ORIGINAL ARTICLE

Alterations in Humoral Immunity in Relatives of Patients With Common Variable Immunodeficiency

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Abstract

Background and objectives: It has been reported that there is a high prevalence of immunodeficiency and autoimmunity in relatives of patients with common variable immunodeficiency (CVID). The aim of this study was to determine the prevalence of immunoglobulin deficiency in relatives of patients with CVID in Iran, where there is a high rate of consanguineous marriage.
Methods: A descriptive study was undertaken in 64 family members of 23 unrelated CVID patients. The group contained 17 fathers, 18 mothers, 18 sisters, 9 brothers, and 2 children. Serum immunoglobulin levels were measured by nephelometry. Immunoglobulin (Ig) G subclass levels were measured in a subgroup of 36 individuals. Serum IgA levels were confirmed by enzyme-linked immunosorbent assay for subjects with suspected IgA deficiency.
Results: The rate of consanguineous marriage in families containing relatives with antibody deficiencies was significantly higher than in those families in whom relatives did not have immune deficiencies. IgA deficiency was observed in 2 relatives of patients with CVID. Also CVID was observed in 2 family members. In 3 fathers and 1 brother, IgM levels were lower than normal. Three relatives had IgG4 deficiency and 1 person had combined IgG4 and IgG2 deficiency. Twenty percent of the relatives had hypogammaglobulinemia (including IgA deficiency, CVID, decreased levels of IgM, and IgG subclass deficiencies).
Conclusion: In our study, alteration in humoral immunity in relatives of CVID patients was higher than previously reported, and this could be attributed to the high rate of consanguineous marriage in Iran. Since the family members of CVID patients are at high risk of hypogammaglobulinemia, it is advisable that they be evaluated for immunodeficiency disorders and monitored throughout their lifetimes.

Key words: Common variable immunodeficiency. Family members. Immunoglobulin deficiency.

Resumen

Antecedentes y objetivos: Se ha observado que existe una elevada prevalencia de inmunodeficiencia y autoinmunidad en familiares de pacientes con inmunodeficiencia variable común (IDVC). El objetivo de este estudio fue determinar la prevalencia de déficit de inmunoglobulina en familiares de pacientes con IDVC en Irán, donde existe un elevado índice de matrimonios consanguíneos.
Métodos: Se llevó a cabo un estudio descriptivo de 64 familiares de 23 pacientes con IDVC sin ninguna relación entre ellos. El grupo constaba de 17 padres, 18 madres, 18 hermanas, 9 hermanos y 2 hijos. Las concentraciones de inmunoglobulina sérica se midieron mediante nefelometría y se calcularon las concentraciones de subclases de inmunoglobulina (Ig) G en un subgrupo de 36 individuos. También se confirmaron las concentraciones de IgA sérica mediante enzimoinmunoanálisis de adsorción en los sujetos que se creía que podían presentar insuficiencia de IgA.
Resultados: El índice de matrimonios consanguíneos en familias en las que existen miembros con déficit de anticuerpos fue significativamente más elevado que en aquellas familias en las que ningún miembro presentaba insuficiencias inmunitarias. Se observó un déficit de IgA en dos familiares de pacientes con IDVC y también en dos miembros de la familia. En 3 padres y 1 hermano, las concentraciones de IgM fueron menores a las normales. Tres familiares presentaban un déficit de IgG4 y 1 persona presentaba déficit de IgG4 combinada con déficit de IgG2. El veinte por ciento de los familiares tenían hipogammaglobulinemia (con déficit de IgA, IDVC, reducción de las concentraciones de IgM y déficit de subclases de la IgG).

Conclusión: En nuestro estudio, la alteración de la inmunidad humoral en familiares de pacientes con IDVC fue más elevada de lo que se había observado previamente y esto se puede atribuir al elevado índice de matrimonios consanguíneos que se dan en Irán. Ya que los familiares de pacientes con IDVC presentan un elevado riesgo de padecer de hipogammaglobulinemia, es aconsejable que se sometan a revisiones sobre posibles trastornos relacionados con la inmunodeficiencia que puedan sufrir y a controles periódicos durante toda su vida.

Palabras clave: Inmunodeficiencia variable común. Familiares. Déficit de inmunoglobulina.

Introduction

Common variable immunodeficiency (CVID) is a primary immunodeficiency disorder that is diagnosed on the basis of decreased concentrations of immunoglobulins in all 3 classes and recurrent infections [1-3]. Apart from recurrent infections, gastrointestinal disorders and diseases with autoimmune features (eg, immune thrombocytopenic purpura and juvenile rheumatoid arthritis) are also common in CVID patients [4,5]. Early diagnosis and initiation of intravenous immunoglobulin therapy may be the most important factor in reducing the incidence of chronic pulmonary disease and severe complications in all patients with hypogammaglobulinemia [6,7]. Most cases of CVID are sporadic but occasional familial clustering has been described [7]. The increased prevalence of immune disorders in relatives of CVID patients and HLA-related genetic susceptibility have been reported in some studies [5,7-9]. Furthermore, selective immunoglobulin (Ig) A deficiency is another common immunodeficiency in white individuals [6]. Screening close relatives of patients with selective IgA deficiency and CVID for serum immunoglobulin levels identified alterations in immunity and antibody deficiency, and it was suggested that a positive family history of IgA deficiency or CVID could be the most significant risk factor for future development of immunodeficiency diseases [8].

Although some studies have analyzed HLA-related genetic susceptibility in immunodeficiency disorders and CVID, few have addressed the prevalence of hypogammaglobulinemia in relatives of CVID patients. The aim of this study was therefore to evaluate the prevalence of hypogammaglobulinemia in first-degree and second-degree relatives of CVID patients in order to determine whether the screening of CVID patients' family members may be useful in the diagnosis of occult immunodeficiency disorders. Given the high rate of consanguineous marriage in our population [10], the findings of our study could be of particular value in Iran and in other countries with a high rate of consanguineous marriage.

Materials and Methods

Study Population

A descriptive study was undertaken in 64 volunteers among first-degree and second-degree immediate relatives of 23 CVID patients (17 fathers, 18 mothers, 18 sisters, 9 brothers, and 2 children of patients).

Diagnosis of CVID

Patients were diagnosed based on clinical history and World Health Organization criteria (defective antibody formation usually accompanied by decreased serum IgG and IgA levels and generally but not invariably decreased IgM levels) [11,12]. For diagnosis of CVID, subjects were excluded if their baseline serum IgG level was known to be higher than 515 mg/dL or secondary causes of hypogammaglobulinemia were diagnosed. Also, in order to enter the study all patients must have had > 2% $CD19^+$ lymphocytes (B cells), as measured by flow cytometry, in order to rule out X-linked and autosomal agammaglobulinemia [1]. Transient hypogammaglobulinemia of infancy was also excluded. In all patients, the disease was controlled and they received intravenous immunoglobulin therapy at the Allergy and Immunology Clinic of the Children's Medical Center, University of Medical Sciences, Tehran. All patients and their relatives were older than 2 years of age.

Study Protocol

A questionnaire including demographic data on the families was completed for all 64 cases and blood samples were collected from the study group. Serum samples were stored at –20ºC and all tests were performed on the same day and under similar conditions. We evaluated hypogammaglobulinemia including selective IgA deficiency, IgG subclass deficiencies, and decreased levels of IgG, IgA, and IgM in family members.

Immunoglobulin Measurement

Nephelometry was used for quantitation of serum immunoglobulins (Minineph human Ig kit, Binding site Ltd, Birmingham, UK). Serum levels of immunoglobulins (IgM, IgG, and IgA) were said to be decreased when at least 2 SD below reference values for the subject's age.

Antibody Deficiencies

Selective IgA deficiency. Serum levels of IgA were measured by nephelometry and confirmed by enzyme-linked immunosorbent assay (ELISA). Finally, individuals with IgA concentrations below 5 mg/dL were classed as having selective IgA deficiency [1].

IgG subclass deficiency. Criteria for diagnosis was based on normal total serum IgG level with subnormal levels of 1 or more IgG subclasses [11]. Serum levels of IgG subgroups of 64 family members were measured by nephelometry in 36 volunteers.

Table. Immunoglobulin Profile of 10 Family Members With Abnormal Immunological Findings

Family Relatedness	Consanguineous Marriage Between Parents	Age, y	IgG[a]	IgM[a]	IgA[a]	IgG Subclasses[a]				Diagnosis
						IgG1	IgG2	IgG3	IgG4	
1. Sister	No	5	616 (463-1236)	89 (43-196)	4 (25-159)	405 (360-810)	107 (60-310)	14 (9-160)	104 39(9-160)	IgA Deficiency
2. Sister	Yes	13	772 (639-1527)	148 (56-352)	199 (70-312)	433 (280-1020)	229 (60-790)	98 (14-240)	7 (11-310)	IgG4 Deficiency
3. Sister	No	8	819 (633-1280)	104 (47-207)	94 (33-202)	320 (280-1740)	22 (80-550)	450 (22-320)	36 (10-170)	IgG2& IgG4 Deficiency
4. Child	Yes	14	879 (639-1527)	109 (56-352)	3 (70-312)	404 (280-1020)	302 (60-790)	70 (14-240)	100 (11-310)	IgA Deficiency
5.Father	No	33	1193 (631-1516)	30 (39-282)	359 (72-374)	526 (280-1020)	457 (60-790)	144 (14-240)	52 (11-310)	Low IgM
6. Father	Yes	34	1318 (631-1516)	34 (39-282)	123 (72-374)	855 (280-1020)	146 (60-790)	250 (14-240)	68 (11-310)	Low IgM
7. Father	Yes	48	1160 (631-1516)	34 (39-282)	220 (72-374)					Low IgM
8. Brother	Yes	18	1220 (631-1516)	20 (39-282)	140 (72-374)	350 (280-1020)	410 (60-790)	200 (14-240)	255 (11-310)	Low IgM
9. Mother	No	42	1349 (703-1503)	164 (48-289)	179 (69-388)	597 (280-1020)	570 (60-790)	165 (14-240)	17 (11-310)	IgG4 Deficiency
10. Mother	Yes	25	902 (703-1503)	126 (48-289)	144 (69-388)	402 (280-1020)	350 (60-790)	127 (14-240)	20 (11-310)	IgG4 Deficiency

Abbreviations: Ig, immunoglobulin

[a] Normal ranges for immunoglobulin concentrations are shown in parentheses in mg/dL. Ranges for children (younger than 18 years old) and normal ranges for IgG suclasses were taken from Ochs et al,[1] and normal ranges for immunoglobulin levels in adults (> 18 years old) were taken from Kardar et al[14]

Consanguineous Marriage

A consanguineous marriage was defined as one in which 2 partners have at least 1 ancestor in common, with the ancestor being no more distant than a great-great grandparent [13]. In our study, consanguineous marriages were classified by the degree of relatedness between couples: first cousins, second cousins, and beyond second cousins. First cousins may either be the children of 2 brothers, of 2 sisters, or of a brother and a sister [10].

Statistical Analysis

Results were shown as mean (SD). The Fischer exact test was used for analysis of qualitative data and the independent *t* test was used for comparison of the means of IgM levels in male and female subjects. Statistical analysis was performed with SPSS 14 for Windows. *P* values less than .05 were considered statistically significant.

Ethical Approval

All subjects provided informed consent to inclusion in the study. The study was approved by the Ethics Committee of the Medical Research Center of Tehran University of Medical Sciences.

Results

Characteristics of Family Members

Sixty-four family members of 23 CVID patients—including 26 males (40.6%) and 38 females (59.4%)—were included in the study over the period of 2005 to 2006. The mean (SD) age of the study population (family members) was 28.2 (14.7) years. Family members included 17 fathers (26.6%), 18 mothers (28.1%), 18 sisters (28.1%), 9 brothers (14.1%), and 2 children (3.1%).

Consanguineous Marriage

The overall rate of consanguineous marriage among parents of CVID patients was 65%. According to the classification of consanguineous marriages, first-cousin marriages were found in the parents of 10 patients (43%) and second-cousin marriages and beyond were identified in the parents of 5 patients (22%).

Families in which deficiencies in humoral immunity were identified in relatives were consanguineous in 6 out of 10 cases, while consanguinity in those families without evidence of abnormal humoral immunity was found in 9 out of 26 cases. This difference was statistically significant ($P < .05$).

History of Immunodeficiency Diseases in Family Members

Thirty family members (47%) had a history of recurrent respiratory infections (pneumonia, chronic sinusitis, etc) but unfortunately we could not specify the nature of the infection as their medical records were not accessible. Evaluating family history of patients revealed that 2 family members of a brother and sister (3.1% of family members) with a documented diagnosis of CVID had died due to recurrent bacterial infections without any definitive diagnosis.

Immunoglobulin Levels

Mean serum immunoglobulin concentrations in family members were grouped by age, sex and family relations in 4 groups: fathers, mothers, sisters, brothers, and children. The mean level of IgM in female subjects was significantly higher than in males ($P = .004$). IgM levels were low in 3 fathers and 1 brother (Table).

IgA Deficiency

A diagnosis of IgA deficiency was made in 2 subjects (4 mg/dL in a 5-year-old sister and 3 mg/dL in a 14-year-old child) (Table). All of these subjects were asymptomatic according to their history and medical records. IgG serum levels in all family members were within the normal range according to reference values [1,14].

There was no association between serum levels of immunoglobulin and parents' sib-ships, nor was there an association between IgA deficiency and parental relatedness.

Analysis of the family history of patients revealed that a father of a patient had CVID and there were 2 cases with definitive diagnosis of CVID among remote relatives of the patients.

IgG Subclass Deficiencies

We randomly selected 39 subjects (24 female [61.5%] and 15 male [38.5%]) from the study population of 64 relatives and measured their serum levels of IgG subgroups. The mean age of this group was 25.1 years (range, 4-55 years). Consanguineous marriage was identified in the parents of 16 of the 39 subjects (41%).

According to levels of IgG subclasses in sera from normal subjects of a similar age, the level of IgG4 was lower than normal in 3 subjects (2 mothers and 1 sister). One sister had IgG2 and IgG4 deficiencies (Table).

Discussion

The aim of this study was to evaluate humoral immunity in family members of CVID patients by determining serum immunoglobulin concentrations. The frequency of hypogammaglobulinemia (including IgA deficiency, CVID, decreased levels of IgM, and IgG subclass deficiencies) was estimated at 20%. Therefore, in view of the gradual progression of the disease in family members of affected patients [7], relatives with abnormal serum immunoglobulin levels may be at risk of developing overt CVID in the future.

In our study, we assessed the associations between serum immunoglobulin levels and sex, as well as with family relations. In general, the mean level of IgM in females was significantly higher than in males ($P = .004$), consistent with the results of other studies [14-16]. The most common alteration in humoral immunity was detected in the serum level of IgM in 3 fathers and a brother. The high rate of IgM deficiency observed in our study will merit further investigation to assess the possibility of genetic susceptibility in family members of CVID patients.

The overall rate of infection in CVID relatives in our study was higher than would be expected in the healthy population; however, we were unable to specify the type of these infections (pneumonia, sinusitis, etc) as medical records of most of these family members were not accessible. The nature and cause of these infections should be addressed in future studies.

Serum concentrations of IgA were lower than normal in 2 female relatives (a child and a sister). The prevalence of selective IgA deficiency in our study was 1/32, which is notably higher than the prevalence reported among the general population (1/600) [1,17]. The high incidence of IgA deficiency among relatives of patients with CVID in our study is comparable to that reported in other studies [5,18]. In some studies it was shown that approximately 20% of patients with CVID had a first-degree relative with selective IgA deficiency [19].

In our study, all IgA-deficient relatives were asymptomatic. In fact, many patients with selective IgA deficiency have no apparent disease [2]. Even though most cases of IgA deficiency and CVID occur sporadically, familial clustering is not uncommon and the 2 disorders can occur in members of the same family. In fact, these heterogeneous disease entities are not always clearly separable. Thus, IgA-deficient individuals may also be deficient in 1 or more IgG subclasses. The familial predisposition to IgA deficiency and CVID suggests that genetic factors influence disease susceptibility [5,18].

Positive associations with 3 HLA DR-DQ haplotypes as well as a strong negative association with DRw15, DQw6, and Dw2 have previously been described in IgA-deficient patients. The same associations were found in CVID patients, although the associations were slightly weaker [5]. A variety of HLA class I, II, and III alleles and haplotypes have been reported to be associated with CVID in different ethnic populations [5,18,20,21]. In a study by Amanzadeh et al [20] the association between HLA antigens and CVID was investigated in Iranian patients. In that study, of the HLA class I antigens A2 and A33 were significantly increased in their patients. Also, the HLA1 and, particularly, HLA-B8 antigens have frequently been reported to be increased in CVID patients from other ethnic backgrounds [18,21,22].

In 1995, Vorechovsky et al [8] screened close relatives of Swedish patients with selective IgA deficiency and CVID for serum immunoglobulin levels and identified positive family history of IgA deficiency and CVID as the most significant risk factor for developing the disease. The relative risk for siblings of patients with IgA deficiency was estimated to be approximately 50. In 12 out of 34 Swedish multiplex families identified in that study, both IgA deficiency and CVID occurred, usually CVID in the parental generation and IgA deficiency in the subsequent generation. In another study by Vorechovsky et al [9], the occurrence of cancer, immunodeficiency, and diseases with possible autoimmune etiology was studied in 355 blood relatives of 12 patients with CVID. Immunologic examinations of 30 first-degree relatives of CVID patients revealed 3 children (2 boys and 1 girl) with selective IgA deficiency, in 1 boy combined with elevated serum IgE levels. In that study, 4 relatives with rheumatoid heart disease, 12 cases of gastric or duodenal ulcer, and 14 relatives with thyroid disease represented the most often encountered diagnosis with a possible autoimmune component in their etiology.

In some previous studies, differential parent-of-origin penetrance in the offspring of IgA-deficient patients was demonstrated [23]. Some researchers had noticed a higher number of affected children born to mothers with IgA deficiency, compared with the number of affected children born to affected fathers [8,21]. The inheritance pattern of IgA deficiency and CVID, with a predominance of maternal transmission and different intrafamilial phenotypic manifestations, is reminiscent of that of mitochondrial defects [23]. In our study, the absence of any affected mothers made it impossible for us to evaluate this hypothesis. However; some kind of familial IgA deficiency and CVID inheritance were noticed in the studies mentioned [8,9,18,21].

In conclusion, the 20% probability of hypogammaglobulinemia estimated in our study in relatives of patients with CVID is markedly higher than in the general population, indicating that relatives of patients with CVID may be at risk of gradual progression of immune diseases and eventual development of overt CVID or other immune disorders. It may therefore be appropriate to screen family members of CVID patients for immune disorders. We nevertheless acknowledge certain limitations in our study. We could not evaluate specific antibody responses via antistreptolysin O, anti-diphtheria toxin antibodies, total protein test, etc, in family members due to technical difficulties at the time of study. Also, blood was only drawn for measurement of IgG subclasses in 36 volunteers from among the family members. We also did not have access to medical data of family members in previous generations of CVID parents, so pedigrees could not be given for those families in which relatives of CVID patients showed signs of humoral deficiency. Further studies are recommended to evaluate immunodeficiency disorders, including humoral, cellular, and phagocytic immunodeficiency, in family members of patients with CVID.

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References

1. Ochs HD, Stiehm RE, Winkelstein JA. Immunodeficiency disorders: general considerations. In: Stiehm RE, Ochs HD, Winkelstein JA, editors. Immunologic Disorders in Infants & Children. 5th ed. Philadelphia: Elsevier Press; 2004. p 289-307.
2. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R,

Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A. Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: Update from the Iranian primary immunodeficiency registry. J Clin Immunol. 2006; 26:519-32.
3. Cunningham-Rumdles C, Bodien C. Common variable immunodeficiency. Clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34-8.
4. Aghamohammadi A, Farhoudi A, Moin M, Rezaei N, Kouhi A, Pourpak Z, Yaseri N, Movahedi M, Gharagozlou M, Zandieh F, Yazadni F, Arshi S, Mohammadzadeh I, Ghazi BM, Mahmoudi M, Tahaei S, Isaeian A. Clinical and immunological features of 65 patients with common variable immunodeficiency. Clin Diagn Lab Immunol. 2005;12:825-32.
5. Olerup O, Smith CI, Bjorkander J, Hammarstrom L. Shared HLA class II - associated genetic susceptibility and resistance, related to the HLA - DQB1 gene, in IgA deficiency and common variable immunodeficiency. Proc Natl Acad Sci USA. 1992;89:10653-7
6. Burrows PD, Cooper MD. IgA deficiency. Adv Immunol. 1997;65:245-76.
7. Nijenhuis T, klasen I, Weemaes CM, Preijers F, de Vries E, van der Meer JW. Common variable immunodeficiency in a family: an autosomal dominant mode of inheritance. Neth J Med. 2001;59:134-9 .
8. Vorechovsky I, Zetterquist H, Paganelli R, Koskinen S, Webster AD, Bjorkander J, Smith CI, Hammarstrom L. Family and linkage study of selective IgA deficiency and common variable immunodeficiency. Clin Immunol Immunopathol. 1995;77:185-92.
9. Vorechovsky I, litzman J, Lokaj J, Sobotkova R. family studies in common variable immunodeficiency. J Hyg Epidemiol Microbiol Immunol. 1991;35:17-26.
10. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, Mirsaeid Ghazi B, Atarod L, Abolmaali K, Mahmoudi M, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Amin R, Kashef S, Hosseini RF, Mohammadzadeh I, Shabestari MS, Nabavi M, Moin M. Consanguinity in primary immunodeficiency disorders; the report from Iranian primary immunodeficiency registry. Am J Reprod Immunol 2006;56:145-51.
11. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R, Geha R. International Union of Immunological Societies Primary Immunodeficiency diseases classification committee. Primary immunodeficiency diseases: An update. J Allergy Clin Immunol. 2004;114:677-87.
12. Chapel H, Geha R, Rosen F. Primary immunodeficiency disease: an update. Clin Exp Immunol. 2003;132:9-15
13. Hafez M, El-Tahan H, Awadalla M, El-Khayat H, Abdel-Gafar A, Ghoneim M. Consanguineous matings in the Egyptian population. J Med Genet. 1983;20:58-60.
14. Kardar GA, Shams SH, Pourpak Z, Moin M. Normal value of immunoglobulins IgA, IgG and IgM in Iranian healthy adults, measured by nephelometry. J Immunoassay Immunochem. 2003;24:359-67.
15. Hatagima A, Cabello PH, Krieger H. Causal analysis of variability of IgA, IgG and IgM immunoglobulin levels. Hum Biol. 1999; 71:219-29.
16. Kacprazak-Bergman I. Sexual dimorphism of heritability of immunoglobulin levels. Ann human Biol. 1994;21:563-9.
17. Buckly RH. Common variable immunodeficiency. In: Behran RE , Kliegman RM, Jenosn HB, editors. Nelson textbook of pediatrics. 17th ed. Philadelphia: Elsevier Press; 2004. p 690-6.
18. Volankis JE, Zhu ZB, Schaffer FM, Macon KJ, Palermos J, Barger BO. Major Histocompatibility Complex Class III genes and susceptibility to immunoglobulin A deficiency and common variable immunodeficiency. J Clin Invest. 1992;89:1914-22.
19. Common variable immunodeficiency No.870, September 2002. Updated 2007 [cited 2007 Dec 5]. Available from: http://www.emedicien.com/derm/topic870.htm.
20. Amanzadeh A, Shokrgozar MA, Samadi Bahrami Z, Aghamohammadi A, Shokri F. Frequency analysis of HLA antigens in Iranian patients with common variable immunodeficiency. Arch Iranian Med .2003;6:16-22.
21. Schroeder HW Jr, Zhu ZB, March RE, Campbell RD, Berney SM, Nedospasov SA, Turetskaya RL, Atkinson TP, Go RC, Cooper MD, Volanakis JE. Susceptibility locus for IgA deficiency and common variable immunodeficiency in the HLA-DR3, B8 and A1 haplotypes. Mol Med 1998;4:72-86.
22. Johnson ML, Keeton LG, Zhu ZB, Volanakis JE, Cooper MD, Schroeder HWJR . Age related changes in serum immunoglobulins in patients with familial IgA deficiency and common variable immunodeficiency (CVID). Clin Exp Immunol. 1997;108:477-83.
23. Verechovsky I, Webster ADB, Plebani A, Hammarstrom L. Genetic Linkage of IgA deficiency to the major histocompatibility complex, evidence for allele segregation distortion, Parent of origin penetrance differences, and the role of anti IgA antibody in disease predisposition. Am J Hum Genet. 1999; 64: 1096-109.

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