Precision Type 1 Diabetes Genetics

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Introduction / Background

Type 1 Diabetes (T1D)

- T1D affects around 5-10% of people with diabetes and can develop at any age.
- T1D is caused by insulin deficiency resulting from autoimmune destruction of the pancreatic beta cells.

T1D Genetics

- Research has revealed a spectrum of disease variants that span between high impact, rare alleles that cause monogenic disease, and common alleles of low effect (Figure 1a)
- T1D risk is commonly polygenic in nature, with many low effect alleles contributing to disease development (Figure 1b – top)
- However, recent genetics research has identified T1D patients whose autoimmune disease risk is largely driven by a single genetic mutation (Figure 1b - bottom)

How to identify patients with possible monogenic T1D?

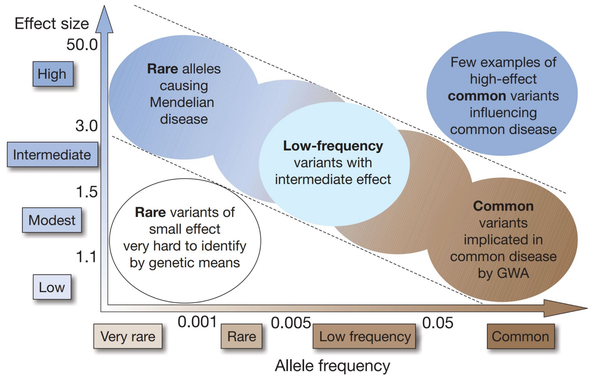
- Strong multigenerational family history of T1D, especially AB+
- And/or strong multigenerational family history of other autoimmune conditions
- And/or individual with T1D and multiple autoimmune conditions

Why does it matter to identify monogenic T1D?

- Therapeutic intervention targets
- Helps patient to understand why they developed diabetes
- Helps to direct follow up functional studies
- There are typically *family member implications*
  - Autosomal dominant forms: 50% chance of passing to children

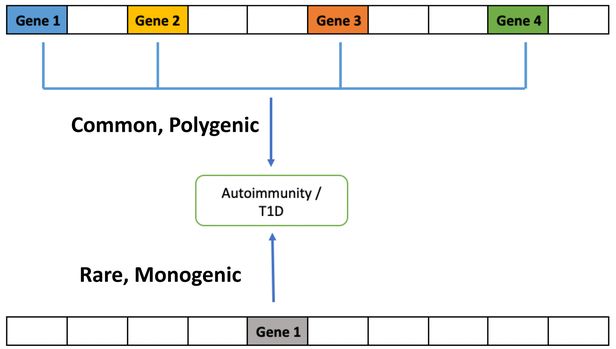
Complexity of Type 1 Diabetes (T1D) Genetics

Figure 1a: Spectrum of T1D Disease Variants



Manolio et al. *Nature* (2009)

Figure 1b. Polygenic vs. Monogenic T1D



Example of Monogenic T1D and comorbid autoimmunity

SKAP2 activating mutation causes T1D and multiple other autoimmunities

Clinical Characteristics

- No family history of T1D or other autoimmunity (**Figure 2a**)
- Diagnosed with T1D at age 12 with HbA1c 8.4% at presentation, 50th percentile BMI
- Other autoimmune conditions: Hashimoto's thyroiditis, eczema, intermittent hemolytic anemia, undifferentiated connective tissue disease, severe food allergies, and Raynaud syndrome, positive for GAD and ICA512 autoantibodies

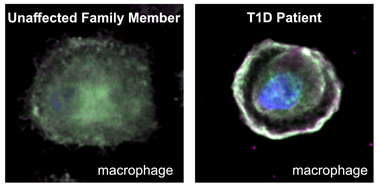
Genetic Analysis and Functional Studies

- Genomic sequencing of the T1D patient identified a de novo variant in the SKAP2 gene within a functionally important lipid-binding loop of the protein (**Figure 2b**).
- Functional studies of immune cells collected from the T1D patient and an unaffected family member demonstrated that the SKAP2 variant is a gain-of-function, pathogenic mutation that alters the immune cells of the T1D patient (**Figure 2c**).

Figure 2a.

Figure 2b.

Figure 2c.



Implications for Diabetes Care and Education Specialists

- It is important to be aware of the unique presentation of T1D patients with possible monogenic disease (as described in Intro/Background section)
- Referral for research-based genetic testing should be considered
- Genetic testing helps identify T1D patients that may benefit from targeted therapy

Resources for patients with unique presentations of T1D

- University of Chicago and University of California San Francisco are conducting a collaborative study to discover genetic insights of autoimmunity and T1D
- Patients may review additional information and sign up for the study at www.precisiont1d.uchicago.edu

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