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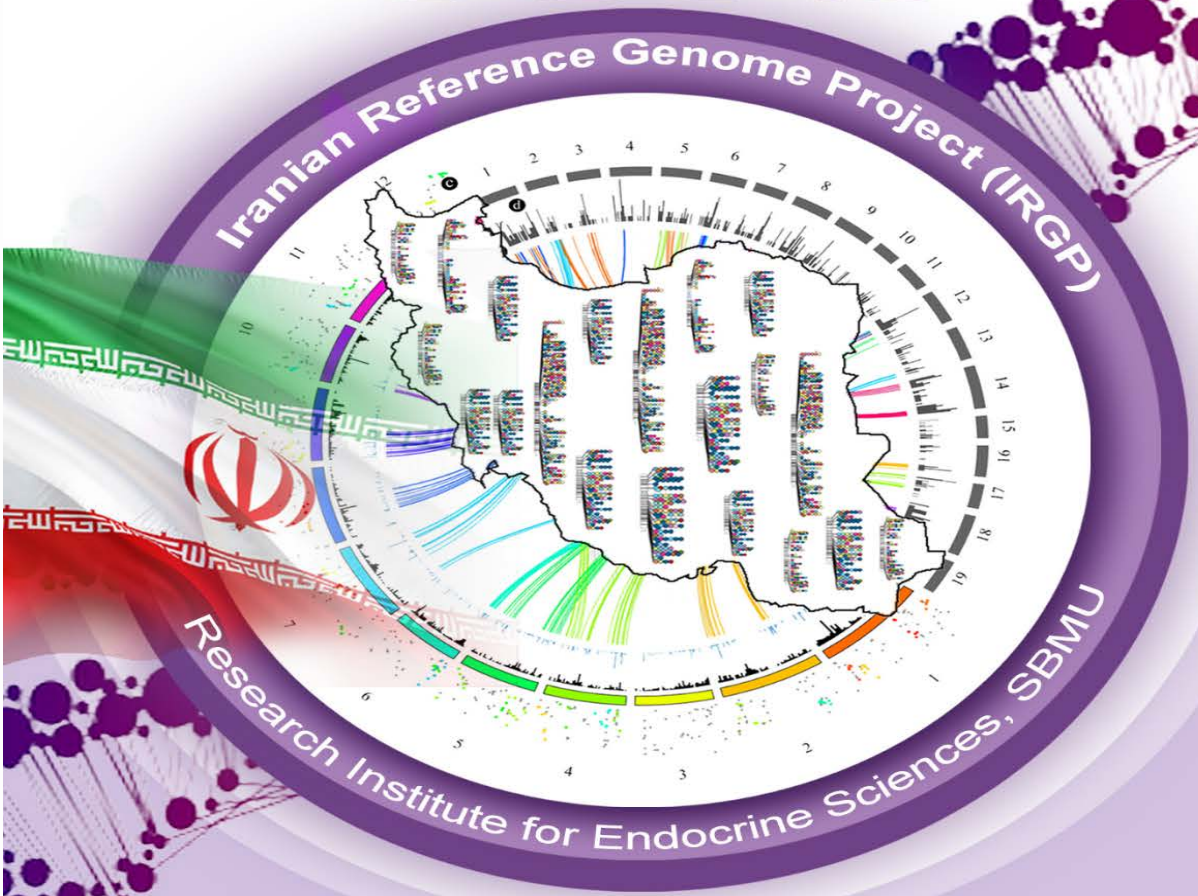

Genetic Risk Score of Type 1 of Diabetes in the Tehran Cardio-Metabolic Genetic Study (TCGS) Population

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Overview

- ✓ Type 1 diabetes: causes and biomarkers
- ✓ Genetics of type 1 diabetes
- ✓ Genetic risk score in the TCGS population

Why Type 1 Diabetes?

- While T1D represents about 2% of all forms of diabetes, it has a large healthcare cost owing to its often early onset, the high cost of insulin, and the elevated risk of complications.

- The rate of type 1 diabetes and diabetic ketoacidosis (DKA) rate is increased after the COVID-19 pandemic among European pediatric populations.

- For precision medicine, it is essential to characterize various forms of a disease.

Type 1 Diabetes

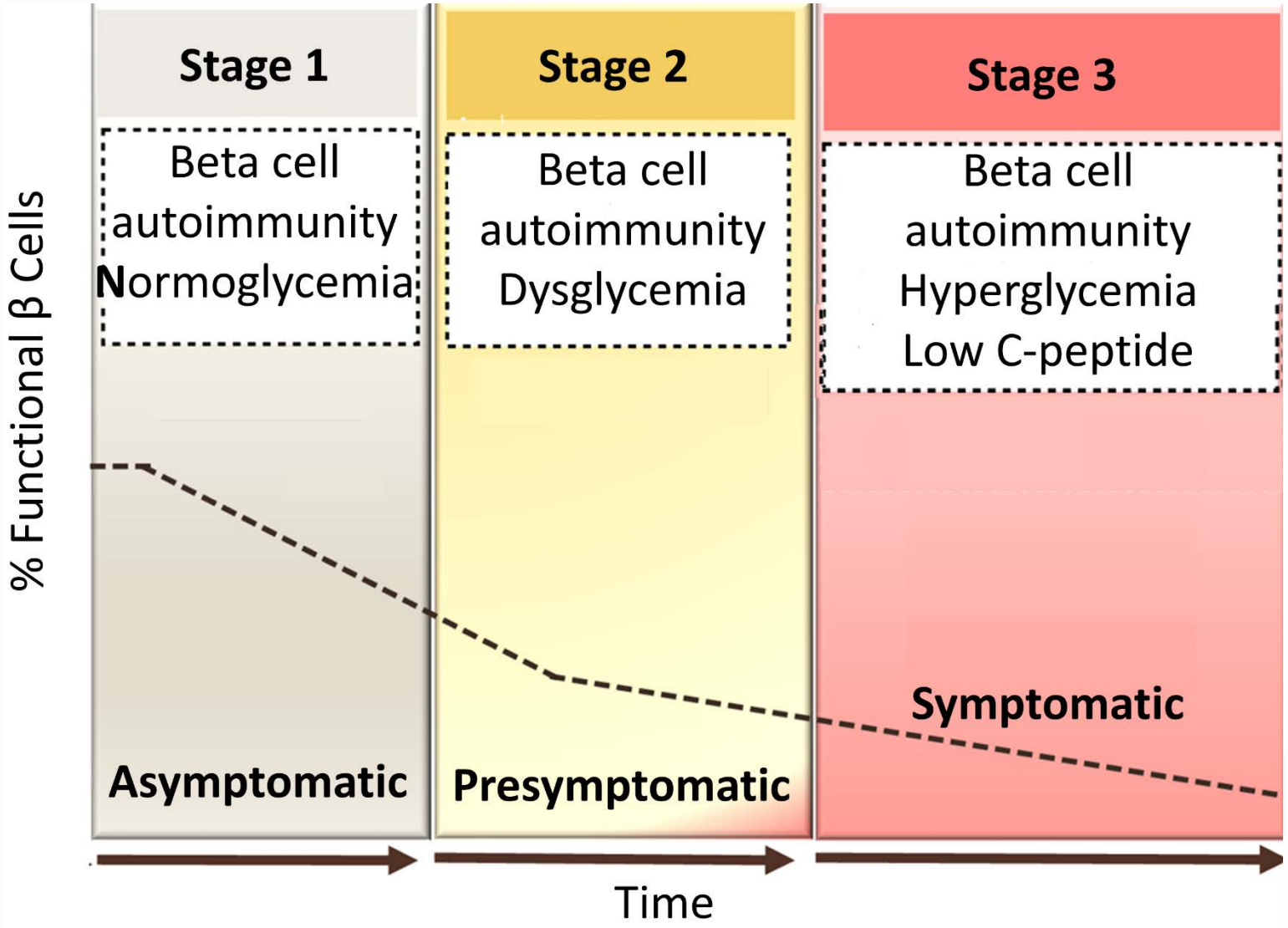
- Type 1 diabetes (T1D) is a multifactorial disease caused by the autoimmune destruction of pancreatic β cells, resulting in severe insulin deficiency.

- Islet autoantibodies against insulin (IAA), glutamic acid decarboxylase (GADA), tyrosine phosphatase-like protein IA-2 (IA-2A), and zinc transporter 8 (ZnT8A).

- Low C-peptide (insulin deficiency) and related clinical symptoms.

- Genetic markers

Staging of Type 1 Diabetes (ADA 2023)



- Age of onset
- Number of autoantibodies
- Autoantibody titer
- Genetic and non-genetic factors

Adult-onset Type 1 Diabetes

- ✓ T1D is the most common type of diabetes in individuals under 20, but 25% of cases are diagnosed in adulthood.
- ✓ Diagnosing T1D in adults, especially those older than 30, is challenging due to the higher prevalence of type 2 diabetes.
- ✓ 4% of diabetes cases in the UK Biobank population were diagnosed as T1D after age 30, with similar clinical characteristics to younger ages.

Discriminative Power of T1D Biomarkers

- Islet autoantibody positivity is lower in adult-onset T1D compared to childhood-onset.

- C-peptide can differentiate between T1D and T2D after honeymoon phase, but it is not effective in diagnosing T1D.

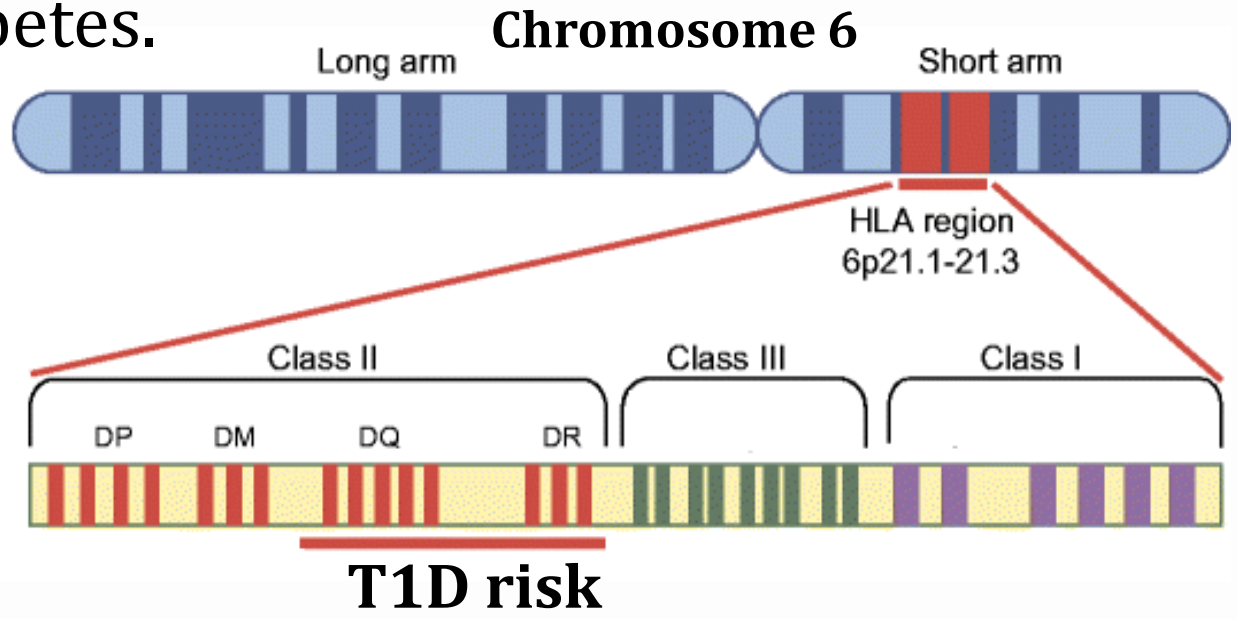
- Genetic factors remain stable over time and can be assessed from birth.

Genetics of Type 1 Diabetes

- Type 1 diabetes is the highly heritable (50-70%) and polygenic disease.
- Genome-wide association studies (GWAS) identified multiple genetic variants associated with type 1 diabetes.
- Approximately 50% of this heritability is attributable to the Human Leukocyte Antigen (HLA) region.

- The HLA region is a cluster of highly polymorphic genes located on chromosome 6 that code for proteins involved in the immune system.

- HLA class-II genes (DR and DQ haplotypes) are strongly associated with the risk of type 1 diabetes.



Type 1 Diabetes Polygenic Risk Score

- ✓ A polygenic risk score (PRS) is a weighted sum of the T1D-associated risk alleles in an individual.
- ✓ Newborn screening to identify genetically high-risk infants.
- ✓ Predicting type 1 diabetes development in non-diabetic autoantibody-positive individuals.
- ✓ **Distinguishing adult-onset T1D from T2D cases**.

Prevalence of T1D in TLGS Population

- T1D is defined based on age onset of diabetes < 40 years old, BMI at the diabetic phase < 30 kg/m^2, and exclusively treatment with insulin.

- Out of 27000 participants, 16 individuals were diagnosed with T1D in the TLGS population. All T1D patients have been verified by the endocrinologist. Prevalence of T1D in this population is 0.06%.

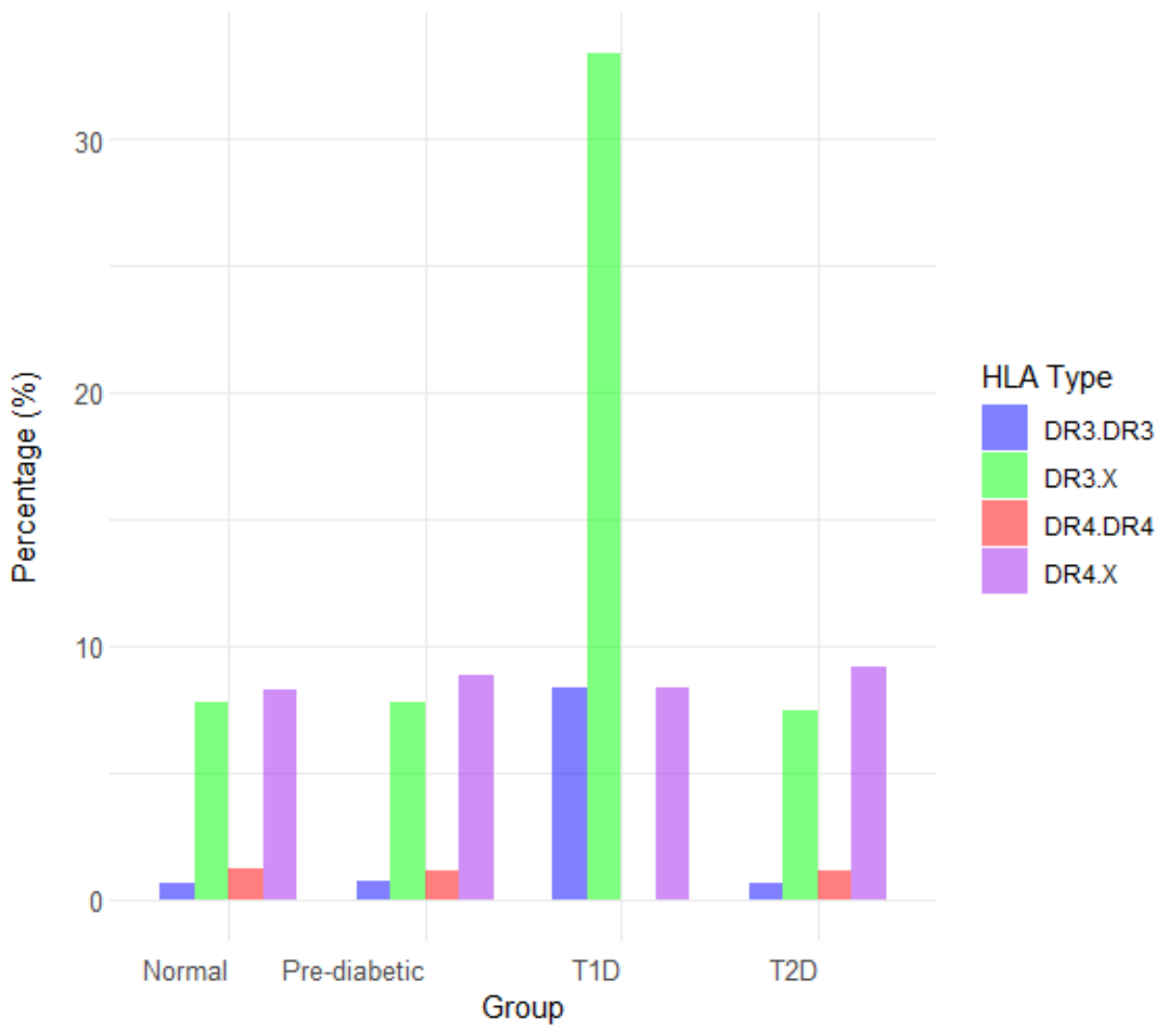
- The genetic information was available for 12 individuals with T1D (TCGS Population).

Characteristics of the TCGS Population

	T1D	T2D	Pre-diabetes	Non-diabetic
Sample Size	12	2185	4450	6681
Female (N)	7	1237	2168	3831
Age onset (mean ± SD)	22 ± 9.21	52.67 ± 14	NA	NA
BMI (mean ± SD)	23 ± 4.7	30.22 ± 5.35	NA	NA

High-risk HLA Haplotype in the TCGS Population

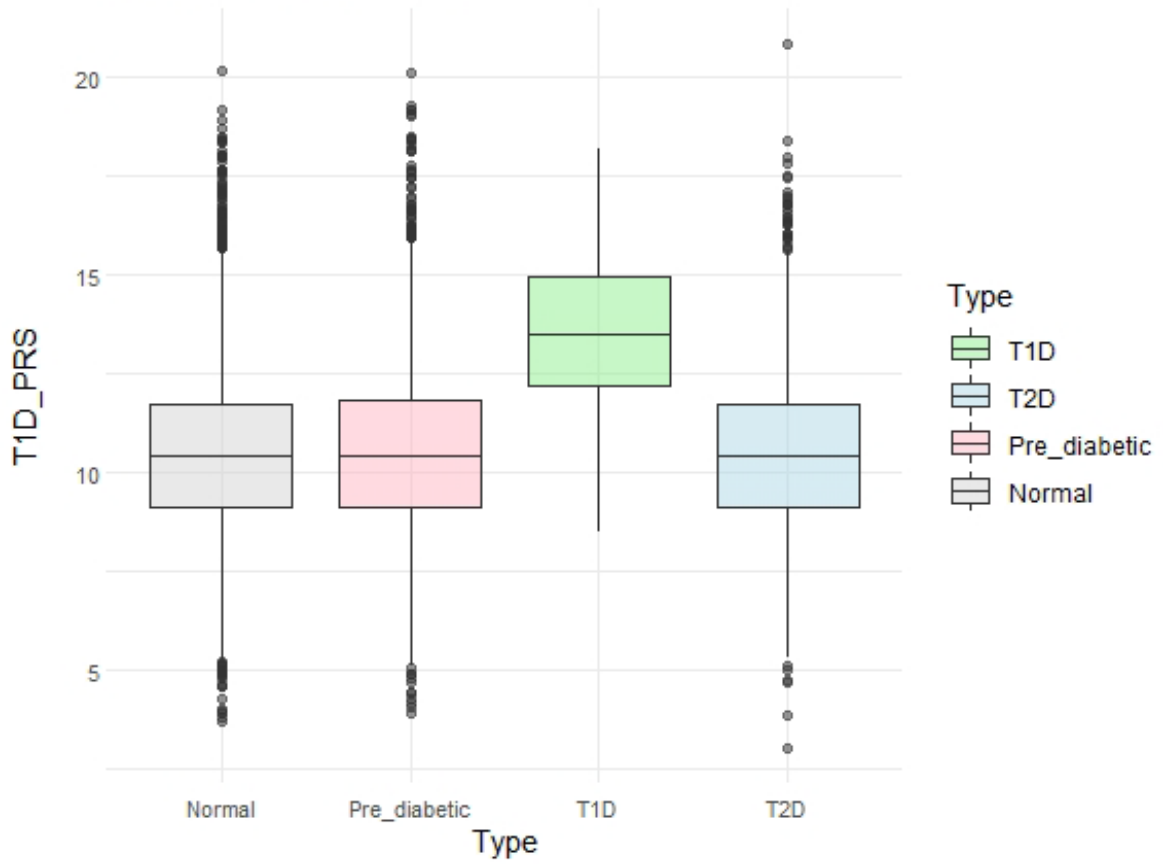
DR3 and DR4 haplotypes are strongly associated with the risk of type 1 diabetes



T1D PRS Distribution in the All Groups of TCGS Population

- Construction of polygenic risk score based on the T1D-associated SNPs

- Based on Wilcoxon rank sum test, there is significant difference in the distribution of PRS between T1D and other groups (p-value = 0.003).

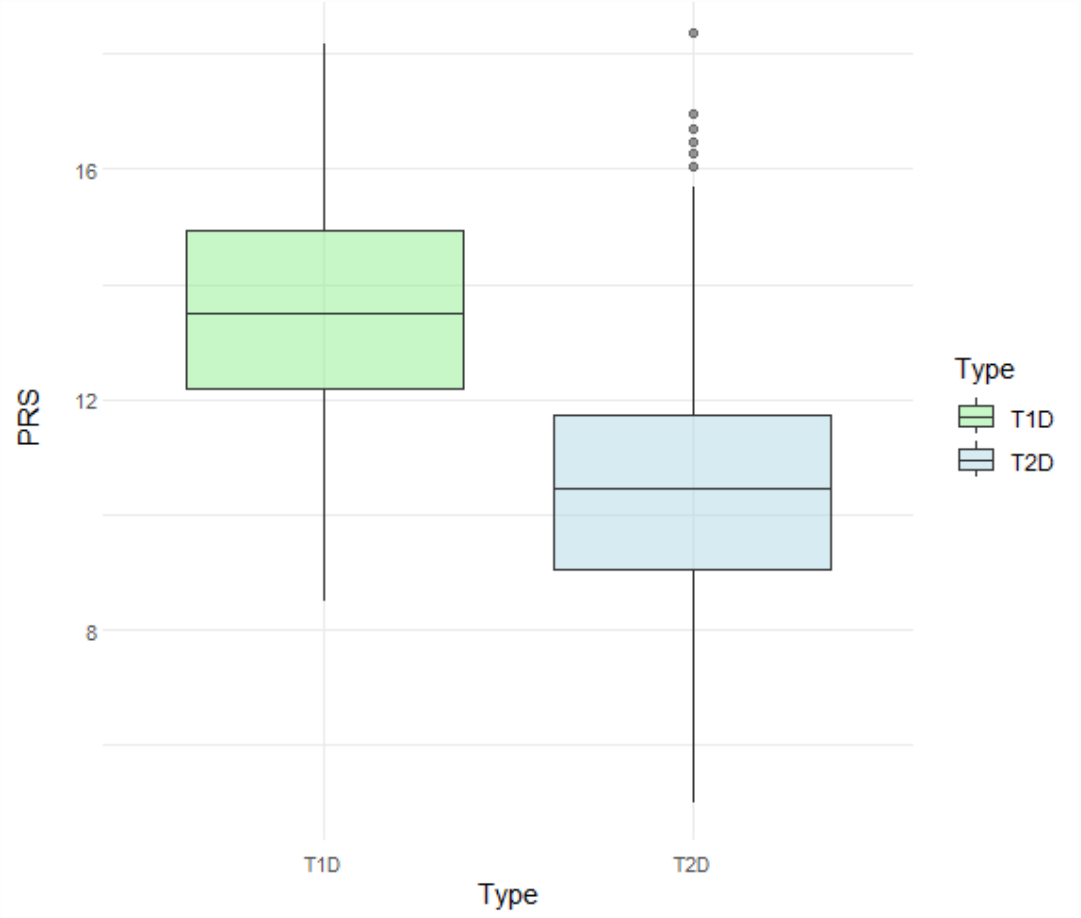


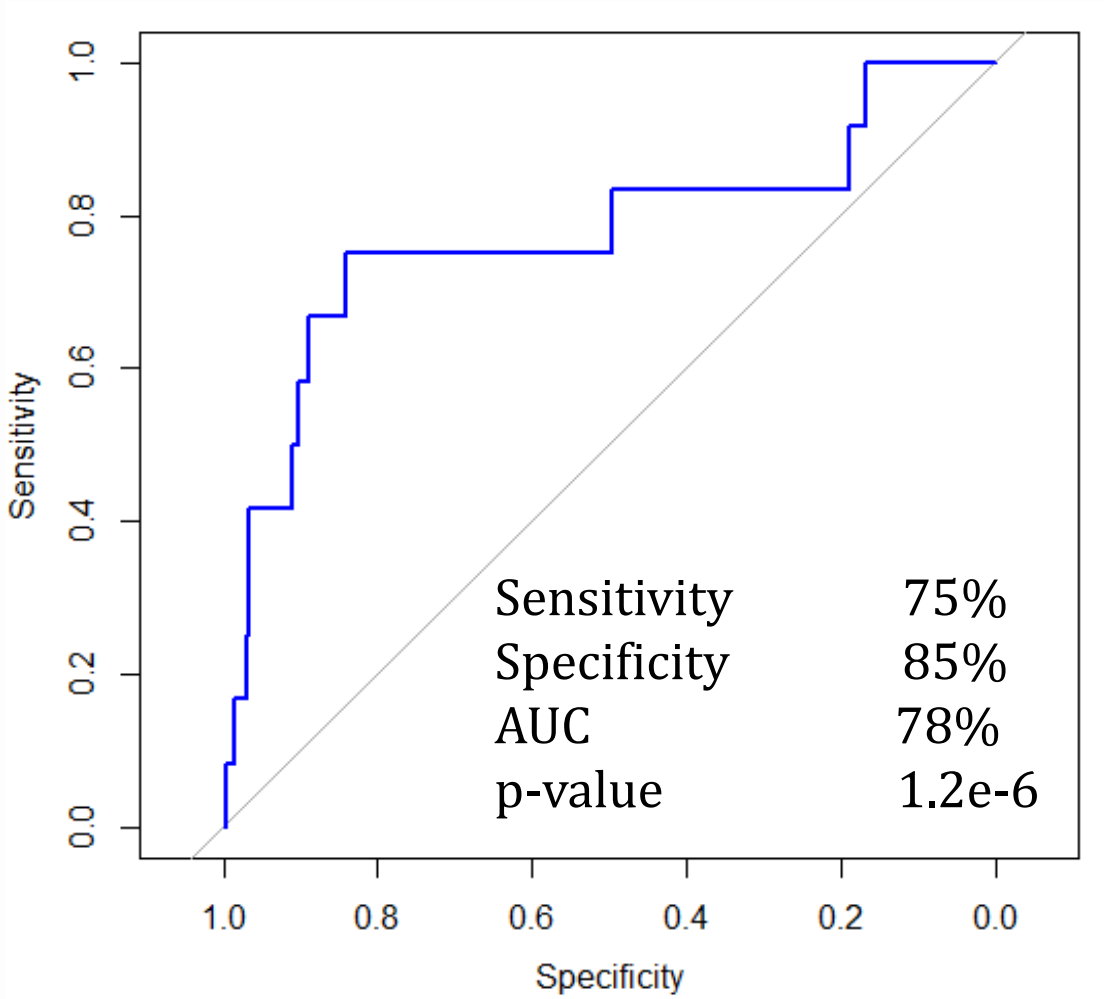
Sample size	Normal	Pre-diabetic	T1D	T2D
	6681	4450	12	2189

Characteristics of the TCGS Diabetic Population With Age Onset Under 40 Years

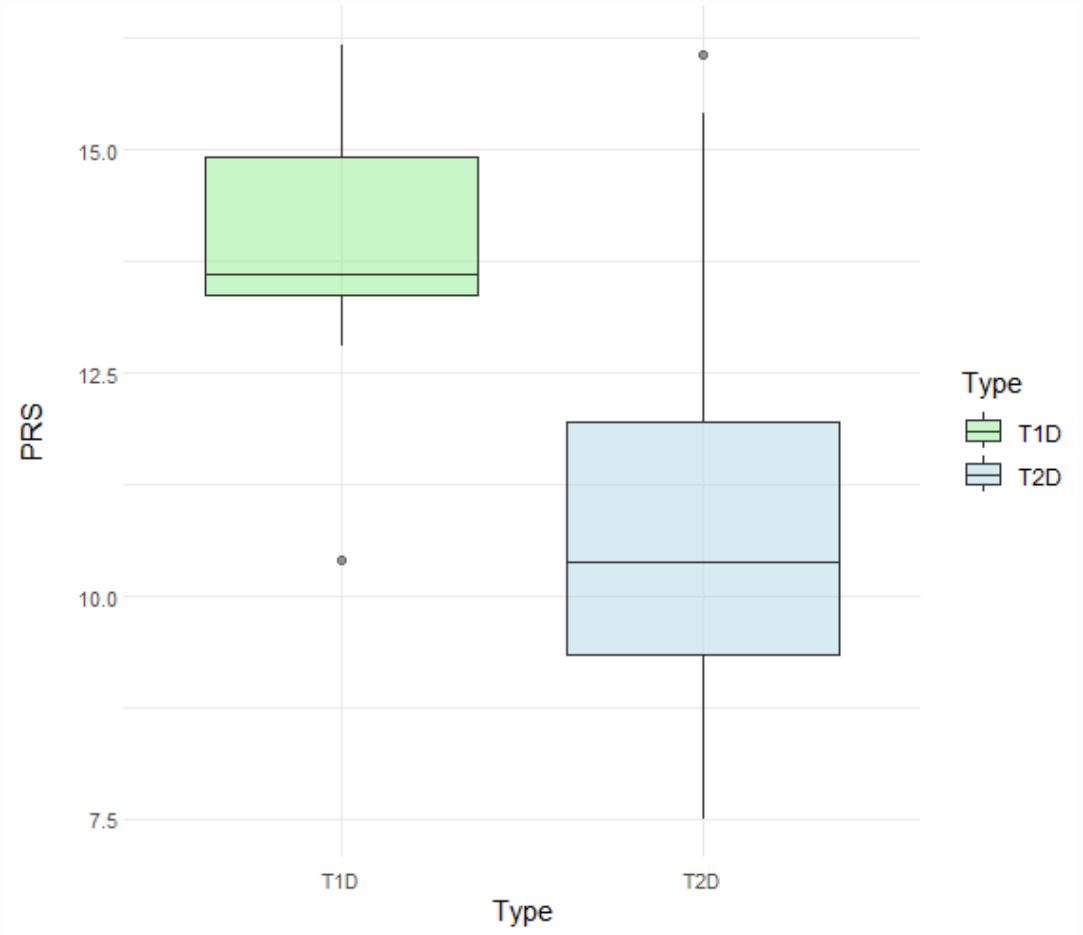
	T1D	T2D
Sample Size	12	375
Female (N)	7	217
Age onset (mean ± SD)	22 ± 9.21	32 ± 7.12
BMI (mean ± SD)	23 ± 4.7	29.8 ± 6.11

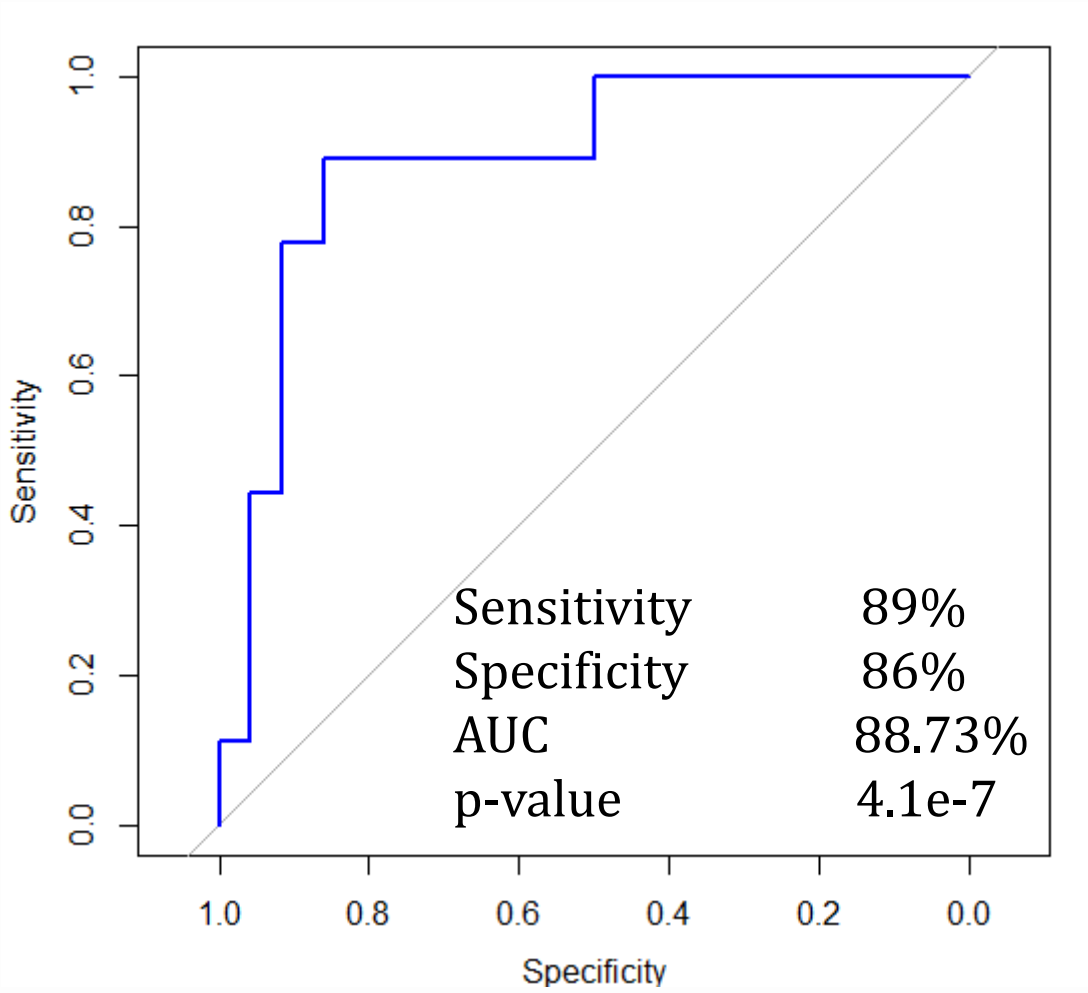
Distinguishing T1D From T2D in Cases With Age Onset Under 40 Years





Discriminative Power of T1D PRS to Distinguish T1D From T2D in Cases with Age Onset Under 25 Years





Conclusion

- ✓ Type 1 diabetes PRS can effectively distinguish T1D from T2D in the TCGS populations.

- ✓ The utilization of T1D PRS provides an example where results of genome-wide association studies can be translated into clinical applications.

Thank you!