International Journal of Biomolecules and Biomedicine (IJBB)
ISSN: 2221-1063 (Print) 2222-503X (Online)
Vol. 3, No. 1, p. 1-11, 2013
http://www.innspub.net

REVIEW PAPER OPEN ACCESS

Type 1 diabetes: basis of causes and away of prevention

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Article Published: 27 January 2013

Key words: Type 1 diabetes, autoimmune, gene, prevention.

Abstract

Type 1 diabetes (T1D) is characterized by autoimmune destruction of insulin-producing β-cells in the pancreas, an organ in the abdomen, produces very little or no insulin caused by a complex interaction of genetic and environmental factors. Insulin is a hormone that helps the body to absorb and use glucose and other nutrients from food, store fat, and build up protein and without insulin, blood glucose (sugar) levels become higher than normal. The genetic factors involved consist of multiple susceptibility genes, at least five of which, HLA, INS, CTLA4, PTPN22 and IL2RA/CD25. The excess mortality associated with the complications of type 1 diabetes and the increasing incidence of childhood type 1 diabetes emphasize the importance of therapeutic strategies to prevent this chronic disorder. Although no current "cure" exists, recent genetic data and preliminary trial results suggest T cells as a target for preventive strategies. Another potentially attainable target is induction of tolerance to the ß-cell proteins such as insulin that are inappropriately recognized. Other strategies involve ß-cell replacement, but currently there are insufficient donor cells available. But researchers revealed that breastfeeding, taking proper exercise, vaccination against causing enterovirous, vitamin D, regulation of maternal diet and keep away from smoking are the best away prevent from type 1 diabetes. This review aims to provide the link of causing type 1 diabetes and the away of prevention to the type 1 diabetes patient.

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Introduction

Type 1 Diabetes (insulin dependent) develops when the insulin-producing β-cell in the pancreas have been destroyed and the body unable to produce insulin which causes the increase of glucose levels in the blood (ASH Fact Sheet. 2012). Glucose is a sugar that the body produces primarily from the digestion of carbohydrates and levels are controlled by the hormone insulin. Insulin is made and stored in the pancreas and helps glucose to enter the cells where it is used as fuel by the body. Without insulin, the body's cells cannot absorb glucose from the blood and as a result, glucose accumulates in the blood, leaving the body's cells and tissues starved for energy. Type 1 Diabetes usually appears in children and young adults but can occur at any age (ASH Fact Sheet. 2012). Studies of neonatal diabetes express that most cases of diabetes diagnosed before 6 months are due to be autoimmune, but those diagnosed after the age of 6 months have the genetic characteristics of T1D (Edghill *et al.*, 2006). Islet autoimmune β-cell destruction occur for the Islet auto antibodies that the combinations of this antibodies to insulin (IAA), (Bottazzo *et al.*, 1985) glutamic acid decarboxylase (GADA) and the tyrosine phosphatase IA-2 (Hawkes *et al.*, 1996) which found in individuals that at risk or who have recently developed T1D.This islet auto antibodies are detected at the age of 5years (Bonifacio *et al.*, 2004) and antibodies to INS (generally the first to appear) have been detected as early as 6–12 months (Roll *et al.*, 1996). It is thought that diabetes play a key role for introducing different types of diseases. People with diabetes are at greater risk of heart disease that high glucose levels affect the walls of the arteries making them more likely to develop fatty deposits which in turn makes it more difficult for the blood to circulate. It also causes high blood pressure, stroke kidney disease, nerve damage leading to limb amputation, eye damage such as retinopathy and lower the levels of the protective HDL cholesterol (ASH Fact Sheet. 2012).

Genetic factor involved in T1D

Type 1 diabetes is a polygenic disease that many different genes are involved to its expression (Rubio-Cabezas and Argente 2008). On the basis of locus or combination of loci, it may be dominant, recessive, or between of them. Though the identifying of a complex disease is challenging but different strategies have been used in efforts to identify T1D susceptibility genes. Among them the most successful were the early studies of gene frequencies in individuals with T1D compared with controls (Mehers and Gillespie 2008).

Human leukocyte antigen

The highly polymorphic human leukocyte antigen (HLA) on chromosome 6p21.3 express the functional differences in how fragments of protein are presented to the immune system. In the early 1970s, several groups of investigator found that HLA class I are associated with T1D (Singal *et al.*, 1973; Cudworth and Woodrow 1975; Mehers and Gillespie 2008). Later, lymphocyte-defined HLA-D antigens, HLA class II DR4 and DR3 were shown to be more closely associated with T1D and the combination of two susceptible alleles together DR3/DR4 which produced a higher risk genetic combination (Todd *et al.*, 19897). The HLA consists of a lots of genes that are close together and transferred from the parent to the child in adjacent 'DNA chunks which are known as linkage disequilibrium. Other natural history of T1D studies have demonstrated that HLA genes are associated with the auto antibodies where IA2-A are associated with specific DR alleles (Williams *et al.*, 2008) IAA are associated with DR4 (Achenbach *et al.*, 2004) GADA are associated with DR3 and the recently discovered ZnT8 antibodies are associated with a single base pair change in the SLC30A8 gene Class II HLA has been reported to be associated not only with acute-onset type 1 diabetes but also with fulminant and slowly progressive type 1 diabetes (Imagawa and Hanafusa 2006; Kobayashi *et al* ., 1993) .It is noted as a report on fulminant type 1 diabetes that high frequencies of class II HLA alleles provide resistance to type 1 diabete

(Imagawa *et al*., 2000). Other studies found that where serological typing of class II HLA showed a higher frequency of the DR4-DQ4 as well as DR2-DQ1 haplotype than in autoimmune type 1 diabetes (Imagawa *et al*., 2005).

INS gene

In 1983, a second locus of a variable number tandem repeat of INS promoter region was indentified that is responsible for regulation of INS production and has a link with susceptibility to T1D (Bell *et al*., 1984). Alleles of this promoter region are consisted of three classes and distinguished by the number of DNA base pair repeats. Class I alleles have 570 base pairs, class II alleles 1200 base pairs and class III alleles have 2200 base pairs. Class I alleles have higher sensitivity to T1D, on the other hand protection from T1D is associated with the class III allele (Bennett *et al*., 1995). INS gene study has been reveal that class I alleles in the pancreas produce higher INS than class III alleles, but on the contrary class I alleles are expressed at 2–3-fold lower levels in the thymus than class III alleles. For this reason class III allele alter the selection of T cells in the thymus and influence tolerance to INS (Vafiadis *et al*., 1997).

CTLA-4

CTLA-4 is known as surface molecule which generally activated the T cells that induces a negative signal for T cell activation. If the CTLA-4 gene is inheritably changed it expression can increase T cell self-reactivity and thus play an important role in causing autoimmune diseases such as T1D. In 2003, Ueda *et al*., reveal that sensitivity of this molecule is responsible for causing T1D.

PTPN22

In 2004, Bottini *et al*. Found that tyrosine phosphatase associated with susceptibility to T1D, is a lymphoid protein produced from a gene PTPN22 on chromosome 1p13.The PTPN22 gene contributes to susceptibility to T1D by increasing the negative regulation **of** T cell activation (Bottini *et al*., 2004). In 2008 Ikegami *et al*., collected Japanese and Korean samples for sequencing of *PTPN22* and revealed the presence of five novel SNPs in the sample and one of these, the -1123 G>C SNP in the promoter region, was found to be associated with type 1 diabetes in both Japanese and Korean populations.

IFIH1

The *IFIH1* gene encodes helicase C domain 1on chromosome 2q24.3 which mediates the interferon response to viral RNA (Von Herrath 2009).The *IFIH1* polymorphisms associated with type 1 diabetes (Nejentsev *et al*., 2009) because of their connection to the inflammatory response caused by infectious agents such as enteroviruses. This viral infection induce islet autoimmunity and influence progression to diabetes (Hyöty and Taylor 2002; Honeyman 2005). In 2008, Qu *et al.,* carried out a study on IFIH1 and genotyped five SNPs in 1767 individuals where found association with T1D.

IL2RA/CD25

Vella *et al*. in 2005 noted that the interleukin 2 receptor alpha (IL2RA) region on chromosome 10p15 was associated with T1D. IL2RA encodes the alpha-chain of the IL-2 receptor complex which is responsible for binding IL-2 that is a key player in the proliferation of regulatory T cells. The *IL2RA* region has been reported to be linked not only with type 1 diabetes but also with autoimmune thyroid diseases (Brand *et al*., 2007) and suggesting that the *IL2RA* region plays a general role in autoimmunity. Qu *et al.,* in 2007 also confirmed that IL2RA has an association with T1D and identified two SNPs which increased the risk **of** T1D. After that Lowe *et al.,* analyzed 288 SNPs and identified the SNP ss52580101 to be the most closely associated with T1D and they found that SNPs are poorly associated with T1D when increased soluble IL2RA expression. So it is reveal that T1D-susceptible alleles are associated with decreased concentrations of IL2RA and suggesting a possible biological mechanism

for autoimmunity through reduced binding of IL-2 which is an essential component for the survival and proliferation of regulatory T cells suppressors of autoreactivity.

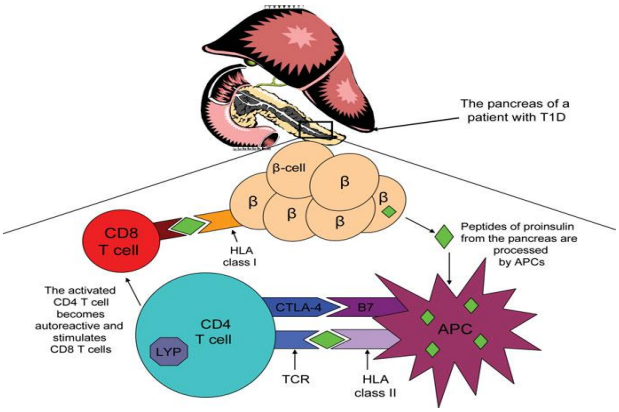

Fig. 1. Peptides of proinsulin from pancreatic b-cells are directed by antigen-presenting cells which are then presented by HLA class II molecules to the T cell receptor on CD4 T cells. Polymorphisms of the CTLA-4 and PTPN22 increase the risk of T cell self-reactivity and autoreactive CD4 T cells then stimulate cytotoxic CD8 T cells that attack pancreatic b-cell expressing proinuslin peptides through HLA class I molecules on their cell surface (Mehers and Gillespie 2008) .

Vitamin D receptor (VDR)

Vitamin D has important immunomodulatory properties and the active form vitamin D3 (1,25 dihydroxyvitamin D3) has been investigated to inhibit T cell proliferation (Muller and Bendtzen 1992).The genetic studies of vitamin D related genes suggest that it has a correlation of T1D. Though one study expressed that there are no association between T1D and the VDR gene after examining 97 SNPS in up to 3763 T1D families from the UK, USA, Finland and Romania but in 2007 investigated the VDR gene against T1D and found a link with the association of CYP27B1 gene on 12q13.1–q13.3 where the C allele of rs10877012 was significantly associated with increased risk **of** T1D (Mehers and Gillespie 2008).

Genome wide association studies

The recent advances technology and knowledge in molecular genetics such as the high density genotyping chips have made it possible to perform genomewide association (GWA) studies with genotyping of hundreds of thousands of single nucleotide polymorphisms (SNPs) across the genome to denote the genetic basis of common human diseases like as type 1 diabetes. In 2007, 2000 individuals and 3000 controls were analyzed for detecting seven major diseases (Todd *et al.*, 2007) where found significant linkages of 12q24, 12q13, 16p13, 18p11, 12p13 and 4q27 for T1D. These loci do not overlap with the previously identified IDDM loci. The further analysis carried out of 4000 individuals and 5000 controls with T1D where 2997 T1D family trios confirmed 12q24, 12q13, 16p13 and 18p11 (Todd *et al.*, 2007).

Environmental factor

Though the Identification of environmental factors are very difficult but the most popular candidates are viruses, with enteroviruses (Hyoty and Taylor 2002), rotavirus (Honeyman *et al.*, 2000) and rubella being suspects. The strongest data to date have supported a role for rubella. Infants generally infected with congenital rubella syndrome are said to be at increased risk of type 1 diabetes (Ginsberg *et al.*, 1985). Yet Finland, where vaccination has effectively eradicated rubella, still has one of the highest incidences of type 1 diabetes (Peltola *et al.*, 2000). There is also some evidence that some enteroviruses (e.g., Coxsackie B viruses) are less prevalent in countries with high incidences of type 1 diabetes (e.g., Finland) than in countries with low incidences but geographically similar populations (e.g., Russian Karelia) (Viskari *et al.*, 2005). This observation may be in keeping with the concept of the hygiene hypothesis (Gale 2002; Bach 2005), which support that environmental exposure to microbes, other pathogens and their products early in life promotes innate immune responses that suppress atopy and perhaps autoimmunity. In Western cultures, the developing immune system of the infant is no

longer exposed to widespread infection which may contribute to the current increases in incidence observed in atopic and autoimmune disease.

Prevention from type 1 diabetes

Breastfeeding

According to a Swedish study, if a mother who has a new infant and a family history of type 1 diabetes, breastfeeding for a long period of time may be at lower risk of developing type 1 diabetes than those who are not (Sadauskaite-Kuehne *et al*., 2004). Breastfeeding children tend to grow more slowly and steadily while formula-fed babies often grow fast because mother's milk contains fewer calories and protein fragments are too small to stimulate the immune system than formula and thus breastfeeding may protect against the development of the antibodies associated with type 1 diabetes (Rewers and Gottlieb 2009). The cow's milk hypothesis is being checked of proper functioning against type 1 diabetes by the Trial to Reduce type 1 diabetes in the Genetically at Risk (Study design of TRIGR., 2007) and the Finnish Intervention Trial for the Prevention of Type I Diabetes (FINDIA) that bovine insulin present in cow's milk triggers islet autoimmunity. So while mothers are unable to breast feed before the 8 months age baby are suggested to give either a formula of extensively hydrolyzed protein (Nutramigen) or a formula based on nonhydrolyzed cow's milk (Enfamil) containing a small amount of Nutramigen that develop of diabetes by the age of 10 years (Rewers and Gottlieb 2009). The recent studies also reveal that longer duration of breastfeeding is associated with lower risk of overweight (Harder *et al*., 2005) and type 1 diabetes (Sadauskaite-Kuehne *et al*., 2004) in later life of the child.

Supplementation of Vitamin D

Recent studies reveal that vitamin D plays an important role of pathogenesis and prevention of type 1 diabetes. The β -cell possesses specific receptors for the activated hormone 1,25-dihydroxy vitamin D3 and vitamin D–dependent calcium-binding proteins ((Mathieu and Badenhoop 2005; Ishida *et al*., 1988). Insulin secretion is impaired by vitamin D deficiency and restored by 1,25-(OH)2D3 administration (Bourlon *et al*., 1996). Active of vitamin D is mediated through its receptor influences gene transcription and affects pancreatic b-cell function. Vitamin D deficiency during pregnancy causes the incidence of autoimmune diseases, such as type 1 diabetes. Islet cell insulin secretion is reduced in vitamin D-deficient animals and if high-dose of vitamin D supplementation is given early in life it may protects against type 1 diabetes (Mathieu and Badenhoop 2005).

Vitamin D can be taken up by two sources one is from food (e.g. fatty fishes and their oils) and another can be achieved through direct ultraviolet B (UV-B)-mediated synthesis in the skin. Sunlight has two types of ultraviolet radiation. When sunshine in the UV-B spectrum strikes the skin, it converts a substance in the skin called 7-dehydrocholesterol into vitamin D_3. The 7-dehydrocholesterol is a very close precursor to cholesterol. UV-B is the short wavelength light that causes sunburn and does not penetrate the skin deeply. It does not penetrate glass. If one get sunlight behind a window, while driving etc, will not get vitamin D. Sunscreens also prevent the formation of vitamin D. The another UV-A radiation has a longer wavelength, and penetrates through the outer skin deep down to the elanocytes, the cells that become cancerous in melanoma cases.

Beta cells regeneration

Yuval Dor, Ph.D professor of Hebrew University Jerusalem revealed in a study that the first time a high rate of glucose converts into energy the cells that are involved influenced beta cells regeneration. Coupled with a mechanism that prevents the immune system from attacking beta cells in the first place, the long-awaited finding may help the way to a full cure for type 1 diabetes (Meier *et al*., 2005). Benjamin Glaser, M.D. of Hadassah Medical Center, used a genetic system to destroy 80 percent of the insulin-producing cells in

adult mice, rendering the mice diabetic. When the researchers compared these mice with control mice, they found that those mice with diabetes and elevated blood glucose levels had regenerated a greater number of new beta cells than mice without diabetes and suggesting that glucose is a key player in beta cell regeneration. The researchers also found that an enzyme, glucokinase are involved the first step in converting glucose for energy that stimulates beta cells to replicate. This study also showed that regeneration depends on glucokinase levels instead of glucose levels and researchers may be able to use drugs to trigger beta cells to regenerate without exposing the body to elevated glucose levels. Another study also found that a single murine adult pancreatic precursor exists that can differentiate into cells with the characteristics of islet ß cells (Seaberg *et al*., 2004) where shown that the pre-existing ß cells, rather than pluripotent stem cells are the main source of new ß cells during adult life and after pancreatectomy in mice (Dor *et al*., 2004).

Maternal diet

Family dietary traits and lifestyle may play an important role for causing of type-1 diabetes within families. If a pregnant woman eats too much carbohydrate, this will raise her insulin levels though insulin itself cannot cross the placenta from mother to foetus but insulin produces antibodies can.This antibodies in the foetus increase glycogen and fat deposits resulting in an abnormally large baby which may make favorable for the baby to type-1 diabetes. Mother diet may play a vital role on the babies diet which is the another example of an elimination of diet trial (Schmid *et al*., 2004).This randomized, unmasked feasibility study is expressing the effect of delaying exposure to gluten until the age of 1 year (Rewers and Gottlieb 2009). Another study launched among the group of Norwegian population by record linkage of the medical birth registry and the National Childhood Diabetes Registry looked at all live births in Norway between 1974 and 1998 (1,382,602 individuals) (Stene *et al*., 2001) where found that increasing incidence of type 1 diabetes direct linear with increasing birth weight. Thus, the way an expectant mother eats can be expected to have an effect on the future health of her offspring. So the mother usually controls a family's food will also influence the way her children eat.

Pancreas transplantation

Pancreatic transplantation has offered a successful therapeutic approach for many years (Burke *et al*., 2004).When type 1 diabetes cannot be controlled or is causing serious problems; the patient may want to decide to a pancreas transplant. For patients with severe type 1 diabetes, a pancreas transplant probably offers the greatest chance of a more "normal" lifestyle, free from insulin shots. Pancreas transplants are safest in people who do not have heart or blood vessel disease. Unfortunately, there are not enough donor pancreases to go around because not enough people sign up to be organ donors, and each pancreas must meet strict guidelines. When a whole pancreas is not available, a person can receive a portion of a pancreas from a living relative. On the other hand Islet transplants are intended to treat advanced type 1diabetes by replacing destroyed islets with new ones where no surgery is needed. The islets cells from a deceased donor's pancreas are removed and injected into a major blood vessel of the patient's liver. The islet cells then begin making insulin. With the use of a combination of daclizumab, sirolimus and tacrolimus and islets from more than 1 donor pancreas per recipient, success rates of 80% at 1 year and 20% at 5 years have been reported (Ryan *et al*., 2005).

Exercise

Exercise has a greater beneficial result than dietary modifications or even weight loss on the management of blood sugar. Regular taking of exercise reduce the risk of obesity and thereby minimize the incidence of causing of diabetes types diseases. By losing of weight and increasing physical activity can neutralize the powerful effect of insulin resistance on progression to type 1 diabetes (Fourlanos *et al*., 2004; Xu *et al*.,

2007). Precise blood glucose control after diabetes resulting in β-cell rest and it is believed that it helps to preserve residual insulin secretion (Brown and Rother 2008). Before the 19th century, it was known that BG concentrations typically decrease with endurance-type exercise in most individuals with diabetes (Michael *et al*., 2006). In someone who already has diabetes, exercise and a nutritionally balanced diet can greatly limit the effects of both types 1 and 2 diabetes. *Intense exercise draws glucose out of the muscle and after then the muscles pulls the glucose out of the bloodstream and into the muscle cells*. The enzyme AMP kinase initiates glucose transport from blood to cells without the use of insulin. This is especially important and helpful in light of the occurrence of insulin resistance in those at risk for diabetes. Exercise is found to increase levels of AMP kinase. During post-exercise, carbohydrate intake is necessary to help replenish liver and muscle glycogen stores and this period, which may last up to 12 to 24 h, insulin sensitivity are elevated and there is a high risk of hypoglycemia in patients with type 1 diabetes .For a patients who tend to manage post-exercise late-onset hypoglycemia during the night, a complex carbohydrate (e.g. uncooked corn starch) or a mixed snack containing fat and protein may be particularly beneficial at bedtime (Michael *et al*., 2006).

Vaccination

It has been thought that viruses might play a role in causing type 1 diabetes by infecting the beta cells of the pancreas. The new research suggests that enteroviral infection of the beta cells in children with type 1 diabetes may initiate a process whereby the body's immune system identifies beta cells as 'foreign' and rejects them. The beta cells are not destroyed in this disease but enteroviral infection of beta cells reduces their ability to release insulin. Vaccination in childhood to prevent enteroviral infections of beta cells might be an attractive means to reduce the incidence of both common forms of diabetes(Gillespie 2006**).**

Conclusions

Type 1 diabetes risk is mainly depending upon a genetic susceptibility, unknown environmental trigger and an uncontrolled autoimmune response that attacks the insulin producing beta cells. Though the scientific community is increasingly able to define the importance of individual genes in susceptibility to T1D and diagnose or predict the onset of diabetes in an individual case but it is now unclear what percentage of absolute genetic risk can be measured by combining all the known risk alleles of the genes. The subsequent lack of insulin of the diabetes patient leads to increased blood and urine glucose. Injection is the most common method of administering insulin. Pancreas transplants have been used to treat type 1 diabetes; however, this procedure is currently still at the experimental trial stage. Some research has suggested that breastfeeding decreased the risk of type 1 diabetes in later life and taking proper exercise and maternal diet may also contribute to prevent diabetes. Giving children 2000 IU of Vitamin D during their first year of life is associated with reduced risk of type 1 diabetes though the actual relationship is unknown. We believe that in the near future scientist can know the roles **of** these genes and their molecular pathways that are related to the risk **of** T1D and may potentially lead to targeted therapies for children for treating or preventing diabetes.

References

Achenbach P, Koczwara K, Knopff A, Naserke H, Ziegler AG, Bonifacio E. 2004. Mature high-affinity immune responses to (pro) insulin anticipate the autoimmune cascade that leads to type 1 diabetes. Journal of Clinical Investigation **114,** 589–597.

Action on smoking and health (ASH) Fact Sheet. 2012. Smoking and diabetes, www.ash.org.uk

Bach JF. 2005. Infections and autoimmune diseases. *J Autoimmun* **25,** 74-80.

Bell GI, Horita S, Karam JH. 1984. A polymorphic locus near the human insulin gene is associated with insulin-dependent diabetes mellitus. Diabetes **33,** 176–183.

Bennett ST, Lucassen AM, Gough SC. 1995. Susceptibility to human type 1 diabetes at IDDM2 is determined by tandem repeat variation at the insulin gene minisatellite locus. Nat Genet **9,** 284–292.

Bonifacio E, Hummel M, Walter M, Schmid S, Ziegler AG. 2004. IDDM1 and multiple family history of type 1 diabetes combine to identify neonates at high risk for type 1 diabetes. Diabetes Care **27,** 2695–2700.

Bottazzo GF, Dean BM, McNally JM, MacKay EH, Swift PG, Gamble DR. 1985. *In situ* characterization of autoimmune phenomena and expression of HLA molecules in the pancreas in diabetic insulitis. N Engl J Med **313,** 353–360.

Bottini N, Musumeci L, Alonso A. 2004. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. Nat Genet **36,** 337–338.

Bourlon PM, Faure-Dussert A, Billauder B, Sutter BC, Tramu G, Thomasset M. 1996. Relationship between Calbindin-D28K levels in the A and B cells of the rat endocrine pancreas and the secretion of insulin and glucagon: influence of vitamin D3 de ficiency and 1,25 dihydroxyvitamin D3. *J Endocrinol* **148,** 223 – 232.

Brand OJ, Lowe CE, Heward JM, Franklyn JA, Cooper JD, Todd JA, Gough SC. 2007. Association of the interleukin-2 receptor alpha (IL-2Ralpha)/CD25 gene region with Graves'disease using a multilocus test and tag SNPs. Clin. Endocrinol **66,** 508-512.

Brown RJ, Rother KI. 2008. Effects of beta-cell rest on beta-cell function: a review of clinical and preclinical data. Pediatr Diabetes **9,** 14–22.

Burke GW, Ciancio G, Sollinger HW. 2004. Advances in pancreas transplantation. Transplantation **15,** 77, S62-7.

Cudworth AG, Woodrow JC. 1975. Evidence for HL-A-linked genes in 'juvenile' diabetes mellitus. Br Med J **3,** 133–135.

Dor Y, Brown J, Martinez OI. 2004.Adult pancreatic beat-cells are formed by self-duplication rather than stem-cell differentiation. *Nature* **429,** 41-6.

Edghill EL, Dix RJ, Flanagan SE. 2006. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes **55,** 1895–1898.

Fourlanos S, Narendran P, Byrnes GB, Colman PG, Harrison LC. 2004. Insulin resistance is a risk factor for progression to type 1 diabetes. Diabetologia **47,** 1661–1667.

Gale EA. 2002. The rise of childhood type 1 diabetes in the 20th century. Diabetes **51,** 3353–3361.

Gillespie KM.2006. Type 1 diabetes: pathogenesis and prevention. Canadian Medical Association Journal 175 (2). doi:10.1503/cmaj.060244.

Ginsberg-Fellner F, Witt ME, Fedun B. 1985. Diabetes mellitus and autoimmunity in patients with the congenital rubella syndrome. *Rev Infect Dis* **7(1),** S170-6.

Harder T, Bergmann R, Kallischnigg G, Plagemann A. 2005.Duration of breastfeeding and risk of overweight: a meta-analysis. American Journal of Epidemiology **162,** 397–403.

Hawkes CJ, Wasmeier C, Christie MR, Hutton JC. 1996. Identification of the 37 kDa antigen in IDDM as a tyrosine phosphatase-like protein (phogrin) related to IA-2. Diabetes **45,** 1187–1192.

Honeyman M. 2005**.** How robust is the evidence for viruses in the induction of type 1 diabetes? Curr Opin Immunol **17,** 616–623.

Honeyman MC, Coulson BS, Stone NL. 2000. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* **49,** 1319-24.

Hyöty H, Taylor KW. 2002. The role of viruses in human diabetes. Diabetologia **45,** 1353–1361.

Hyoty H. 2002. Enterovirus infections and type 1 diabetes. Ann Med **34,** 138–147.

Ikegami H, Noso S, Babaya N, Hiromine Y, Kawabata Y.2008.Genetic basis of Type 1 Diabetes: similarities and differences between east and west. The Review of Diabetic Studies Vol. **5** , No. 2. DOI 10.1900/RDS.2008.5.64

Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y. 2000. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related antibodies. *N Engl J Med* **342,** 301-307.

Imagawa A, Hanafusa T, Uchigata Y, Kanatsuka A, Kawasaki E, Kobayashi T, Shimada A, Shimizu I, MaruyamaT, Makino H. 2005. Different contribution of class II HLA in fulminant and typical autoimmune type 1 diabetes mellitus. *Diabetologia* **48,** 294-300.

Imagawa A, Hanafusa T. 2006. Pathogenesis of fulminant type 1 diabetes. *Rev Diabet Stud*. **3,** 4, 169-177.

Ishida H, Norman AW.1988.Demonstration of a high affinity receptor for 1,25- dihydroxyvitamin D3 in rat pancreas. Mol Cell Endocrinol **60,**109–117.

Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Kosaka K. 1993. Immunogenetic and clinical characterization of slowly progressive IDDM. *Diabetes Care* **16,** 780-788.

Lowe CE, Cooper JD, Brusko T. 2007. Large-scale genetic fine mapping and genotype–phenotype associations implicate polymorphism in the IL2RA region in type 1 diabetes. Nat Genet **39,** 1074–1082.

Mathieu C, Badenhoop K.2005. Vitamin D and type 1 diabetes mellitus: state of the art. TRENDS in Endocrinology and Metabolism.

Mehers KL , Gillespie KM. 2008. The genetic basis for type 1 diabetes. British Medical Bulletin **88,** 115–129

Meier J, Bhushan A, Butler AE. 2005**.**Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: Indirect evidence for islet regeneration? Diabetologia **48,** 2221-8.

Michael C, Riddell PhD, Bruce A, Perkins MD MPH.2006. Type 1 Diabetes and Vigorous Exercise: Applications of Exercise Physiology to Patient Management. Canadian Journal of Diabetes **30(1),** 63-71**.**

Muller K, Bendtzen K. 1992.Inhibition **of** human T lymphocyte proliferation and cytokine production by 1,25-dihydroxyvitamin D3. Differential effects on

CD45RA+ and CD45R0+ cells. Autoimmunity **14,** 37–43.

Nejentsev S, Walker N, Riches D, Egholm M, Todd JA. 2009. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. Science **324,** 387–389.

Peltola H, Davidkin I, Paunio M. 2000. Mumps and rubella eliminated from Finland. *JAMA* **284,** 2643-7.

Qu HQ, Marchand L, Grabs R, Polychronakos C. 2008**.**The association between the IFIH1 locus and type 1 diabetes. Diabetologia **51**, 473–475.

Qu HQ, Montpetit A, Ge B, Hudson TJ, Polychronakos C. 2007. Toward further mapping **of** the association between the IL2RA locus and type 1 diabetes. Diabetes **56,** 1174–1176.

Rewers MDM, Gottlieb **MDP.** 2009. Immunotherapy for the Prevention and Treatment of Type 1 Diabetes. Diabetes Care **32(10)**, 1769–1782.

Roll U, Christie MR, Fuchtenbusch M, Payton MA, Hawkes CJ, Ziegler AG. 1996. Perinatal autoimmunity in offspring of diabetic parents. The German Multicenter BABY-DIAB study: detection of humoral immune responses to islet antigens in early childhood. Diabetes **45,** 967–973.

Rubio-Cabezas O, Argente J.2008. Current Insights into the Genetic Basis of Diabetes Mellitus in Children and Adolescents. Journal of Pediatric Endocrinology & Metabolism, **21,** 917-940.

Ryan EA, Paty BW, Senior PA. 2005. Five-year follow-up after clinical islet transplantation. *Diabetes* **54,** 2060-9.

Sadauskaite-Kuehne V, Ludvigsson J, Padaiga Z, Jasinskiene E, Samuelsson U.2004.Longer breastfeeding is an independent protective factor against development of type 1 diabetes mellitus in childhood. Diabetes/Metabolism Research and Reviews. **20,** 150–157.

Schmid S, Buuck D, Knopff A, Bonifacio E, Ziegler AG. 2004**.**BABYDIET, a feasibility study to prevent the appearance of islet autoantibodies in relatives of patients with type 1 diabetes by delaying exposure to gluten. Diabetologia ***47,*** 1130–1131.

Seaberg RM, Smukler SR, Kieffer TJ. 2004.Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic lineages. *Nat Biotechnol* **22,** 1115-24.

Singal DP, Blajchman MA. 1973**.** Histocompatibility (HL-A) antigens, lymphocytotoxic antibodies and tissue antibodies in patients with diabetes mellitus. Diabetes **22,** 429–432.

Stene LC, Magnus P, Lie RT, Søvik O, Joner G. 2001.The Norwegian Childhood Diabetes Study Group. Birth weight and childhood onset type 1 diabetes: population based cohort study. *BMJ* **322,** 889-892.

Study design of the Trial to Reduce IDDM in the Genetically at Risk (TRIGR). 2007.Pediatr Diabetes **8,** 117–137.

Todd JA, Bell JI, McDevitt HO. 1987. HLA-DQ beta gene contributes to susceptibility and resistance to insulin-dependent diabetes mellitus. Nature **329,** 599–604.

Todd JA, Walker NM, Cooper JD. 2007. Robust associations of four new chromosome regions from genome-wide analyses of type 1 diabetes. Nat Genet **39,** 857–864.

Ueda H, Howson JM, Esposito L. 2003**.** Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. Nature **423,** 506–511.

Vafiadis P, Bennett ST, Todd JA. 1997. Insulin expression in human thymus is modulated by INS VNTR alleles at the IDDM2 locus. Nat Genet **15,** 289–292.

Vella A, Cooper JD, Lowe CE. 2005. Localization of a type 1 diabetes locus in the IL2RA/CD25 region by use of tag single-nucleotide polymorphisms. Am J Hum Genet **76,** 773–779.

Viskari H, Ludvigsson J, Uibo R. 2005.Relationship between the incidence of type 1 diabetes and maternal enterovirus antibodies: time trends and geographical variation. *Diabetologia* **48,** 1280-7.

Von Herrath M. 2009. Diabetes: a virus-gene collaboration. Nature **459,** 518–519.

Williams AJ, Aitken RJ, Chandler MA, Gillespie KM, Lampasona V, Bingley PJ.2008. Autoantibodies to islet antigen-2 are associated with HLA-DRB1*07 and DRB1*09 haplotypes as well as DRB1*04 at onset **of** type 1 diabetes: the possible role **of** HLA-DQA in autoimmunity to IA-2. Diabetologia **51,** 1444–1448.

Xu P, Cuthbertson D, Greenbaum C, Palmer JP, Krischer JP.2007. Role of insulin resistance in predicting progression to type 1 diabetes. Diabetes Care **30,** 2314–2320.