The Egyptian Journal of Medical Human Genetics (2014) **15**, 265–272

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com

ORIGINAL ARTICLE

The association of polymorphic sites in some genes with type 1 diabetes mellitus in a sample of Egyptian children

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Received 24 April 2014; accepted 15 May 2014
Available online 23 June 2014

KEYWORDS

Genes;
Genomic DNA;
Single nucleotide polymorphism;
Type 1 diabetes mellitus

Abstract *Background:* The major histocompatibility complex (MHC) genes have been implicated as the major genetic component in the predisposition to type 1 diabetes mellitus (T1DM). Other loci outside the MHC had also been reported to contribute in the susceptibility of T1DM. The aim of this study was to examine the role of some variants of polymorphic sites in some genes associated with T1DM in a sample of Egyptian children.

Patients and methods: 60 patients with T1DM from the diabetes clinic at Alexandria University Children's Hospital, and 60 healthy individuals were enrolled in this study. Genomic DNA was extracted using isopropanol precipitation method. *Interleukin 18* (*IL-18*), *interleukin 10* (*IL-10*), *vitamin D receptor* (*VDR*), *protein tyrosine phosphatase non-receptor type 22* (*PTPN22*) and *cytotoxic T-lymphocyte antigen-4* (*CTLA-4*) were genotyped.

Results: The findings obtained from logistic regression analysis suggest that the *IL-18* single nucleotide polymorphisms *SNP-137 G > C* (*rs#187238*), the *VDR Fok1 SNP T > A* (*rs#2228570*) and the *SNP-1123 C > G* (*rs#2488457*) in *PTPN22* gene showed a significant difference between patients and controls ($P = 0.026$, 0.030, and 0.003, respectively). The genotype distributions of *PTPN22 SNP-1858*, *CTLA-4 SNP 49*, *IL-10 SNP-819*, *IL-18 SNP-607*, and *VDR BsmI SNP G > A* did not show any significant difference.

Conclusion: The *IL-18 SNP-137 G > C* (*rs#187238*), *VDR SNP-Fok1 T > A* (*rs#2228570*), and the *SNP-1123 C > G* (*rs#2488457*) in *PTPN22* gene may have an effect on the occurrence of

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Peer review under responsibility of Ain Shams University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.ejmhg.2014.05.002

T1DM in Egyptian children. Further large-scale, population-based, case-control studies are needed.

1. Introduction

Type 1 diabetes mellitus (T1DM) is a common, chronic metabolic disorder characterized by hyperglycemia as a cardinal biochemical feature and disturbances of carbohydrate, fat and protein metabolism, associated with absolute or relative deficiencies in insulin secretion and/or action [1]. This is usually due to autoimmune destruction of the pancreatic beta cells (type 1A) [2].

The incidence varies from more than 40 per 100,000 children in Finland to less than two per 100,000 in Japan. A rise in the numbers of children and adolescents with T1DM has been observed since the mid-1950s, both in high- as well as low risk countries. The current global prevalence rate is 0.025% for children under 15 years of age, with the average increase in the annual incidence rate for this age group being 3% [3,4].

T1DM is a complex polygenic disorder and cannot be classified strictly by dominant, recessive, or intermediate inheritance, making identification of disease susceptibility or resistance genes difficult [5,6].

The major histocompatibility complex (MHC) genes have been implicated as the major genetic component in the predisposition to T1DM but other genes are likely to be involved such as *Interleukin-10* (*IL-10*), *Interleukin-18* (*IL-18*), *cytotoxic T-lymphocyte antigen-4 gene* (*CTLA-4*), Toll-like receptors 2 (*TLR2*), *insulin gene* (*INS*), protein tyrosine phosphatase non-receptor 22 (*PTPN22*), *interleukin 2 receptor alpha* (*IL2RA*/*CD25*), *glutamate decarboxylase 2* (*GAD2*), *vitamin D-receptor* (*VDR*) *gene* and others. These loci have all been proved important in the pathogenesis of autoimmunity when globally considered, whereas the insulin gene is a disease-specific T1DM predisposition locus [5,6].

At least 20 different chromosomal regions have been linked to T1DM susceptibility in humans, using genome screening, candidate gene testing and studies of human homologues of mouse susceptibility genes [7].

Since 2001 a significant number of genome-wide association (GWA) studies have been reported. Data from The International Type 1 Diabetes Genetics Consortium (T1DGC), collected through multiple GWA studies and large scale meta-analyses, identified more than 40 loci that affect the previously reported as regions associated with T1DM susceptibility. Eighteen additional regions showed significant association with T1DM and several of them contain new candidate genes of possible relevance to T1DM (*IL19*, *IL20*, *GLIS3*, *CD69* and *IL27*). Most of the listed genes mediate the immune response, some exert their functions in the process of destruction of pancreatic β cells and some have a dual role [8]. Additional functional studies provided evidence of causality of several genes within established loci, such as several cytokines and their receptors, immunomodulatory molecule. However, for the majority of associated regions the most likely causal gene still needs to be identified [9].

The aim of this study was to examine the role of some variants of polymorphic sites in some genes associated with T1DM in a sample of Egyptian children.

2. Patients and methods

A total of 60 patients with type 1 diabetes (25 male/35 female) from the Diabetes Clinic at Alexandria University

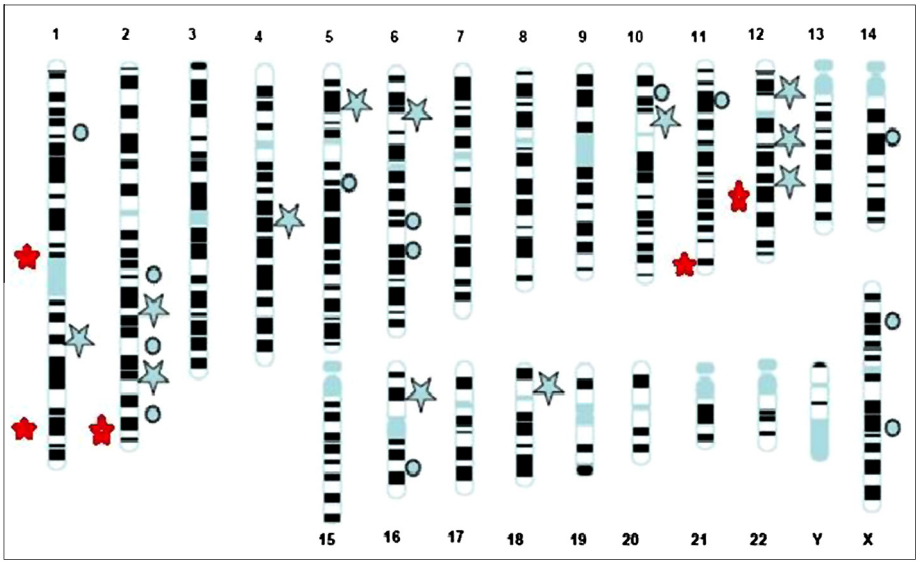

Figure 1 The type 1 diabetes risk gene loci paced over the genome. Stars are the loci that have shown evidence of association to T1DM, dots are the loci identified in linkage studies [10]. The red stars are genes loci that were investigated on chromosomes.