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Study of familial aggregation of autoimmune rheumatic diseases in Asian Indian patients with systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) and other autoimmune rheumatic diseases (AIRD) tend to co-aggregate in families, making positive familial history a risk factor. We aimed to estimate familial aggregation of AIRD in SLE patients and to compare between ones having a positive and negative family history of autoimmunity in our cohort. We included families of 157 consecutive SLE patients in a hospital-based, cross-sectional design for a three-generation pedigree study. Clinical and laboratory parameters of these patients were recorded. AIRD was seen in families of 39 SLE patients amounting to a familial prevalence of 24.8% [95% confidence interval (CI) 18.1, 31.6] with a relative risk (λ) of 4.3 for first-degree relatives (FDRs) and 1.1 for second-degree relatives (SDRs). SLE was the commonest AIRD seen in families of 19 patients with a familial prevalence of 12.1% (95% CI 7.0, 17.2) and λ of 78.2 for FDRs and 18.1 for SDRs. AIRD as a whole and SLE alone were seen more commonly with parental consanguinity ($p < 0.05$). Familial aggregation in SLE patients also showed a relatively higher percentage of affected males and lesser presentation with constitutional features ($p < 0.05$) than sporadic SLE patients. Rheumatoid arthritis (RA) was the second most common AIRD seen in 16/39 (41%) families with a RR of 3.1 in FDRs of SLE patients. In conclusion, Asian Indian SLE patients seem to have a high familial aggregation of AIRD, which is more pronounced in the background of parental consanguinity. SLE is the commonest AIRD seen amongst FDRs and SDRs of SLE patients, followed by RA, with FDRs being at highest risk.

Keywords SLE · Lupus · Autoimmune rheumatic disease · Familial lupus · Familial autoimmunity

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Introduction

Familial aggregation is described as clustering of certain traits, behaviours or disorders within a given family. Familial aggregation studies provide a unique framework for evaluating the epidemiology of a disease, assessing the phenotypic expression of a disease and such studies can identify disparities, if any. Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease. Genetic component plays a strong role in SLE pathogenesis, as confirmed by genome-wide association studies which have identified more than 30 susceptibility loci [1]. It is a commonly encountered clinical experience that autoimmune diseases (AID) are clustered in families. SLE tends to occur within families (10–12%), but without a clear pattern of mendelian inheritance [2, 3]. Moreover, SLE is known to co-aggregate with other autoimmune rheumatic diseases (AIRD) as reported in the literature [4, 5]. This could be attributed to the single-nucleotide polymorphisms described in studies and such associations are common to multiple AIDs [6].

Concordance rates for SLE are also higher for monozygotic (24–56%) than dizygotic twins (2–5%), which suggests an important role of genetic predisposition to SLE [7–10]. Proportion of the phenotypic heterogeneity justified by genetic factors, also known as heritability, is estimated to be 66% in SLE [11]. Monogenic SLE, which is being reported more in recent literature, is considered in a clinical scenario when a child less than 5 years (more so when < 2 years) presents with a lupus-like phenotype. Monogenic causes concern genes related to early complement deficiencies, nucleic acid repair (TREX1), clearance of self-antigen (DNASE1L3), DNA sensing (STING), apoptosis (FASL) and type I interferon (IFN) pathways [12]. All of the above evidence strengthens a strong genetic contribution to the pathogenesis of SLE.

Prevalence data of a disease is essential for the calculation of familial aggregation rates. The overall prevalence of SLE varies from 19 to 241 per 100,000 population as reported in different studies involving different geographic regions and ethnicities [13, 14]. There is a paucity of prevalence data on SLE and AIRD from India. Two studies providing some insight into the prevalence of SLE in India are quoted below. Three decades ago, the prevalence of SLE was studied in a single survey in rural north India and was reported to be 3.2 per 1,00,000; however, this data seems to be an under-representation of the actual prevalence as the diagnostic modalities have improved over the years [15]. Recent (2015) data from bone and joint disease (BJD) Community Oriented Program for Control of Rheumatic Diseases (COPCORD) survey in India showed a prevalence of SLE to be 0.02% [16].

Relative risk (RR or λ) of AIRD and SLE in relatives of SLE patients is ~ 1.5 and 5.8–16.9, respectively, which has been estimated from 2 pedigree studies and 2 large scale population studies till date [5, 17–19]. To the best of our knowledge, no familial aggregation studies in SLE have been done till date in Asian Indian population. As of today, we do not have any clear data on familial aggregation and transmission amongst Asian Indian patients with SLE. Our objectives were: (1) to find the prevalence of all AIRD including SLE in families of SLE patients (2) characterization of clinical and immunological profile of SLE patients with familial clustering of autoimmune diseases including SLE, in comparison with those without familial clustering. We also intended to estimate familial aggregation by calculating RR for the development of AIRD (including SLE) in families of SLE patients.

Methods

We studied, over a period of 1 year, families of 157 consecutive SLE patients satisfying the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria [20] and/or Updated American College of Rheumatology (ACR) 1997 criteria for SLE [21], in a tertiary care, teaching hospital-based, cross-sectional design. All SLE patients including paediatric onset ones, attending Rheumatology Clinics of the Department of Clinical Immunology and Rheumatology, Christian Medical College Hospital, Vellore in India between June 2015 and May 2016, were recruited after receiving their written informed consent.

The study was approved by the institutional review board and ethics committee (IRB no 9459, dated 5/6/2015) and carried out in accordance with guidelines of good clinical practice and Declaration of Helsinki.

Details of demography, clinical manifestations including organ involvement, disease activity score by SLE disease activity index (SLEDAI) [22] and medical treatment records were noted at the time of enrolment. A detailed three generation pedigree analysis was performed as described in Standardized Human Pedigree Nomenclature [23]. Detailed family history approach was used to gather data about all AIDs in family members of patients with SLE. Enquiry about AIDs included that for systemic autoimmune connective tissue diseases including SLE, rheumatoid arthritis (RA), mixed connective disease (MCTD), undifferentiated connective tissue disease (UCTD), primary sjogren's syndrome, polymyositis/dermatomyositis,systemic sclerosis (SSc), antiphospholipid syndrome (APS), vasculitic disorders and other inflammatory arthropathies like psoriatic arthritis and spondyloarthropathies, as well as, for organ based autoimmunity like hypothyroidism, pernicious anemia, myasthenia gravis, autoimmune hemolytic anemias and idiopathic thrombocytopenic purpura. We also

verified if the relatives of SLE patients with suspected AID, met the classification criteria for any defined AID whenever possible or sought a consensus agreement with the physician's diagnosis.

Confirmation of the diagnosis of AIRD in 20 relatives was done by evaluation of electronic medical records, as they were being treated in our hospital. In 17 other relatives, the diagnosis of AIRD was confirmed by telephonic conversation and electronic mail/electronic media based evaluation of their symptomatology, diagnostic and treatment records as they were diagnosed and treated elsewhere. In two relatives (posthumous), the diagnosis of AIRD was confirmed through the questioning of immediate family members and evaluation of the medical records via electronic mail/media based platform.

Calculation of familial aggregation

We used the pedigree approach for estimation of familial aggregation by calculation of RR (λ) with the help of formulae as below:

$$\text{RR [SLE]} = \frac{\text{prevalence of SLE in relatives of patients with SLE}}{\text{highest prevalence of SLE in general population}},$$

$$\text{RR [AIRD]} = \frac{\text{prevalence of AIRD in relatives of patients with SLE}}{\text{highest prevalence of AIRD in general population}}.$$

Statistical analysis

Sample size for the study was calculated based on findings of a study by Bengtsson et al. [24] from southern Sweden, where 53% of patients with SLE had a family history of AID. We calculated a sample size of 150 patients with SLE, allowing a precision between 7 and 10% with 95% confidence interval (CI). Statistical analysis was performed using SPSS version 16. The prevalence rate of AIRD as a whole and familial SLE was presented in percentage with 95% CI. The measurement data is expressed as mean (± standard deviation) or median (with inter-quartile range) based on the normality of distribution of values. Normality of distribution of numerical variables was verified with the Shapiro–Wilk test. We used independent sample *t* test to test for the difference in means between familial prevalence of AIRD/SLE and those with no AIRD/SLE. For non-normally distributed data, we used Wilcoxon rank sum test. To test the association between factors such as clinical features with the family history of autoimmune diseases, we used Chi square test or Fisher's exact *t* test.

Results

Demographics

Median age [inter-quartile range (IQR)] of the 157 SLE patients studied was 28 (15) years with a female to male ratio of 13:1 (139:18). Their median age at onset of symptoms was 23 (10.5) years and mean duration of illness prior to presentation to us was 43 (62) months. Parental consanguinity rate in our cohort was 5.6% (seen in 9 families). Geo-ethnic distribution of our patients was as follows: 74/157 (47.1%) patients recruited were from Southern India, 69/157 (43.9%) patients were from Eastern India, 11/157 (7%) from North-eastern India, 2 (1.3%) patients were from Western India and only 1 (0.7%) patient from Northern India. Baseline clinical and immunological parameters of the cohort have been shown in Table 1.

Familial aggregation of AIRD and SLE

Among the 157 families of SLE patients studied, AIRD was seen in 39 families with a familial prevalence of 24.8% (95% CI 18.1, 31.6) (Table 2). Twenty relatives in whom we confirmed AIRD diagnosis were being treated in our hospital. In 2 relatives who had expired and in 17 other relatives who were diagnosed and treated elsewhere, we sought consensus for diagnosis of AIRD via electronic communication with the affected relatives and/or treating physician opinion. Among the relatives of 157 SLE patients accounted, 767 were first degree relatives (FDRs) and 2488 were second-degree relatives (SDRs). RR (λ) for familial aggregation of AIRD for all relatives was 1.9; however, λ was 4.3 for FDRs and 1.1 for SDRs. Family history of SLE was seen in 19 families with a familial prevalence of 12.1% (95% CI 7.0, 17.2). RR for familial aggregation of SLE for all relatives was 32.2; again, λ was 78.2 for FDRs and 18.1 for SDRs. AIRD as a whole and SLE alone were seen more commonly with parental consanguinity ($p < 0.05$, Table 1) with no specific mendelian inheritance pattern. The most commonly affected relation was the patients' sibling as seen in 15 instances, followed by a parent or an aunt/uncle in 11 instances each (Table 2). Most prevalent co-existent organ-specific AID was auto-immune thyroid disease (AITD), predominantly hypothyroidism, seen in 43 (27.4%) families, which also co-existed in 27 (17.2%) SLE patients themselves. Familial aggregation in SLE patients was more pronounced in male patients and they had lesser constitutional features ($p < 0.05$) than patients without family history of SLE; otherwise, there was no significant difference in clinical or immunological parameters of patients with familial and those without familial aggregation of SLE (Tables 3; Supplementary Table 1).

Table 1 Baseline clinical characteristics of the 157 systemic lupus erythematosus patients in our cohort

Parameters	Values
Age (median with IQR) in years	28 (15)
Males: *n* (%)	18 (11.5)
Female: *n* (%)	139 (88.5)
Age at onset of symptoms in years (median with IQR)	23 (10.5)
Adult onset SLE: *n* (%)	34 (21.7)
Childhood onset SLE: *n* (%)	123 (78.3)
Duration of illness in months (median with IQR)	43(62)
Parental consanguinity: *n* (%)	9 (5.7)
Musculoskeletal features: *n* (%)	120 (76.4)
Muco-cutaneous involvement: *n* (%)	112 (71.4)
Renal involvement: *n* (%)	109(69.4)
Haematological features: *n* (%)	69 (43.9)
Constitutional features: *n* (%)	61 (38.9)
Central nervous system involvement: *n* (%)	31(19.7)
Peripheral nervous system involvement: *n* (%)	11 (7.0)
Serositis: *n* (%)	34 (21.7)
Cardio-pulmonary involvement: *n* (%)	14 (9)
Vasculitis: *n* (%)	16 (10.3)
Gastro-intestinal involvement: *n* (%)	10 (6.4)
Myositis: *n* (%)	9 (5.7)
Anti SSA positivity: *n* (%)	38/100 (34.5)
Anti SSB positivity: *n* (%)	14/105 (13.4)
Anti smith positivity: *n* (%)	9/27 (33.4)
Anti U1 RNP positivity: *n* (%)	34/60 (56.7)
LA positivity: *n* (%)	51/57 (32.5)
ACL positivity: *n* (%)	27/152 (17.8)
Baseline anti DS DNA titres in IU/ml (median with IQR) ($n = 106$)	393 (665)
Baseline SLEDAI at first presentation (median with IQR) ($n = 112$)	12(8)
Co-existing secondary APS: *n* (%)	26 (16.5%)
Coexistent organ-specific AID in the family: *n* (%)	46 (29.3)
Co-existent organ specific AID in SLE patients: *n* (%)	30 (19.1)

IQR inter-quartile range, *SLE* systemic lupus erythematosus, *U1RNP* U1 Ribonuclear protein, *LA* lupus anticoagulant, *ACL* anti-cardiolipin, *DS DNA* double stranded deoxyribonucleic acid, *SLEDAI* systemic lupus erythematosus disease activity index, *APS* antiphospholipid antibody syndrome, *AID* autoimmune disease

Table 2 Autoimmune diseases in relatives of systemic lupus erythematosus patients in our cohort, according to degree of familial relation

Disease	First degree relatives			Second degree relatives			Total relatives	Total SLE patients
	Parents	Offspring	Siblings	Grandparents	Maternal or paternal uncles/aunts	Nephews/nieces		
SLE	3	2	7	1	5	3	21	19
RA	4	0	4	2	4	2	16	16
Other AIRD[a]	4	0	4	2	2	2	14	9
AITD[b]	20	2	8	3	7	3	43	31
Other AID[c]	2	1	0	0	2	2	7	5

SLE systemic lupus erythematosus, *RA* rheumatoid arthritis, *AIRD* auto-immune rheumatic disease, *AITD* auto-immune thyroid disease

[a]Sjogren's syndrome, systemic sclerosis, undifferentiated arthritis, vasculitis , inflammatory myosits, psoriatic arthritis, mixed connective tissue disease, undifferentiated connective tissue disease, antiphospholipid antibody syndrome, spondyloarthritis ($n = 1$ each)

[b]Hypothyroidism ($n = 42$), Grave's disease ($n = 1$)

[c]Psoriasis ($n = 5$) , Vitilgo ($n = 1$) , Lichen planus ($n = 1$)

Table 3 Distribution of systemic lupus erythematosus patients in relation to demographical parameters and clinical features

Parameter	Positive family history of AIRD	No family history of AIRD	*p* value	Familial SLE patients	Sporadic SLE patients	*p* value
Males: *n* (%)	5/18 (27.8%)	13/118 (11%)	0.7	5/18 (27.8%)	13/139 (10.1%)	0.0
Female: *n* (%)	34/39 (87.2%)	105/118 (88.9%)	0.5	14/19 (73.7%)	125/138 (90.6%)	0.3
Age at onset in years (median with IQR)	23 (18)	23 (9)	0.8	24 (19)	23 (11)	0.1
Adult vs child onset SLE (*n*)	31 vs 9	92 vs 26	0.8	15 vs 4	108 vs 30	0.9
Parental consanguinity: *n* (%)	5/39 (12.8%)	4/118 (3.4%)	0.04	4/19 (21 %)	5/138 (3.6%)	0.01
Musculoskeletal features: *n* (%)	33/39 (84.6%)	87/118 (73.7%)	0.16	16/19 (84.2%)	104/138 (75.4%)	0.39
Muco-cutaneous involvement: *n* (%)	25/39 (64.1%)	87/118 (73.7%)	0.24	13/19 (68.4%)	99/138 (71.7%)	0.76
Renal involvement: *n* (%)	23/39 (59.0%)	86/118 (72.9%)	0.1	12/19 (63.2%)	97/138 (70.3%)	0.52
Haematological features: *n* (%)	15/39 (38.5%)	54/118 (45.8%)	0.42	7/19 (36.8%)	62/138 (44.9%)	0.5
Constitutional features: *n* (%)	11/39 (28.2%)	50/118 (42.4%)	0.11	3/19 (15.8%)	58/138 (42.0%)	0.02
Central nervous system involvement: *n* (%)	9/39 (23.1%)	22/118 (18.6%)	0.54	6/19 (31.6%)	25/138 (18.1%)	0.16

p value of < 0.05 considered significant

SLE systemic lupus erythematosus, *AIRD* auto-immune rheumatic disease, *SD* standard deviation, *IQR* inter-quartile range

RA was the second most common autoimmune disease aggregated in 16/39 (41%) families with a RR of 3.1 in FDRs of SLE patients. All other AIRDs like Sjogren's syndrome, SSc, MCTD, UCTD, undifferentiated inflammatory arthritis, inflammatory myositis, vasculitis, APS, spondyloarthritis and psoriatic arthritis were seen in 1 family each (Table 2). In six families, there were either multiple affected members or more than 1 AID in the same affected person (Table 4).

Discussion

Ours is the first study in the Asian Indian context to report on familial aggregation of SLE and other AIRDs in families of SLE patients. We used data from BJD India COPCORD 2015 study on prevalence of RA (0.34%), SLE and other connective tissue diseases (0.02%) and AIRD as a whole (0.84%), as the denominator for calculation of RR [16].

The familial prevalence rate of 25% for AIRD in our cohort of SLE patients, is in the mid-range of reported familial prevalence rates, least being 14.1% in Grupo Latino Americano de Estudio del lupus (GLADEL) cohort and highest being 53% in a Swedish study [5, 24]. The RR of 1.9 for familial aggregation of AIRD for all relatives was slightly higher than the observation in GLADEL cohort with RR of 1.5. SLE was the most common AIRD followed by RA in families of SLE patients, similar to what was observed in the GLADEL cohort [5].

The 12% familial prevalence of SLE in our cohort is similar to a Brazilian study (12.5%) [19], but is slightly higher than the 8.7% prevalence reported in the multinational Latin American GLADEL cohort [5]. However, certain regions such as Kuwait report a higher prevalence of 27.4% for familial SLE. It should be noted that the rate of consanguinity in our cohort was only 5.6% in comparison to 44% in the study from Kuwait [25]. The rate of consanguinity in our cohort is less than the average reported rate of consanguinity (16%) in India, but our study sample is truly not reflective of the general population and is also small in size [26]. RR for familial aggregation of SLE for all relatives in our cohort was 32.2; λ was 78.2 for FDRs and 18.1 for SDRs. In GLADEL cohort, highest RR (for SLE) amongst FDRs was 29 when an assumption of intermediate (0.01%) SLE prevalence rate in general population was made and RR (for SLE) was 58 when a low (0.05%) SLE prevalence rate in general population was assumed for calculation. RR (for SLE) amongst SDR was 19.5 for an intermediate population prevalence assumption for SLE and it was 39 when low population prevalence for SLE was assumed [5]. A higher RR for SLE in FDRs of SLE patients in our cohort could be truly due to higher familial recurrence rate owing to genetic factors or could be falsely high due to low prevalence data of SLE in general population reported by only a single study from our region [16]. These caveats could be a future topic of research from our region.

In a 2015 nation-wide population-based family study of 23,658,577 individuals registered under the Taiwan National

Table 4 Familial aggregation studies of all autoimmune diseases/systemic lupus erythematosus alone amongst systemic lupus erythematosus patients from various geographic regions

Authors	Year of publication	Type of study	Geographic region	Study population (*n*)	Findings
Sestak et al.	1999	Pedigree	Oklahoma, United States of America	8 SLE patients 51 relatives	15/51 (29%) blood relatives had autoantibodies 9/51 had AID (7 with SLE, 1 SS, 1 psoriasis)
Donato Alarco´n-Segovia et al.	2005	Pedigree	34 centres contributing to GLADEL cohort from 9 Latin American countries	1177 SLE patients from the GLADEL cohort	Relatives (*n*) with SLE—116 RA—79 AITD—23 SSc—3 PM—1 Other AID—16 RR (for sibling) for SLE—5.8–29.0 RA—3.2–5.3 RR (for sibling)—1.5 for all AID in general
Chang-Fu Kuo et al.	2015	Population based	Taiwan	*n* = 23,658,577 people registered in Taiwan National Health Insurance Research Database; 18,283 had SLE	RR (for SLE) in Siblings—23.7 Parents—11.4 Offspring—14 RRs (in FDR) for SS—5.9 SSc—5.4 MG—2.9 Myositis—2.8 RA—2.7 MS—2.6 Type 1 DM—1.7 IBD—1.4 Vasculitis—0.9
Constance Jensina Ulff-Møller et al.	2017	Population based	Denmark	*n* = 5,237,319 Danish residents registered in Civil Registration System; 3612 had SLE	HRs (for SLE) in FDRs—10.4 SDRs—3.6 HRs (for any AID) in FDRs—1.5 SDRs—1.3
Nailú Angélica Sinicato et al.	2019	Pedigree	Brazil	392 SLE patients; childhood onset disease-112 14,869 realtives FDRs—2574 SDRs—5490 TDRs—6805	RR (for SLE) in FDRs—19.4 SDRs—5.4 TDRs—3.0 Familial recurrence rates higher in childhood onset SLE patients
Current Study	2019	Pedigree	Vellore, India	157 SLE patients 3255 relatives FDRs—767 SDRs—2488	RR (for AIRD)—1.9 all relatives FDRs—4.3 SDRs—1.1 RR (for SLE)—32.2 all relatives FDRs—78.2 SDRs—18.1 RR (for RA) in FDRs- 3.1

SLE systemic lupus erythematosus, *AID* auto-immune disease, *SS* sjogren's syndrome, *GLADEL* Grupo Latino Americano de Estudio del lupus, *RA* rheumatoid arthritis, *AITD* auto-immune thyroid disease, *SSc* systemic sclerosis, *PM* polymyositis, *RR* relative risk, *MG* myasthenia gravis, *MS* multiple sclerosis, *DM* diabetes mellitus, *IBD* inflammatory bowel disease, *HR* hazard ratio, *FDR* first degree relative, *SDR* second degree relative, *TDR* third degree relative, *AIRD* auto-immune rheumatic disease

Health Insurance Research Database, RRs for SLE in FDRs of the patients ranged from 11.1 to 23.7 and for twins it was 315.9 [18]. In a Danish population-based study, a cohort of 5,237,319 Danish residents from Civil Registration System were followed up from 1977 to 2013. In that study, they observed that hazard ratios (HR) for SLE in FDRs of SLE patients was 10.3 and for SDR or third-degree relatives (TDR) of SLE patient was 3.6. HRs for any AID in FDRs was 1.5 and 1.3 in SDR or TDRs of SLE patients [17].

Both AIRD and SLE were seen to be significantly higher in the setting of parental consanguinity. As expected, RR for development of all AIRD as well as SLE alone, in families of SLE patients was higher in FDRs than SDRs, as patients share 50% of genes with FDRs as against only 25% of genes with SDRs.

It was further observed in our cohort, similar to multiple other studies, that the patients with family history of SLE did not differ from those patients without any family history of SLE, in any of the clinical parameters, except for higher percentage of affected males and lesser constitutional features ($p < 0.05$) in familial SLE patients. This observation was not reported in any other study till date. However, this finding needs further validation from larger studies. There was no difference in disease severity or serological parameters that were studied, between patients with positive and negative familial history of SLE (Supplementary Table 1). Hence, majority of published studies conclude that familial and sporadic SLE are clinically and immunologically similar for all practical purposes [25, 27–33]. In a juvenile SLE cohort from Sultanate of Oman, it was reported that familial SLE was associated with worse SLEDAI score at onset of diagnosis [32] and in a multi-ethnic cohort from Oklahoma, USA it was noted that white familial SLE patients had more arthritis when they studied for differences between familial and non-familial cases stratified by ethnicity [33]. It was reported in another study from Saudi Arabia, that familial cases of SLE were younger and had an earlier age at onset in comparison to sporadic cases [31].In a recent Brazilian pedigree study of 392 SLE patients with 112 being childhood onset cases, it was reported that familial recurrence rates of SLE was higher in childhood-onset SLE cases [19]; however, we did not observe similar results in our study.

RR for RA (3.1) in FDRs of SLE patients in our study was similar to other studies like GLADEL cohort and Taiwanese study [5, 18]. AITD, especially presenting as hypothyroidism, was the most prevalent (27%) non-rheumatic organ-specific AID in our cohort of patients, similar to the observation of GLADEL cohort [5], followed by psoriasis seen in 11%.

Ours was a hospital-based study with pedigree approach; however, a large scale population-based study would be best suited to evaluate our research question. Another limitation is the confirmation of AIRD diagnosis not being uniformly classification criteria based and in some of the relatives, it was confirmed with cross-sectional examination of their past medical records through e-mail/electronic media based platforms and telephonic interviews. Such limitations were present even in GLADEL cohort study and Taiwanese study [5, 18].

We also found that the familial aggregation rates were similar in Southern, Eastern and North-eastern parts of India (data not shown). However, our study was not powered to study regional differences within our country for familial aggregation rates, further limited by the paucity of recruitment of patients from Northern and Western parts of India. This is the first study from the Indian subcontinent in the last 3 decades providing vital data on familial aggregation of SLE and other AIDs in SLE. The information provided here also serves as the first step towards future genetic studies from our region on familial cases of auto-immunity to identify unique genetic signatures specific to our region, which may have role in immune pathogenesis of the disease.

Conclusion

In Asian Indian SLE patients, there is a high familial aggregation of AIRD, which is more pronounced in the background of parental consanguinity. SLE is the commonest AIRD seen amongst relatives of SLE patients followed by RA, with FDRs being at highest risk. Familial aggregation of SLE was more pronounced in male SLE patients in our cohort, which needs further validation. SLE patients with a familial history of AIRD (including SLE) showed significantly lesser constitutional symptoms in clinical presentation.

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Compliance with ethical standards

Conflict of interest The author(s) of the manuscript declare no conflict of interest.

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