (Oliver and Silman 2009). Dehydroepiandrosterone sulphate and oestrone concentrations have been found to be lower in male rheumatoid arthritis patients compared with healthy controls (Tengstrand et al. 2003) while oestradiol was higher and correlated with inflammation levels. Oestrogen and prolactin are both proinflammatory hormones and the increased exposure in women may, in part, explain the high female: male ratio (Oliver and Silman 2009). The use of the oral contraceptive pill and pregnancy are both associated with a decreased risk though, temporarily. Estrogens have attracted significant interest as potential modulators of autoimmune disease. The diseases generally improve during pregnancy, suggesting, if estrogen has a role, then estrogen is an immunosuppressive factor (Lang 2004). However, the postpartum period has been highlighted as a risk period for the development of rheumatoid arthritis. Furthermore, breastfeeding after a first pregnancy poses the greatest risk (Barrett et al. 2000). Exposure to infection may act as a trigger for rheumatoid arthritis, and a number of agents have been implicated (for example, Epstein–Barr virus, parvovirus and some bacteria such as *Proteus* and *Mycoplasma*) (Silman and Pearson 2002). Some studies also confirm that sera from rheumatoid arthritis patients contain high titres of Epstein–Barr virus (EBV) antigens and of antibodies to latent and replicative EBV antigens (Tobón et al. 2010). Hence, sex hormones may seem to influence the disease condition.

The age at onset was identified as one of the epidemiological factors, which could help in the delineation of genetic heterogeneity of arthritides. According to American College of Radiology (ACR), juvenile rheumatoid arthritis is found to occur before 16 years of age whereas rheumatoid arthritis and osteoarthritis are usually reported to occur between 20-40 years (Grant et al. 2001; Simard et al. 2010) and 45-64 years (Brandt 2001; Ickinger and Tikly 2010) respectively. The observations reveal that juvenile rheumatoid arthritis occurs in first and second decade of life, while rheumatoid arthritis commonly occurs in third and fourth decade and osteoarthritis occurs in fifth and sixth decade of life. Some studies suggests that in juvenile arthritis early onset, mental disorders and childhood adversities are associated with increased risks of developing diverse physical diseases, including diabetes, heart disease, and asthma, as well as arthritis and other chronic pain conditions (Korff et al. 2009). Thus, the study could pinpoint that the three types of arthritides is found to be age related and can help in delineation of heterogeneity.

The present study, revealed an early age at onset in simplex families in juvenile rheumatoid arthritis and rheumatoid arthritis, while an early age at onset in multiplex families was observed in osteoarthritis highlighting a greater genetic predisposition in the aetiopathogenesis of the condition. The monozygotic twin concordance rates of juvenile idiopathic arthritis range between 25 percent and 40 percent, and the prevalence of juvenile idiopathic arthritis among siblings of probands is 15- to 30-fold greater than that of the general population (Prahalad and Glass 2008) The subtypes of juvenile idiopathic arthritis share genetic and phenotypic features with other autoimmune disorders, which are believed to result from the interplay of genetic and environmental factors (Sheila Han and Prahalad 2010). Arthritis is found to be clustered in families and was more concordant in monozygotic (30 percent) than dizygotic (5 percent) twins (Hemminki et al. 2009). An increased risk of rheumatoid arthritis was found in first degree relatives (Schur 1994) and second degree relatives (Grant et al. 2001) of the patients. Twin studies suggest rheumatoid arthritis is approximately 65 percent heritable (Raychaudhuri 2010). Patients with rheumatoid arthritis frequently have a positive family history of rheumatoid arthritis. In fact, several extended families with rheumatoid arthritis have

been reported and there are many affected sibling pairs with rheumatoid arthritis. The availability of such affected sibling pairs has been conducive to the performance of at least three genomewide scans of linkage in rheumatoid arthritis (MacKay et al. 2002). Although there are studies that report an increased prevalence of inflammatory arthritis among relatives of patients with juvenile rheumatoid arthritis a family history of inflammatory arthritis is less common in children, and extended multiplex pedigrees are extremely rare in juvenile rheumatoid arthritis (Prahalad and Glass 2002).

The disease also appeared to occur in a genetic background in which multiple common genetic risk factors are inherited, and family studies have supported the concept that multiple genes are important in rheumatoid arthritis. Twin studies in osteoarthritis has estimated that heritability of radiographic osteoarthritis at certain sites to range from 36 to 68 percent with a two fold increase of risk in first degree relatives and points to a multifactorial aetiology (Mustafa et al. 2000). Particular types of osteoarthritis, such as osteoarthritis occurring in early life, especially that of the fingers are known to run in families. Linkage studies on informative osteoarthritis families have revealed evidence of particular gene/s involvement. Though the molecular cause of osteoarthritis is still unknown, genetic, environmental, and metabolic and biochemical factors are thought to contribute to its pathogenesis (Moskowitz et al. 1992).

In our study with respect to parental consanguinity juvenile rheumatoid arthritis group did not seem to vary when compared to the juvenile control group, while parental consanguinity was found to be low in rheumatoid arthritis and osteoarthritis cases compared to the adult control group, suggesting the presence of common recessives in the population, so that inbreeding is not necessary to bring about homozygosity of the condition. A clearly higher familial risk in siblings than in offspring of affected parents would suggest that there is a contribution of recessive genetic effects or shared childhood environmental effects (Hemminki et al. 2009). Earlier data also suggests that parental consanguinity has no effect on disease severity and the frequency of consanguinity is not increased among the parents of patients with rheumatoid arthritis (Cefle et al. 2009). Analyses on familial segregation of arthritides with respect to parental phenotypes and parental consanguinity revealed indefinite multifactorial mode of inheritance. The risk to develop arthritis was found to be high, if there is a history of the disease in the patient's family, indicating an increased prevalence of inflammatory arthritis among relatives of patients with arthritides (Prahalad and Glass 2002). Some studies reported the first population- based segregation analysis of radiographic hand and knee of osteo arthritis patients and found evidence of a major recessive gene with residual multifactorial effects (Felson et al. 1998). Another study reported a segregational analysis of radiographic hand of osteoarthritis in the Russian federation and found a major gene effect with residual multifactorial component (Livshits et al. 2002). Further, in the present study, Penrose's relative frequency also confirmed the multifactorial mode of inheritance of the disease condition, which is in confirmation of earlier reports (Janet McDonagh 2001; Tobón et al. 2010; Ickinger and Tikly 2010). Therefore, the study indicates typical features of a complex genetic disease with interplay of both genetic and environmental factors.

Hence, our study could pinpoint that sex variation, age at onset and familial history as some of the epidemiological factors in the pathogenesis of arthritides. Further, arthritis is a complex genetic disorder found to follow multifactorial mode of inheritance with interplay of both genetic and environmental factors in the aetiopathogenesis of arthritides. Therefore identification of genetic factors associated with susceptibility/protection from autoimmune disease is essential as it could lead to our understanding of disease pathogenesis for better diagnosis.

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REFERENCES

Altman Roy D 1991. Criteria for classification of clinical osteoarthritis. *J Rheumatol*, 18(27): 10-12.

Arden Nigel, Nevitt Michael C 2006. Osteoarthritis: Epidemiology. *Best Practice and Research Clinical Rheumatology*, 20(1): 3-25

Arnett Frank C, Edworthy Steven M, Bloch Daniel A, McShane Dennis J, Fries James F, Cooper Norman S, Healey Louis A, Stephen R Kaplan, Liang Matthew H, Luthra Harvinder S, Medsger Jr Thomas A., Mitchell M Donald, Neustadt David H , Pinals Robert S, Schaller

Jane G, Sharp John T, Wilder Ronald L, Hunder Gene G 1988. The American Rheumatism Association 1987 revised criteria for the classification of RA. *Arthritis Rheum*, 31(3): 315-324.

Barrett JH, Brennan P, Fiddler M, Silman A 2000. Breast-feeding and postpartum relapse in women with rheumatoid and inflammatory arthritis. *Arthritis Rheum*, 43: 1010-1015.

Brandt Kenneth D 2001. Osteoarthritis. Harrison 15th edition. *Principles of Internal Medicine*, 2 (321): 1987-1994.

James Thomas Cassidy, Levinson JE, Bass JC, Baum J , Brewer EJ Jr, Fink CW, Hanson V, Jacobs JC, Masi AT, Schaller JG 1986. A study of classification criteria for a diagnosis of juvenile rheumatoid arthritis. *Arthritis Rheum*, 29: 274-281.

James Thomas Cassidy, Rose E Petty 2005. Chronic arthritis in childhood. In: JT Cassidy, RE Petty, RM Laxer, CB Lindsley (Eds.): *Textbook of Pediatric Rheumatology*, 5th Edition. Philadelphia: Elsevier Saunders, pp. 206-260.

Cefle K, Cefle A, Yazici A, Selek A 2009. The effect of parental consanguinity on the clinical and laboratory findings of rheumatoid arthritis. *Int J Clin Pract*, 63(7): 1056-1060.

Corti Maria Chiara , Rigon Chiara 2003. Epidemiology of osteoarthritis: Prevalence, risk factors and functional impact. *Aging Clinical and Experimental Research*, 15(5): 359-363.

Karen Davies, Stiehm ER, Woo P, Murray KJ 2001. Juvenile idiopathic polyarticular arthritis and IgA deficiency in the 22q11 deletion syndrome. *J Rheumatol*, 28(10): 2326-2334.

Fairweather DeLisa, Sylvia Frisancho-Kiss, Noel R Rose 2008. Sex differences in autoimmune disease from a pathological perspective. *American Journal of Pathology*, 173: 600-609.

Debbie Ehrmann Feldman, Sasha Bernatsky, Michelle Houde 2009. The incidence of juvenile rheumatoid arthritis in Quebec: A population data-based study. *Pediatric Rheumatology*, 7: 20.

Felson DT, Couropmitree NN, Chaisson CE, Hannan MT, Zhang Y, McAlindon TE, LaValley M, Levy D, Myers RH 1998. Evidence for a Mendelian gene in a segregation analysis of generalized radiographic osteoarthritis: The Framingham Study. *Arthritis Rheum*, 41: 1064–1071.

Fernández-Moreno Mercedes, Rego Ignacio, Carreira-Garcia Vanessa, Blanco Francisco J 2008. Genetics in Osteoarthritis. *Curr Genomics*, 9(8): 542–547.

Fischer RA 1934. The effect of methods of ascertainment upon the estimation of frequencies. *Ann Exgen Lond*, 6: 13-25.

Ghodke Yogita, Joshi Kalpana, Chopra Arvind, Patwardhan Bhushan 2005. HLA and Disease. *European Journal of Epidemiology*, 20(6): 475-488.

Goronzy Jörg J, Weyand Cornelia M 2009. Developments in the scientific understanding of rheumatoid arthritis. *Arthritis Research and Therapy*, 11: 249.

Grant Struan FA, Gudmar Thorleifsson, Michael L. Frigge, Jón Thorsteinsson, Brynja Gunnlaugsdóttir, Árni Jón Geirsson, Magnús Gudmundsson, Arnór Vikingsson, Kristján Erlendsson, Júlíus Valsson, Helgi Jónsson, Daniel F. Gudbjartsson, Kári Stefánsson, Jeffrey R. Gulcher, Kristján Steinsson 2001. The inheritance of rheumatoid arthritis in Iceland. *Arthritis Rheum*, 44: 2247-2254.

Sheila Angeles Han, Prahalad Sampath 2010. The Genetics of Juvenile Idiopathic Arthritis: What Is New in 2010? *Curr Rheumatol Rep*, 12: 87–93.

Hemminki Kari, Xinjun Li, Jan Sundquist, Kristina Sundquist 2009. Familial Associations of Rheumatoid Arthritis With Autoimmune Diseases and Related Conditions. *Arthritis and Rheumatism*, 60(3): 661–668.

Ickinger Claudia, Tikly M 2010. Current approach to diagnosis and management of osteoarthritis. *SA Fam Pract*, 52(5): 382-390.

Issa Sakeba N, Sharma Leena 2006. Epidemiology of osteoarthritis: An update. *Current Rheumatology Reports*, 8: 7-15.

Jirholt Johan, Lindqvist Anna-Karin B, Holmdahl Rikard 2001. The genetics of rheumatoid arthritis and the need for animal models to find and understand the underlying genes. *Arthritis Res*, 3: 87–97.

Ki Hwan Kim, Dong Soo Kim 2010. Juvenile idiopathic arthritis: Diagnosis and differential diagnosis. *Korean J Pediatr*, 53(11): 931-935.

Kochi Yuta 2010. Genetic background of tolerance breakdown in rheumatoid arthritis. *Japanese Journal of Clinical Immunology*, 33(2): 48-56.

Korff Michael Von, Jordi Alonso, Johan Ormel, Matthais Angermeyer, Ronny Bruffaerts, Clara Fleiz, Giovanni de Girolamo, Ronald C. Kessler, Viviane Kovess-Masfety, José Posada-Villa, Kate M. Scott, Hidenori Uda 2009. Childhood psychosocial stressors and adult onset arthritis: Broad spectrum risk factors and allostatic load. *Pain*, 143(1-2): 76–83.

Lang Thomas J 2004. Estrogen as an immunomodulator. *Clin Immunol*, 113: 224-230.

Lawrence C Reva,David T Felson, Charles G Helmick, Lesley M Arnold, Hyon Choi, Richard A Deyo, Sherine Gabriel, Rosemarie Hirsch, Marc C Hochberg, Gene G Hunder, Joanne M Jordan, Jeffrey N Katz, Hilal Maradit Kremers, Frederick Wolfe 2008. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*, 58: 26–35.

Livshits Gregory, Kalichman Leonid, Cohen Z, Kobyliansky E 2002. Mode of inheritance of hand osteoarthritis in ethnically homogeneous pedigrees. *Hum Biol*, 74: 849–860.

MacKay Kirsten, Eyre Stephen, Myerscough Anne, Milicic Anita, Barton Anne, Laval Steven, Barrett Jenny, Lee Dorothea, White Sarah, John Sally, Brown Matthew A, Bell John, Silman Alan, Ollier William, Wordsworth Paul, Worthington Jane 2002. Whole-genome linkage analysis of rheumatoid arthritis susceptibility loci in 252 affected sibling pairs in the United Kingdom. *Arthritis Rheum*, 46: 632-639

McDonagh Janet E 2001. Osteoporosis in juvenile idiopathic arthritis. *Curr Opin Rheumatol*, 13(5): 399-404.

Miterski Bianca, Drynda Susanne, Böschow Gundula, Klein Wolfram, Oppermann Joachim, Kekow Jörn, Epplen Jörg Thomas 2004. Complex genetic predisposition in adult and juvenile rheumatoid arthritis. *BMC Genetics*, 5: 2-2.

Moskowitz Roland W, Pun Y, Haqqi TM 1992. Genetics and osteoarthritis. *Bull Rheum Dis*, 41(1): 4-6.

Mustafa Zehra, Chapman Kay, Irven C, Carr AJ, Clipsham K, Chitnavis J, Sinsheimer JS, Bloomfield VA, Mc Cartney M, Cox O, Sykes B, Loughlin J 2000. Linkage analysis of candidate genes as susceptibility loci for

osteoarthritis-suggestive linkage of COL9A1 to female hip osteoarthritis. *Rheumatology,* 39: 299–306.

Oliver Jacqueline E, Silman Alan J 2009. Why are women predisposed to autoimmune rheumatic diseases? *Arthritis Research and Therapy*, 11: 252.

Prahalad Sampath, David N Glass 2002. Is juvenile rheumatoid arthritis/juvenile idiopathic arthritis different from rheumatoid arthritis? *Arthritis Res*, 4: 303-310.

Prahalad Sampath, David Glass N 2008. A comprehensive review of the genetics of juvenile idiopathic arthritis. *Pediatr Rheumatol Online J*, 6: 11.

Rak Justyna M, Maestroni L, Balandraud N, Guis S, Boudinet H, Guzian, MC, Yan Z, Azzouz D, Auger I, Roudier C, Martin M, Didelot R, Roudier J, Lambert NC 2008. Transfer of the shared epitope through microchimerism in women with rheumatoid arthritis. *Arthritis Rheum*, 60: 73-80.

Raychaudhuri Soumya 2010. Recent advances in the genetics of rheumatoid arthritis. *Current Opinion in Rheumatology*, 22(2): 109-118.

Roth Andrea Rubbert, Finckh Axel 2009. Treatment options in patients with rheumatoid arthritis failing initial TNF inhibitor therapy: a critical review. *Arthritis Research and Therapy,* 11(1): 1.

Samanta Ash, Jones A, Regan M, Wilson S, Doherty M 1993. Is osteoarthritis in women affected by hormonal changes or smoking? *Br J Rheumatol*, 32(5): 366-370.

Schur Peter H 1994. Arthritis and autoimmunity. *Arthritis and Rheumatism*, 37(12): 1818- 1823.

Silman Alan J 2001. Rheumatoid arthritis. In: AJ Silman, McHockberg (Eds.): *Epidemidogy of the Rheumatic Diseases.* 2nd Edition. Oxford: Oxford University Press, pp. 31-71.

Silman Alan J, Pearson Jacqueline E 2002. Epidemiology and genetics of rheumatoid arthritis. Supplement Review. *Arthritis Res*, 4 (3): S265-S272.

Simard Julia F, Costenbader Karen H, Hernán Miguel A, Liang Matthew H, Murray A Mittleman, Elizabeth Karlson W 2010. Early life factors and adult-onset rheumatoid arthritis. *J Rheumatol*, 37(1): 32–37.

Tengstrand Birgitta, Carlström Kjell, Felländer-Tsai Li, Hafström Ingiäld 2003. Abnormal levels of serum dehydroepiandrosterone, estrone, and estradiol in men with rheumatoid arthritis: high correlation between serum estradiol and current degree of inflammation. *J Rheumatol*, 30: 2338-2343.

Theodore P Pincus, Kavanaugh A, Sokka T 2004. Benefit/risk of therapies for rheumatoid arthritis: underestimation of the 'side effects' or risks of RA leads to underestimation of the benefit/risk of therapies. *Clin Exp Rheumatol*, 22(35): 2-11.

Tobón Gabriel J., Youinou Pierre, Saraux Alain 2010. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. *Autoimmunity Reviews*, 9: A288–A292.

Valdes Ana M, Spector Tim D 2010. The genetic epidemiology of osteoarthritis. *Curr Opin Rheumatol*, 22(2): 139-43.

Valdes Ana M, Spector Tim D 2011. Genetic epidemiology of hip and knee osteoarthritis. *Nature Reviews Rheumatology*, 7: 23-32.

Jennifer E Weiss, Norman T Ilowite 2007. Juvenile idiopathic arthritis. *Rheum Dis Clin North Am*, 33: 441-470.

Yannis Alamanos, Paraskevi V Voulgari, Alexandros A Drosos 2005. Rheumatoid arthritis in southern Europe: Epidemiological, clinical, radiological and genetic considerations. *Current Rheumatology Reviews*, 1(1): 33-36.

Zandman-Goddard Gisele, Peeva Elena, Shoenfeld Yehuda 2007. Gender and autoimmunity. *Autoimmunity Reviews*, 6 (6): 366-372.

Zhang Yuqing, Jordan Joanne M. 2010. Epidemiology of osteoarthritis. *Clinics in Geriatric Medicine*, 26(3): 355-369.