

# Analysis of population dynamics in beta-cell destruction lead to identification of novel candidate genes for type 1 diabetes

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## Abstract

A major difficulty in the genetic study of type 1 diabetes (T1D) is the lack of means to identify candidate disease genes, as the exact disease etiology is still unclear. We have developed a minimal model for T1D where we mathematically formulate the population dynamics for the most critical components in  $\beta$ -cell destruction: macrophages, T lymphocytes,  $\beta$  cells and  $\beta$ -cell autoantigens. System dynamic stability analysis revealed that the disease process for adult individuals is critically regulated by several major gene regulation pathways. Together they provide a comprehensive picture of where the candidate genes most likely lie. We will present our model, our bioinformatics platform to retrieve and update the gene information involved in the pathways, and our candidate gene database. In addition we will present our plan of candidate gene genotyping. Our approach represents **the first time** understanding the disease dynamics is integrated with the genetic study of a complex disease.

## 1. MINT1D and candidate genes for T1D

Type 1 diabetes (T1D) is a complex genetic disease that results from the selective destruction of pancreatic islet  $\beta$  cells by the immune system [1]. It is the most common chronic disease for children. Despite the extensive genetic studies, major disease genes are still not known, especially the genetic grounds for the onset delay in adult patients. This is largely due to current poor understanding of disease etiology, and hence the lack of means to identify candidate disease genes.

We have developed a novel approach to the genetic study of complex disease that integrates with mathematical modeling and bioinformatics. The aim is to identify candidate genes through the understanding of the disease dynamic process. The most essential cell populations in the  $\beta$  cell local milieu [2] include: (1)  $\beta$ -cells ( $\beta$ ). (2)  $\beta$ -cell released autoantigens ( $A$ ). (3) Resting tissue macrophages ( $M$ ), and activated macrophages ( $M_A$ ). (4) T lymphocytes that have infiltrated islet ( $T$ ). Their most critical kinetics and interactions are formulated using set of differential equations

$$\begin{aligned}\dot{M} &= a + (k + b)M_A - cM - gMA \\ \dot{M}_A &= gMA - kM_A \\ \dot{T} &= sM_A T - tT \\ \dot{\beta} &= r\beta - e\beta + N - lM_A - pT - qM_A T \\ \dot{A} &= n(e\beta + lM_A + pT + qM_A T) - mA\end{aligned}\tag{1}$$

We call this the minimal model of T1D (MINT1D). The parameters are rate constants for the corresponding process. For more detail see [2]. The equations describe the local event in the pancreatic islet that lead to  $\beta$ -cell destruction. A healthy individual is able to sustain the internal equilibrium of the body or homeostasis in spite of the modifications of the environment. When homeostasis fails it can lead to destruction of the system, which manifests as human disease. Therefore we investigate the key factors that contribute to the dynamic stability of the local interacting system, the conditions when the system is able to maintain healthy state, and when the  $\beta$ -cell destruction will perpetuate. We found the major predictions are consistent with existing laboratory and

clinical findings. Specifically, the model revealed that adult disease susceptibility is critically determined by 5 major pathways: (1)  $\beta$ -cell autoantigen release, (2)  $\beta$ -cell turnover rate, (3) cytokine induced  $\beta$ -cell death, (4) phagocytosis, and (5) macrophage activation. They together provide a comprehensive picture of where the candidate genes most likely lie.

## 2. Candidate gene database

Much information exists, though scattered, in literature and public databases. For example, the gene networks regulating immune mediated  $\beta$ -cell death in T1D have been extensively profiled and examined [3, 4]; signal transduction pathways leading to phagocytosis is well understood [5]. We have developed a bioinformatics procedure to collect information on genes regulating the major pathways. The estimated total is ~100-150 genes. We have also build a candidate gene database, and an interface with dbSNP/Ensembl and HapMap for SNP information retrieval and update. Figure 1 gives the entity-relationship diagram for our candidate gene database. For each key pathway, we collect the constituting genes in human, mouse and rat, as well as the sequence and polymorphism (SNP) information of the genes.

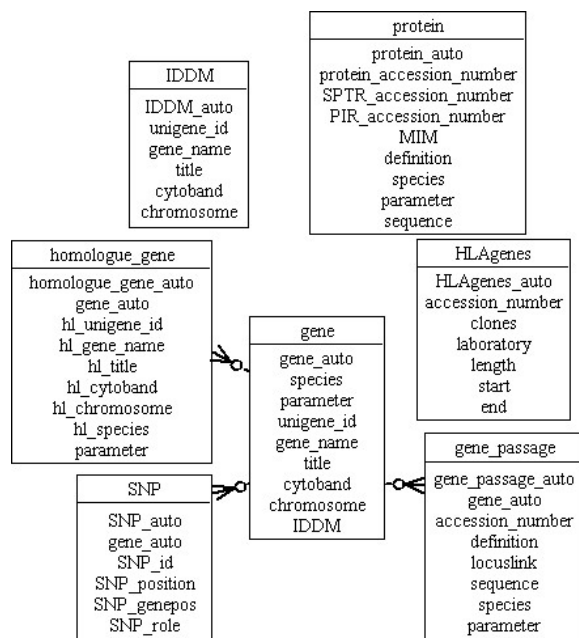


Figure 1. Entity-relationship diagram of MINT1D candidate gene database.

Using the database, study design can be conveniently developed by choosing the appropriate candidate genes and their polymorphisms. Currently, we are carrying out the world's largest whole genome scan study of adult-onset T1D using patient samples in Finland. We plan to perform a candidate gene study utilize the same sample collection. Finnish population-specific SNPs and allele frequencies will be examined; representative SNPs of candidate genes will be typed in 2000 cases and 2000 controls. Analysis of result, including a model-based novel logistic regression with latent variables approach will be performed. We expect our approach to hold more promise than currently available methodologies to make breakthroughs in T1D, and to identify disease-causing variant and genetic explanation for the delay of onset.

Our innovative approach integrates bioinformatics and mathematical modeling with genetic study. It is the first of its kind, our work may provide model approach for genetics study of other complex disease, as lack of means to identify candidate disease genes is a common problem.

It is important to understand genetic background for the disease onset delay in adult patients. For it may reveal important factors that contribute to risk, and may lead to means of disease prevention or intervention. In addition,

## 3. References

- [1] Tisch, R. and H. McDevitt, *Insulin-dependent diabetes mellitus*. Cell, 1996. **85**(3): p. 291-7.
- [2] Wang, X., Z. He, and S. Ghosh, *A mathematical model shows that difference in beta-cell turnover rate may cause the heterogeneity between young and adult onset type 1 diabetes*. Journal of Theoretical Biology, 2004: p. submitted.
- [3] Mandrup-Poulsen, T., *Apoptotic signal transduction pathways in diabetes*. Biochem Pharmacol, 2003. **66**(8): p. 1433-40.
- [4] Eizirik, D.L. and T. Mandrup-Poulsen, *A choice of death-the signal-transduction of immune-mediated beta-cell apoptosis*. Diabetologia, 2001. **44**(12): p. 2115-33.
- [5] Kwiatkowska, K. and A. Sobota, *Signaling pathways in phagocytosis*. Bioessays, 1999. **21**(5): p. 422-31.