

Unmet Needs

The main autoimmune disorders in the Middle Eastern and North African (MENA) region include psoriasis, multiple sclerosis, Type 1 diabetes, inflammatory bowel disease (IBD) and rheumatoid arthritis. As these disorders continue to take lives, the importance of conducting clinical trials regionally cannot be underestimated.

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When exposed to pathogenic challenges such as bacteria, virus or parasites, the immune system acts as the body's defence mechanism. The immune system consists of two major arms: the innate or natural immune system, which provides an immediate first line defence that is given at birth, recognises patterns of molecules on pathogens but cannot be enhanced; and the adaptive/acquired immune system, which is slower to react, recognises specific molecular markers or antigens on pathogens, and becomes stronger with repeated infections or immunisations. The immune system normally distinguishes between 'self' and 'foreign'; however, autoimmune diseases

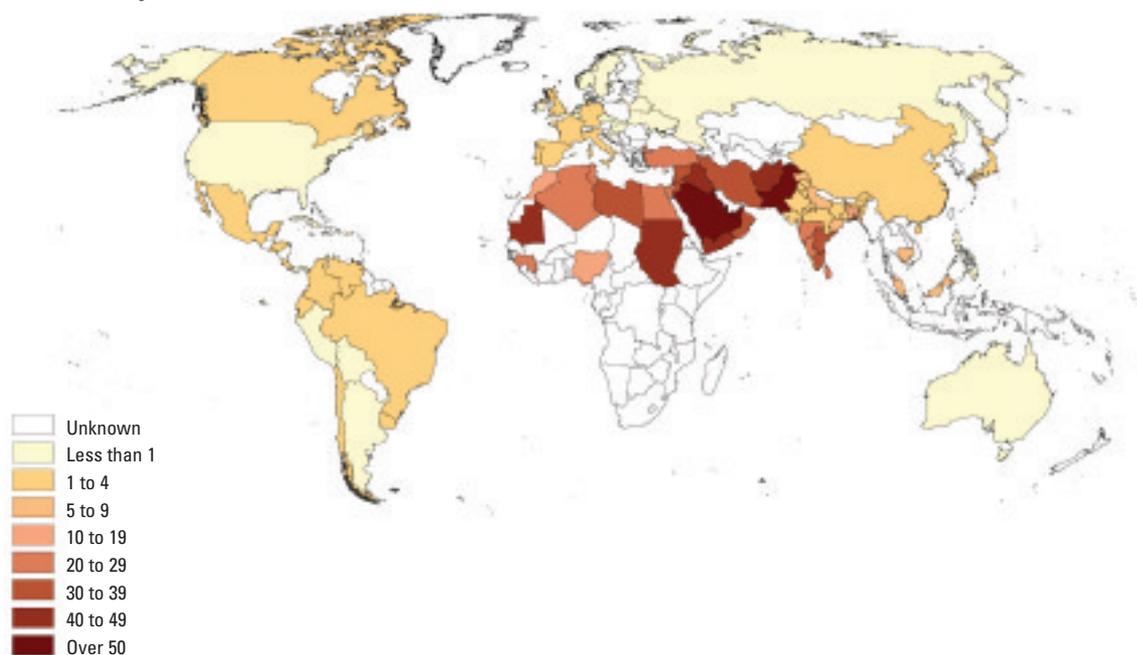
occur when healthy tissue is mistakenly identified as foreign and attacked. Autoimmune disorders represent a huge economic burden worldwide.

Genetic Interlink with Autoimmune Disorders

Genome-wide association studies (GWAS) have revealed various genetic risk factors in autoimmune disease development. MJH Coenen *et al* have demonstrated that several of the associated genes and underlying pathways associated with various autoimmune diseases, such as rheumatoid arthritis (RA) and coeliac

disease (CD), are common (1). The results of this study showed that the two chromosomal regions 4q27 and 6q23.3 are shared between RA and CD. This study also showed that chromosome 4q27 which contains the interleukin IL-2 and IL-21 genes has also been associated with psoriatic arthritis, Grave's disease and Type 1 diabetes. Furthermore, the 6q23.3 locus containing the OLIG3 and TNFAIP3 genes has also been associated with systemic lupus erythematosus and Type 1 diabetes. These results strongly suggest that overlapping genetic mechanisms underlie the development of multiple autoimmune disorders (1).

Figure 1: Consanguineous marriages (%).
Over 20 to 50 per cent in MENA region
Source: www.consang.net



It is therefore important to gain an understanding of these shared genes as they could contribute to the susceptibility of additional autoimmune diseases. Genetic profiles of different regions may vary, and hence it is imperative to conduct regional clinical research to better understand the ethnic and racial factors that contribute to autoimmune pathogenesis, as well as the response to drugs used for the treatment of autoimmune disorders – in other words, pharmacogenomics.

Consanguineous Marriages in the MENA Region

Consanguinity (related by blood) includes marriage between persons biologically related as cousins or closer. As estimated by www.consang.net, 20 to 50 per cent of the incidence of these in the world is in the MENA region (see Figure 1). Consanguinity is a deeply rooted cultural trend that is widely followed in the MENA region. There is a general belief that marrying within the family reduces the possibilities of hidden health challenges and financial uncertainties by keeping the wealth within the family. However, many studies have shown a positive association between parental consanguinity and birth defects in the offspring.

Healthy unrelated parents have an estimated chance of two to four per cent of having a child with a genetic disease, developmental problem or congenital defect. In contrast, in consanguineous marriages the risk is five to seven per cent, depending on the degree of the relationship between the parents and their ethnicity (2).

Rheumatoid Arthritis

Studies conducted in Lebanon have shown that rheumatoid arthritis (RA) severity in Lebanese patients is comparable to that reported in western populations; however, functional status differs, possibly reflecting cultural differences (3). L Kalouche Khalil *et al*, have demonstrated the milder nature of the disease in eastern Mediterranean countries in comparison with northern Europe. This study in Lebanese patients

Figure 2: Clinical trial status in Gulf Cooperation Council countries for autoimmune disorders

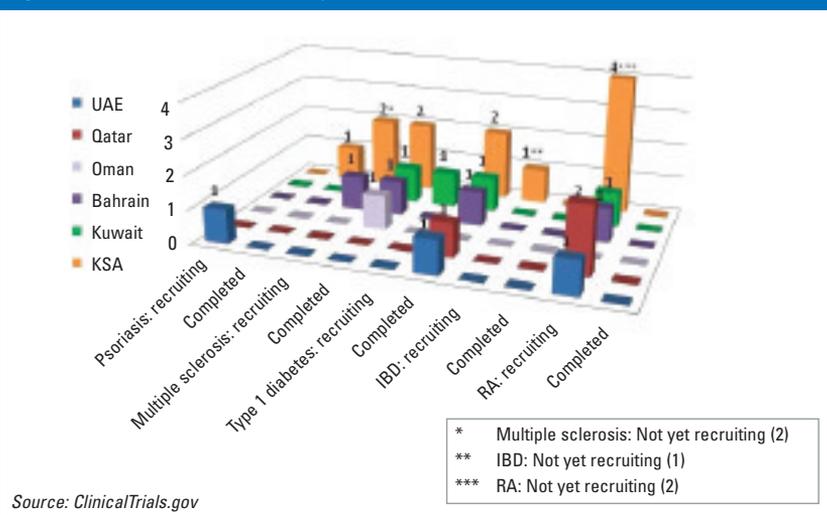
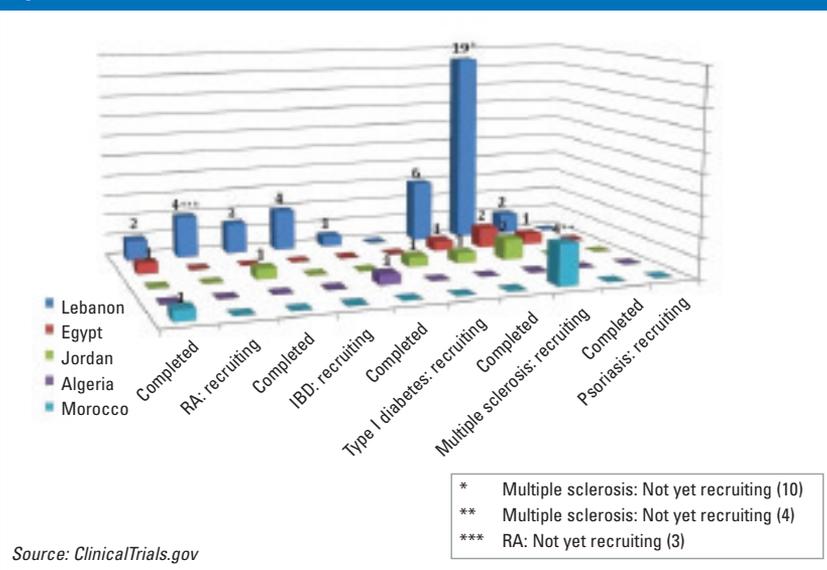


Figure 3: Clinical trial status in Levant and North African countries for autoimmune disorders



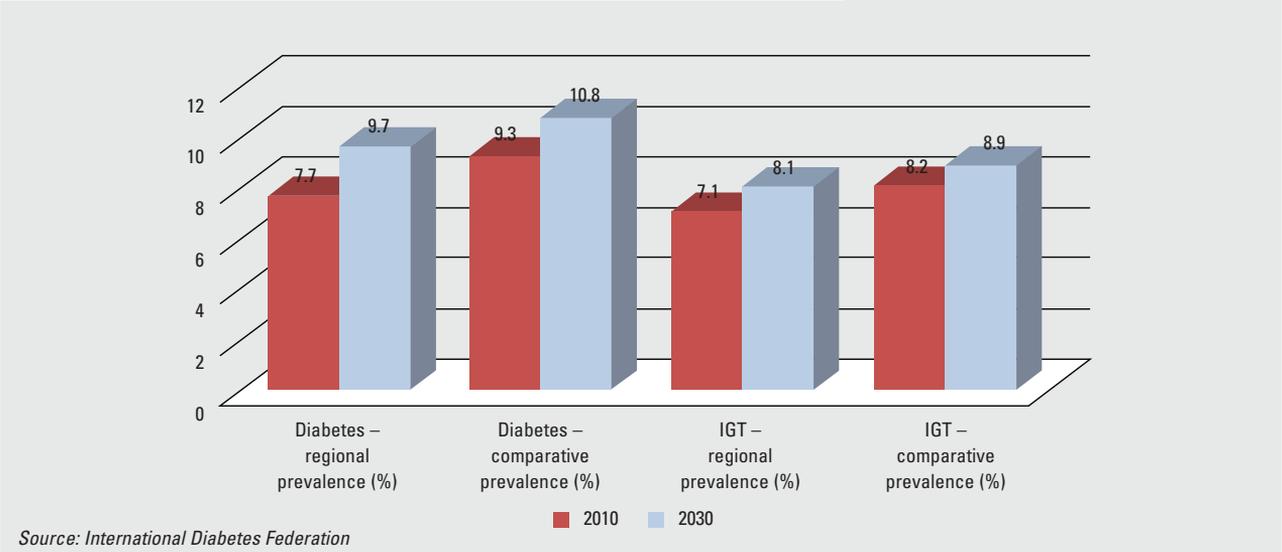
with RA reported that disease severity was less and there were fewer extra articular manifestations in Mediterranean countries than in other geographical areas (4). In agreement with these findings is the report from a study conducted in the United Arab Emirates, where most Arab patients with RA tended to have non-aggressive and non-disabling disease. The authors reported a marked lack of non-articular manifestations with insignificant functional incapacity (5).

Attar SM *et al* reported on the frequency of radiological changes of the hands and the feet in a well-defined hospital population of patients with RA in

Jeddah, Saudi Arabia. The authors indicated that the proportion of patients with erosions is lower than data reported from western European and North American populations but higher than previous information from the central region of Saudi Arabia (6).

A histocompatibility study in 85 Arab patients in Kuwait with classical and definite RA (HLA – A, B, C, and DR) showed a significant increase in the frequency of HLA-A10, B8, B21, and DR3 antigens when compared to an age and sex-matched control population. HLA-DR3 was present in 34 per cent of the patients compared with two per cent of the controls (p is more than 0.001). The

Figure 4: Diabetes and impaired glucose tolerance (IGT)



study reported an association of RA in the Arab population with HLA-DR3 rather than HLA-DR4 or HLA-DR1 as shown for other ethnic groups (7).

Genetic influences can modulate the radiological severity of RA. An understanding of the genetics of clinical responsiveness and ethnic differences has the potential to improve safety, tolerability and cost-effectiveness, especially in the light of the growing number of biological agents now undergoing clinical trials.

Psoriasis

In Egypt, high rates of hepatitis C virus (HCV) infection have been observed in all age groups, indicating an ongoing high risk. Egypt has a population of 62 million and contains the highest prevalence of hepatitis C in the world. The national prevalence rate of HCV antibody positivity has been estimated to be between 10 and 13 per cent of the entire population (8).

The dermatological manifestations associated with chronic HCV infection and their association with liver status were assessed in 155 Egyptian patients. This demonstrated that 71 (45.8 per cent) had dermatological conditions, and of these, psoriasis was noted in 1.9 per cent of the subjects (9). The management of patients with psoriasis

and concomitant HCV infection is often difficult because treatments for HCV, such as recombinant interferon-α and ribavirin, can trigger or exacerbate psoriasis and psoriatic arthritis. In addition, most systemic therapies for psoriasis, including immunosuppressants (cyclosporine) and other potentially hepatotoxic drugs (acitretin and methotrexate), are relatively contraindicated in HCV infection (10). Given the severity of skin involvement and the contraindications for the use of other systemic drugs in association with HCV infection, the treatment selected should be well-tolerated with minimal adverse effects. Hence it is important to study the safety profile of the drugs in a local population.

Studies conducted to evaluate the co-morbidities associated with psoriasis in Kuwait showed that patients with psoriasis had a higher risk of inflammatory arthritis, coronary heart disease, obesity, diabetes mellitus 2, hypertension, dyslipidaemia, and metabolic syndrome. The patients were receiving significantly wider varieties of drugs including anti-diabetic drugs, anti-hypertensives, and hypolipidaemic drugs. An unexpected finding has also been reported in the Kuwaiti population in that significantly higher levels of B-cells infiltrated the psoriatic lesions and they numerically exceeded the T lymphocyte infiltrate. This has previously

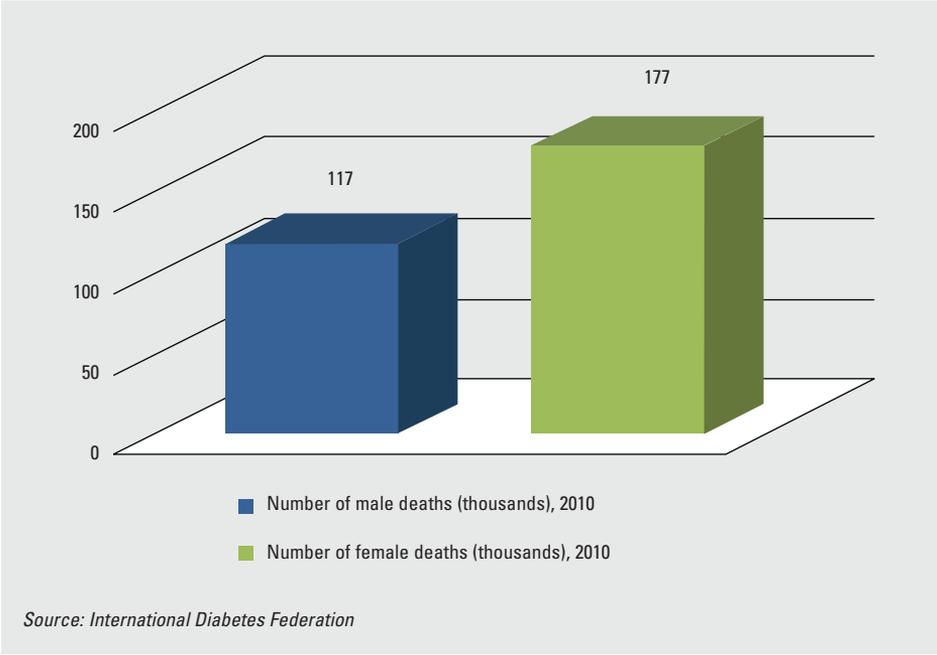
been reported only in cases of psoriasis with concurrent arthritis. None of the subjects had arthritis, suggesting an immunopathological variant of psoriasis possibly specific to this population group (11). The prevalence of psoriasis amongst the paediatric population is four per cent, which is higher than reported in other ethnic groups (12).

Multiple Sclerosis

Currently a number of clinical trials studying multiple sclerosis (MS) are ongoing in the MENA region as the prevalence of MS among Arabs has a wide reported range. A group of MS experts in the Middle East also met to develop recommendations for the routine assessment of quality of life in patients with MS. This approach should allow long-term monitoring of the key features of MS that are important to the patient’s well-being and aid decision-making regarding their management, including the use of disease-modifying drugs.

Data on MS is available for the Kuwaiti, Jordanian, Libyan, Saudi, Iraqi, Palestinian and Omani populations. The clinical pattern of MS is similar to that in western countries; however, one study from Oman found a high rate of optic-spinal disease (affecting one third of patients) and a low rate of oligoclonal bands (only one third of patients). This

Figure 5: Diabetes mortality across the MENA region



commonly in juveniles. Unlike people with Type 2 DM, those with T1DM are generally not obese and may present initially with diabetic ketoacidosis. The distinguishing characteristic of T1DM is that if an exogenous supply of insulin is withdrawn, ketosis and eventually ketoacidosis will develop. T1DM patients are totally dependent on exogenous insulin due to the autoimmune destruction of the pancreatic cells that make the hormone insulin.

Six countries in the MENA region are amongst the world's top 10 for diabetes prevalence. These countries are Bahrain, Egypt, Kuwait, Oman, Saudi Arabia and United Arab

Emirates. Socio-economic changes and an increase in sedentary lifestyle have resulted in a dramatic increase in the diagnosis of diabetes. Its overall prevalence in the population of the MENA region is nearing 10 per cent.

The highest prevalence of children with T1DM occurs in Egypt. Here, the prevalence of T1DM in school-aged children, was reported as 1.12 to 1.9 per 1,000 in a number of studies (16,17). T1DM is also a common chronic disease in Kuwaiti children, the prevalence being 269.9 per 100,000 among six to 18 year old children (18). In addition, a high incidence of childhood T1DM has been reported in north-west Saudi Arabia, with the Al Madinah region recording the highest reported incidence of childhood T1DM across the whole of the MENA region (19).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) includes two chronic diseases, ulcerative colitis and Crohn's disease. It is understood that both autoimmune and immune-mediated phenomena are heavily involved in the development of this disease. Many studies have shown an increased prevalence of IBD amongst relatives of patients with Crohn's disease and ulcerative colitis. First degree

pattern resembles that of MS described in other Asian countries (13).

Dubai, in the United Arab Emirates, is a region with a medium to high MS prevalence rate. In a study conducted to determine the prevalence of MS in Dubai, 284 MS patients were identified of which 158 (55.6 per cent) were Dubai natives and 126 (44.4 per cent) were immigrants. This shows that the prevalence and incidence of the natives and immigrant residents of Dubai are very similar.

MS clinical trials have been ongoing in Lebanon for the past six years. Reports on a study conducted with the objective to identify early predictors of

disability amongst MS patients in Lebanon were similar to predictors in western countries (14).

In relation to the high percentage of parental consanguinity, the MENA region may face a higher risk factor for familial multiple sclerosis (FMS) throughout inbred communities. FMS is prevalent amongst Saudi MS patients and MS patients with a history of parental consanguinity were more likely to have FMS, suggesting a potential role of consanguinity (15).

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) can occur at any age; however, it occurs most

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relatives are at the greatest risk, particularly siblings, but more distant relatives also display an increased prevalence of the disease.

IBD has a low incidence in Africa and ulcerative colitis is also rare in populations of Sub-Saharan African (20). However, in patients with Jewish ethnicity, IBD is highly prevalent compared with other neighbouring ethnicities.

A racial influence on the prevalence of IBD is strongly indicated in emerging literature. In the same countries, black people seem to be less affected than white and the Jewish population generally appears to be at higher risk.

Conclusion

Although autoimmune clinical data are extrapolated to the population of the MENA region, clinical trials performed locally can provide a more useful source of clinical data on efficacy and tolerability to the drug in the local population. This will allow the influence of ethnic factors on disease susceptibility and drug responses to be evaluated most appropriately.

References

1. Coenen MJM, Trynka G, Heskamp S *et al*, Common and different genetic background for rheumatoid arthritis and coeliac disease, *Human Molecular Genetics* 18(21): pp4,195-4,203, 2009
2. Genetics of pregnancy encyclopaedia – consanguinity, www.geneticsofpregnancy.com/encyclopedia/consanguinity.aspx?pid=15&cid=44
3. Baddoura R, Haddad S, Awada H, Al-Masri AF, Merheb G, Attoui S, Okais J, Messayke J and Ghandour F, Severity of rheumatoid arthritis: the SEVERA study, *Clin Rheumatol* 25(5): pp700-704, 2006
4. Khalil LK, Baddoura R, Okais J and Awada H, Rheumatoid arthritis in Lebanese patients: characteristics in a tertiary referral centre in Beirut city, *Ann Rheum Dis* 65(5): pp684-685, 2006
5. Al Attia HM, Gatee OB, George S and Masri MM, Rheumatoid arthritis in a

- population sample in the Gulf: clinical observations, *Clin Rheumatol* 12(4): pp506-510, 1993
6. Attar SM and Al-Ghamdi A, Radiological changes in rheumatoid arthritis patients at a teaching hospital in Saudi Arabia, *East Mediterr Health J* 16(9): pp953-957, 2010
7. Sattar MA, al-Saffar M, Guindi RT, Sugathan TN, White AG and Behbehani K, Histocompatibility antigens (A, B, C and DR) in Arabs with rheumatoid arthritis, *Dis Markers* 8(1): pp11-15, 1990
8. Mohamed MK, Epidemiology of HCV in Egypt 2004, *The Afro-Arab Liver Journal* 3(2): pp 41-52, 2004
9. Raslan HM, Ezzat WM, Abd El Hamid MF, Emam H and Amre KS, Skin manifestations of chronic hepatitis C virus infection in Cairo, Egypt, *East Mediterr Health J* 15(3): pp692-700, 2009
10. Cecchi E and Bartoli L, Psoriasis and hepatitis C treated with anti-TNF alpha therapy (etanercept), *Dermatology Online Journal* 12(7): p4, 2006
11. Mahmoud F, Abul H, al Saleh Q, Hassab-el Naby H, Kajeji M, Haines D, Burseson J and Morgan G, Elevated B-lymphocyte levels in lesional tissue of non-arthritis psoriasis, *J Dermatol* 26(7): pp428-433, 1999
12. Nanda A, Al-Hasawi F and Alsaleh QA, A prospective survey of paediatric dermatology clinic patients in Kuwait: an analysis of 10,000 cases, *Pediatr Dermatol* 16(1): pp6-11, 1999
13. Benamer HT, Ahmed ES, Al-Din AS and Grosset DG, Frequency and clinical patterns of multiple sclerosis in Arab countries: a systematic review, *J Neurol Sci* 15; 278(1-2): pp1-4, 2009
14. Yamout B, Itani S, Arabi A, Hamzeh D and Yaghi S, Prognostic factors of multiple sclerosis in Lebanon, *Int J Neurosci* 120(3): pp206-210, 2010
15. Al Jumah M, Kojan S, Al Khathaami A, Al Abdulkareem I, Al Blawi M and Jawhary A, Familial multiple sclerosis: does consanguinity have a role? *Mult Scler* 17(4): pp487-489, 2011
16. Aziz HF and Assad M, An epidemiological study of insulin dependent diabetes mellitus in Egyptian school aged pupils and students, *Egypt J Commun* 6: pp183-193, 1990
17. Ghali I and Abd El-Dayem S, Prevalence of IDDM among Egyptian school aged children, *Egypt J Pediatr* 3:210-241, 1990
18. Moussa MA, Alsaaid M, Abdella N, Refai TM, Al-Sheikh N and Gomez JE, Prevalence of Type 1 diabetes among six to 18-year-old Kuwaiti children, *Med Princ Pract* 14(2): pp87-91, 2005
19. Habeb AM *et al*, High incidence of childhood Type 1 diabetes in Al-Madinah, North West Saudi Arabia (2004-2009), *Pediatric Diabetes*, Abstract e-published ahead of print, 21 March 2011
20. Katsanos KH and Tsianos EV, Inflammatory bowel disease in coloured Middle East and black African immigrant population groups: individual and familial cases, *Annals of Gastroenterology* 19(2): pp125-129, 2006

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