Molecular Epidemiology of Insulin-dependent Diabetes Mellitus: WHO Diamond Project

Janice Dorman,* on behalf of the WHO DiaMond Molecular Epidemiology Sub-Project Group'"

Resumen

El anteproyecto de Epzdemzología molecular Diamond IDDM de la Organzzaczon Mundial de la Salud (WHO en inglés) está probando la hipótesis de que la varzaczónde la frecuencia en la población de alto rzesgo de los alelos HLA-DQ es un determinante primario de los patrones globales de la incidencia IDDM Los datos están disponibles actualmente para 16 poblaciones y revelan variaciones significativas en las frecuencias de los alelos HLA DQAl y DQBl sobre los casos y grupos control

De cualquzermaneraDQAI Arg-52 (R)yDQBI*no-Asp-57 (nd)fueron marcadores consistentes e independientes de susceptibilidad IDDM en todas las poblaciones, excepto Japón*

*Los individuos o sujetos qienes portaban únicamente alelos DQAI*R y DQBI*ND tuvieron un rzesgo IDDM similar al observado en parientes de primer grado de los sujetos afectados (3%-5%) Tal información es esencial para el desarrollo de estrategias clínicas o aproxi-maczones a la prevención de la enfermedad para la población general o sujetos de alto riesgo Entonces el anteproyecto de Epzdemzología molecular Dzamond provee un excelente modelo que puede ser seguido para fijar o determinar el zmpacto de nuevos descubrimientos genéticos en la medicina y la práctzca de la salud púbhca la diabetes y otras enfermedades crónzcas*

Palabrasclave: *Diabetes mellitus insulino-dependiente (DMID), HLA-DQ, epidemiología molecular, incidencia, genética.*

Summary

*The WHO DiaMond Molecular IDDM Epidemiology Sub-Project is testing the hypothesis that population varzakon in the frequency of high-risk HLA-DQ alleles u a przmary determinant of the global patters of IDDM incidence Data are currently available for 16 populations, and reveal significant variations m the frequencies of HLA-DQA1 and DQB1 alleles among the case and the control groups. However, DQA1*Arg-(52) and DQB1*non-Asp-57 (ND) were consistent and independent markers of IDDM susceptibility in all populations, except Japan Individuals who carrzed only DQA1*R and DQB1*ND alleles had an IDDM risk similar to that observed for jirst degree relatives of affected individuals (3%-5%) Such information is essential for the development of clinical strategies or disease prevention approaches for the general population or individuals at high nsk Thus, the DiaMond Molecular Epidemiology Sub-Project provzdes an excellent model that can be followed to assess the impact of new genetic discoveries on medicine and public health practice for diabetes and other chronzc diseases*

Key words: *Insulin-dependent diabetes mellitus (IDDM), HLA-DQ, molecular epidemiology, Incidence, genetics.*

** Department of Epidemiology. Graduate School of Public Health. University of Pittsburgh, Universitvof Pittsburgh, Pittsburgh, PA. 15261.*
*** Investigators of the WHO DiaMond Molecular Epidemiology Sub-Project Group who contributed to this report included Argentina O Ramos and the Buenos Aires IDDM Research Group. China Bao MZ, Chile: E Carrasco M, Garcia de los Rios, G López; Finland. J Tuomilehto E Tuomilehto-Wolf, G Viogren, Italy-Milan E Bosi, V Lampasona. Italy-Turin G Bruno, A Pagano G Pagano and the Piedmonr IDDM Study Gorup Japan N Matsuura N Tajima; Korea K Ko. Y Park México C Gorooezky, C Robles-Valdés; New Zealand R Elliot, N Beckman, Perú: S Secien, O Núñez, M Y Rojas, C Torres. Spain M Serrano Rios M Calvillan, M Gutiérrez-López, M T Martínez Larrad, F Pérez-Bravo; USA-Alabama J Roseman, C Slvie A Rahman USA-Pennsylvania J S Dorman, B MaCarthy, E McCarnes, M K Kramer, A R Steonkiste, E Siulc, R J Vcrgona, R Stone, M Trucco.*
Correspondencia y solicitud de sobretiros: Janice S. *Dorman*. Ph.D., Department of Epidemiology, *Graduate Schoolof* Public Health, University of *Pittsburgh*. Pittsburgh, PA 15261, Telephone: *1-412-692-5169. FAX:1-412-692-8329.*

Introduction

Insulin-dependent diabetes mellitus (IDDM) is a disease that frequently occurs in children and young adults.[1] Although the etiology of IDDM rernains unclear, the disease process appears to be based on an underlying genetic susceptibility, upon which environmental influences, which likely occur early in life, interact to cause destruction of the beta cells of the pancreas. Recent studies suggest that possible environmental triggers include infant nutrition,[2-4] viruses,[5-7] stress,[8,9] and socio-economic status.[10,11] Although it is knows that such exposures contribute to the etiology of IDDM, the mechanisms by which these potential risk factors operate have not been well-defined.

Genetic susceptibility and IDDM

The major locus of genetic susceptibility for IDDM is located in the HLA region of chromosome 6.[12-14] However, recent genome-wide screens have revealed that at least five additional loci also appear to contribute to disease susceptibility.[15,16] Whether these loci acts independently, or interactively, to confer additional risk in not known. However, their roles appear to be minor in comparison to genes in the HLA region.

A number of recent molecular studies have focused on the HLA-DQ sub- region, (i.e., DQAI and DQB1 alleles, which code for the alpha and beta chain, respectively, of the DQ molecule).[12-14,17-21] Of the eight DQAI alleles that have been evaluates by rnost studies, four contain DNA sequences coding for arginine in position 52 (DQA1*Arg-52 or DQA1*R alleles). Six of the 14 DQB1 alleles contain DNA sequences coding for an arnino acid other than aspactic acid in position 57 (DQB1*non-Asp-57 or DQB1*ND alleles). DQA1*R and DQB1*ND alleles are considered to confer to disease susceptibility, particularly in individuals homozygous at both loci. Residue 52 of the DQ chain and position 57 of the DQ chain are located in the cleft of the DQ molecule, which is an important area in terms of its immunological functioning.[22] Thus, these genes nay not only serve as markers of host susceptibility, but they may also code for proteins that are directly involved in the etiology of IDDM.

WHO multinational project for childhood diabetes

The WHO Multinational Project for the Childhood Diabetes, known as the WHO DiaMond project,[23] is a large international study that began in 1990. Its primary objective is to monitor the incidence of disease, across the world, to the year 2000. Currently, more than 165 Participating Centers, representing 68 countries from all rnajor continents, are contributing to this investigation.

One of the most important findings from the WHO DiaMond Project, to date, is the observation of the drarnatic variation in the incidence of IDDM across countries.[24] Rates are extremely high in Scandinavia, but very low in the Asian Populations, as well as in some countries in Central and South America. In North America, Caucasians have higher incidence rates than Hispanics or African Americans from the same geographical area. However, all such populations remains at moderate-high IDDM risk. In South America, there are also areas (i.e., Argentina, Brazil, Colombia) with moderate IDDM incidence rates. However, other populations, such as Mexico, Peru and Chile, have extraordinarily low disease incidents rates, which approximate those of the Asian countries.

WHO *DiaMond molecular IDDM epidemiology Sub-*Project

Reasons for this extraordinary variation in IDDM risk are unclear. However, one hypothesis, which is currently being tested by the WHO DiaMond Molecular IDDM Epidemiology Sub-Project, is that population variation in the frequency of high-risk HLA-DQ alleles is a primary determinant of the global patterns of IDDM incidence.[17,25] More than 20 DiaMond Participating Centers are currently involved in the molecular Epidemiology Sub-Project. They include areas of high, low and moderate IDDM incidence. The epidemiologic design is a case-control study. IDDM cases are selected from the population-based registries developed by the Participating Centers. Controls are identified and recruited from the general populations, using standardized epidemiologic methods; they represent individual at-risk for developing IDDM during the years of case registration.

Data from the WHO DiaMond IDDM Epidemiology Sub-Project are currently available for 16 populations. Although the results are detailed elsewhere[18,19] there are four majors conclusions from the Project to date. First, there was significant variation of the frequencies of HLA-DQa1 and DQB1 alleles among the case groups and control populations. Secondly, DQA1*R and DQB1*ND were consistent and independent markers of IDDM susceptibility in all populations, except Japan. There findings were consistent with our pilot data, obtained from only five populations.[17] Thirdly , HLA-DQA1 and DQB1 molecular typing permitted the identification of a sub-group of individuals from the general population who had an IDDM risk similar to that observed for first degree relatives (3%-5%).[26] This finding is particularly important given that more than 90% of the IDDM cases are from families with no other individual with IDDM. Finally, there was a positive correlation between the frequencies of high-risk alleles and IDDM incidences rates for some of the Caucasian populations. However, in countries such as Mexico, Chile and Peru, there was a much grater proportion of individuals who carries high-risk IDDM susceptibility genes than expected, given their very low IDDM incidence rates.. This is extremely important because potential changes in environmental risk factors could lead to an epidemic of IDDM in these areas.

DiaMond molecular IDDM epidemiology Sub-Project and public health

Given that molecular epidemiology is an essential link between basic science research and public health,[27] an obvious question is, "How can information from the DiaMond Molecular Epidemiology Su-Project be utilized for IDDM prevention?" In other words, is it possible to utilize these results to begin to develop approaches for the prevention of the disease?.

To answer these questions, several issues must be considered. As previously indicated, individuals who have high genetic risk, using HLA molecular typing, can now be identified from the general population. However, in most areas, less than 10% of residents carry only high-risk HLA-DQ alleles. Thus, if genetic screening strategies were developed and implemented, only a small proportion of a population would be identified as being at high risk for the disease. However, their absolute risk of IDDDM is only 5%; approximately 95% will remain disease free. Thus, to be effective, other risk factors, which would improve the predictive value of the screening test (i.e., autoantibodies), would also need to be evaluated. In addition, HLA molecular typing is currently still expensive. Therefore, this technique would not be a cost effective method for genetic screening at the present time. Finally, there is currently no available treatment to prevent IDDM. Therefore, even if a very sensitive and specific screening test could be developed, it would be very difficult in the general population, given that there is no therapeutic approach for IDDM prevention. In summary, after consideration of each of these issues, it appears that the information from the DiaMond Molecular IDDM Epidemiology Sub-Project cannot currently be utilized to prevent IDDM.

Molecular epidemiology model for prevention of chronic diseases

The model that is being developed for the WHO DiaMond Molecular IDDM Epidemiology Project. however, extremely is important, and represents an approach that can be followed in the future to develop prevention strategies for other non-communicable diseases. The current DiaMond model is based upon: 1) the determination of disease incidence rates in defined populations, 2) the selection of appropriate case and control groups, using standardized epidemiological methods, and 3) the identification of the strong genetic markers of host susceptibility. Current molecular IDDM epidemiology studies are now being expanded to include assessments of potential environmental risk factors and measurements of autoimmunity. This will permit the evaluation of risk factor-specific IDDM incidence rates, which may lead to the identification of sub-groups of the population at particulary high-risk, based on their genotype and/or environmental or immunological exposures. With estimates of relative, absolute and attributable IDDM risks, it will be possible to make decisions regarding the development of appropriate and cost-effective of genetic/

environmental screening programs for the general population, or high risk sub-groups. It is among these individuals that disease prevention strategies will likely be most effective.

Molecular epidemiology, therefore, represents a very exciting field that has great potential for disease prevention in the future. The model being developed for IDDM is an excellent basis upon which approaches for the prevention of other non-communicable disease can also be developed.

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