Subgroups of young-onset type 2 diabetes in India reveal insulin deficiency as a major driver

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ESM Methods

Comparability of laboratory measurements

C peptide was measured by ELISA (DBC) in the WellGen and Assam study, and by ECLIA (Roche) in the ANDIS and DIREVA study and by CLIA (MAGLUMI) in Ahmedabad study; all based on mouse anti-C-peptide antibody and calibrated against WHO International Reference Reagent for C-peptide of human insulin for immunoassay (IRR code 84/510). This highlights comparability of the assays.

GWAS QC and Imputation

SNP exclusion criteria included missingness threshold of > 0.05% MAF<1% and Hardy-Weinberg equilibrium p-value<0.05. Imputation was performed on the Michigan Imputation server using 1000G Phase 3 v5 (GRCh37/hg1) as a reference panel along with Eagle v2.4 phasing and SAS (South Asian) as population type.
### ESM Tables

| Characteristics       | Ahmedabad |   |   |
|-----------------------|-----------|---|---|
|                       | Men       | Women | All |
| Number                | 138 (73.79) | 49 (26.20) | 187 |
| Age at Diagnosis (y)  | 36.6 (6.75) | 37.47 (6.72) | 36.83 (6.74) |
| BMI (Kg/m²)           | 27.44 (3.7) | 28.28 (4.16) | 27.66 (3.83) |
| Fasting glucose (mmol/L) | 10.70 (4.64) | 11.37 (4.78) | 10.87 (4.68) |
| HbA1c (mmol)          | 72.61 (26.2) | 72.91 (25) | 72.69 (25.82) |
| HbA1c (%)             | 8.8 (4.5) | 8.8 (4.4) | 8.8 (4.5) |
| Fasting C-peptide (nmol/L) | 0.45 (0.21) | 0.41 (0.16) | 0.44 (0.20) |
| HOMA2-B               | 37.41 (31.54) | 30.35 (23.94) | 35.56 (29.84) |
| HOMA2-IR              | 1.5 (1.1) | 1.48 (1.01) | 1.49 (1.07) |

**ESM table 1:** Clinical and Biochemical characteristics of participants enrolled in Ahmedabad study with age at diagnosis less than 45 years
| Characteristics          | Men                  | Women                | All       |
|-------------------------|----------------------|----------------------|-----------|
| Number                  | 135 (65.85)          | 70 (34.15)           | 205       |
| Age at Diagnosis (y)    | 32.93 (4.86)         | 30.99 (5.8)          | 32.26 (5.27) |
| Duration of Diabetes (y)| 2.87 (3.38)          | 4.33 (3.85)          | 3.37 (3.60) |
| BMI (Kg/m²)             | 23.46 (3.86)         | 23.21 (3.65)         | 23.37 (3.79) |
| Fasting glucose (mmol/L)| 10.32 (4.85)         | 10.90 (4.93)         | 10.52 (4.87) |
| HbA1c (mmol)            | 82.3 (33.38)         | 82.15 (30.98)        | 82.25 (32.5) |
| HbA1c (%)               | 9.7 (5.2)            | 9.7 (5.0)            | 9.7 (5.1) |
| Fasting C-peptide (nmol/L)| 0.40 (0.31)      | 0.45 (0.38)          | 0.42 (0.34) |
| HOMA2-B                 | 38.96 (35.35)        | 34.93 (28.45)        | 37.58 (33.14) |
| HOMA2-IR                | 1.55 (2.71)          | 2.26 (4.98)          | 1.79 (3.65) |

**ESM table 2:** Clinical and Biochemical characteristics of participants enrolled in PHENOEINDY-2 study from Assam with age at diagnosis less than 45 years.
### ESM table 3: Clinical and Biochemical characteristics of participants enrolled in DIREVA study with age at diagnosis less than 45 years.

| Characteristics     | Men       | Women     | All       |
|---------------------|-----------|-----------|-----------|
| Number              | 243       | 177       | 420       |
| Age at Diagnosis (y)| 36.78 (7.23) | 36.44 (6.95) | 36.6 (7.1) |
| Duration of Diabetes (y) | 14.78 (12.06) | 13.85 (12.30) | 14.39 (12.16) |
| BMI (Kg/m$^2$)      | 31.62 (6.59) | 31.63 (6.60) | 31.62 (6.6)  |
| Fasting glucose (mmol/L) | 9.19 (3.06) | 8.74 (3.25) | 9.01 (3.15) |
| HbA1c (mmol/mol)    | 59.32 (16.93) | 56.48 (16.84) | 58.13 (16.93) |
| HbA1c (%)           | 7.5 (3.7)  | 7.3 (3.7)  | 7.5 (3.7)  |
| Fasting C-peptide (nmol/L) | 0.60 (0.51) | 0.59 (0.41) | 0.59 (0.47) |
| HOMA2-B             | 46.80 (36.26) | 53.61 (36.17) | 49.67 (34.09) |
| HOMA2-IR            | 1.73 (1.36)  | 1.65 (1.03) | 1.69 (1.23) |

*Note: Values are mean (SD).*
| Sl No | SNP            | Gene         | Major allele | Minor allele | Risk allele | Odds Ratio | Weight |
|-------|----------------|--------------|--------------|--------------|-------------|------------|--------|
| 1     | rs2187668      | HLA-DRB1     | C            | T            | T           | -          | -      |
| 2     | rs7454108      | HLA-DQ8      | C            | T            | C           | -          | -      |
|       | rs3957146      |              | C            | T            | C           | -          | -      |
| 3     | rs1264813      | HLA_A_24     | C            | T            | T           | 1.54       | 0.43   |
| 4     | rs2395029      | HLA_B_5701   | T            | G            | T           | 2.5        | 0.92   |
| 5     | rs3129889      | HLA_DRB1_15  | G            | A            | A           | 14.88      | 2.7    |
| 6     | rs2476601      | PTPN22       | A            | G            | A           | 1.96       | 0.67   |
| 7     | rs689          | INS          | A            | T            | T           | 1.75       | 0.56   |
| 8     | rs12722495     | IL2RA        | T            | C            | T           | 1.58       | 0.46   |
| 9     | rs2292239      | ERBB3        | G            | T            | T           | 1.35       | 0.3    |

**SNPs**

- rs2187668, rs7454108* (proxy 1: rs3957146)

**Haplotypes**

| Haplotypes | Haplotypes | Haplotype allele score | Odds ratio | Weights |
|------------|------------|------------------------|------------|---------|
| DR3/DR4    | CT/CT      | 6                      | 48.18      | 3.87    |
| DR4/DR4    | CC/CC      | 5                      | 21.98      | 3.09    |
| DR3/DR3    | TT/TT      | 4                      | 21.12      | 3.05    |
| DR4/X      | CC/CT      | 3                      | 7.03       | 1.95    |
| DR3/X      | CT/TT      | 2                      | 4.53       | 1.51    |
| X/X        | CC/TT      | 1                      | 1          | 0       |

*Barker et.al., Winkler et.al.*

**ESM table 4.** List of type 1 diabetes associated SNPs used to construct genetic risk scores for T1D presented with the risk alleles.
Included (N=560) | Excluded (N=1052) | P-value
---|---|---
Age at Diagnosis (y) | 37.212 (5.832) | 36.863 (5.749) | 0.25
BMI (Kg/m²) | 26.371 (4.028) | 26.079 (4.09) | 0.167
Fasting glucose (mmol/l) | 9.278 (3.265) | 9.251 (3.38) | 0.879
HbA1c (mmol/mol) | 71.271 (22.532) | 73.185 (22.737) | 0.106
HbA1c (%) | 8.3 (4.2) | 8.8 (4.3) | 0.106
Fasting C-Peptide (nmol/l) | 0.748 (0.51) | 0.779 (0.434) | 0.213
HOMA2B | 54.428 (37.141) | 59.419 (42.854) | 0.015
HOMA2IR | 2.102 (1.558) | 2.144 (1.257) | 0.58

Values are mean (SD)
*Bonferroni corrected significant $p$ values

$p$ values were calculated using $t$ test

**ESM table 5**: Patient characteristics for those included in the T1D GRS calculation compared to those excluded.
## WellGen-Total (1612)

| Cluster | SIDD | SIRD | MOD | MARD | SIDD | SIRD | MOD | MARD | P (SIDD) | P (SIRD) | P (MOD) | P (MARD) |
|---------|------|------|-----|------|------|------|-----|------|---------|----------|---------|---------|
| Number (%) | 264 (45.5) | 10 (1.7) | 259 (44.7) | 47 (8.1) | 587 (56.9) | 8 (0.8) | 349 (33.8) | 88 (8.5) | 0.588 | 0.095 | 0.006* | 0.346 |
| Age at Diagnosis (y) | 37.1 (6.0) | 37.0 (5.4) | 37.0 (5.5) | 41.3 (3.9) | 36.8 (5.7) | 41.0 (3.4) | 35.7 (5.7) | 40.6 (4.0) | -- | -- | -- | -- |
| Duration of diabetes (y) | 1.9 (1.5) | 1.5 (1.7) | 1.9 (1.5) | 2.1 (1.4) | 14.3 (7.0) | 12.6 (6.6) | 13.7 (7.2) | 13.9 (7.7) | -- | -- | -- | -- |
| BMI (Kg/m²) | 24.7 (3.5) | 29.3 (6.3) | 28.4 (4.1) | 23.9 (2.3) | 25.1 (3.4) | 28.4 (5.3) | 28.4 (3.9) | 22.8 (2.4) | 0.074 | 0.419 | 0.804 | 0.013 |
| Fasting glucose (mmol/L) | 10.4 (3.0) | 5.7 (0.79) | 7.4 (1.9) | 6.7 (1.5) | 10.9 (3.5) | 6.0 (1.8) | 8.2 (2.6) | 6.4 (1.4) | 0.047 | 0.700 | 0.0001* | 0.188 |
| HbA1c (mmol/mol) | 88.1 (21.0) | 53.4 (11.9) | 57.1 (12.9) | 46.1 (10.6) | 86.5 (18.5) | 60.9 (14.1) | 59.2 (12.8) | 47.9 (10.3) | 0.257 | 0.247 | 0.054 | 0.338 |
| HbA1c (%) | 10.2 (4.1) | 7.0 (3.2) | 7.4 (3.3) | 6.4 (3.2) | 10.1 (3.9) | 7.7 (3.4) | 7.5 (3.3) | 6.5 (3.2) | 0.257 | 0.247 | 0.054 | 0.338 |
| Fasting C-Peptide (nmol/L) | 0.75 (0.40) | 2.1 (0.47) | 0.96 (0.46) | 0.67 (0.29) | 0.65 (0.39) | 2.0 (0.72) | 0.84 (0.49) | 0.54 (0.28) | 0.001 | 0.856 | 0.004* | 0.014 |
| HOMA2B | 42.2 (24.4) | 218.9 (32.7) | 85.8 (41.7) | 77.1 (33.6) | 35.6 (20.9) | 210.1 (51.57) | 71.3 (41.2) | 71.9 (29.8) | 0.0001 | 0.665 | 0.0001* | 0.361 |
| HOMA2IR | 2.2 (1.3) | 4.7 (1.2) | 2.4 (1.2) | 1.6 (0.79) | 2.03 (1.47) | 4.7 (2.0) | 2.19 (1.31) | 1.31 (0.73) | 0.169 | 0.992 | 0.048 | 0.016 |

## WellGen-Male participants (902)

| Cluster | SIDD | SIRD | MOD | MARD | SIDD | SIRD | MOD | MARD | P (SIDD) | P (SIRD) | P (MOD) | P (MARD) |
|---------|------|------|-----|------|------|------|-----|------|---------|----------|---------|---------|
| Number (%) | 180 (52.6) | 2 (0.6) | 120 (35.1) | 40 (11.7) | 367 (65.5) | 3 (0.5) | 110 (19.6) | 80 (14.3) | 0.726 | 0.440 | 0.281 | 0.570 |
| Age at Diagnosis (y) | 37.1 (5.9) | 43.8 (0.21) | 36.9 (5.5) | 41.0 (4.1) | 36.9 (5.5) | 41.2 (3.9) | 36.2 (5.3) | 40.5 (4.1) | -- | -- | -- | -- |
| Duration of diabetes (y) | 1.9 (1.5) | 3.5 (0.27) | 1.9 (1.5) | 2.06 (1.3) | 14.8 (7.5) | 11.06 (7.2) | 14.0 (7.4) | 13.9 (7.9) | -- | -- | -- | -- |
| BMI (Kg/m²) | 24.2 (3.2) | 27.9 (1.6) | 28.1 (3.1) | 24.1 (2.3) | 24.5 (3.0) | 29.3 (4.8) | 29.5 (4.1) | 23.0 (2.3) | 0.208 | 0.715 | 0.003 | 0.015 |
| Fasting glucose (mmol/L) | 10.1 (2.9) | 5.9 (0.71) | 7.3 (2.1) | 6.7 (1.6) | 10.4 (3.4) | 5.6 (1.3) | 7.9 (2.7) | 6.4 (1.6) | 0.331 | 0.792 | 0.073 | 0.252 |
| HbA1c (mmol/mol) | 87.9 (23.5) | 53.5 (13.1) | 56.7 (11.8) | 46.9 (9.2) | 83.0 (18.8) | 46.1 (9.5) | 63.4 (14.2) | 47.9 (10.4) | 0.008 | 0.507 | 0.0001 | 0.609 |
| HbA1c (%) | 10.2 (4.3) | 7.0 (3.3) | 7.5 (3.2) | 6.4 (3.0) | 9.7 (3.9) | 6.4 (3.0) | 7.9 (3.4) | 6.5 (3.1) | 0.008 | 0.507 | 0.0001 | 0.609 |
| Fasting C-Peptide (nmol/L) | 0.73 (0.41) | 2.28 (0.04) | 1.05 (0.45) | 0.70 (0.31) | 0.63 (0.37) | 2.10 (0.62) | 1.12 (0.57) | 0.56 (0.29) | 0.002 | 0.723 | 0.290 | 0.014 |
| Cluster | SIDD | SIRD | MOD | MARD | SIDD | SIRD | MOD | MARD |
|---------|------|------|------|------|------|------|------|------|
| Number (%) | 84 (35.3) | 8 (3.4) | 139 (58.4) | 7 (2.9) | 220 (46.6) | 5 (1.1) | 239 (50.6) | 8 (1.7) |
| Age at Diagnosis (y) | 36.9 (6.3) | 35.4 (4.6) | 37.0 (5.9) | 42.9 (1.1) | 36.6 (5.9) | 40.9 (3.6) | 35.5 (5.9) | 41.2 (3.2) |
| Duration of diabetes (y) | 1.9 (1.5) | 0.99 (1.5) | 2.0 (1.5) | 2.4 (1.9) | 13.6 (6.0) | 13.4 (6.8) | 13.6 (7.1) | 13.9 (6.3) |
| BMI (Kg/m²) | 25.8 (3.8) | 29.6 (7.1) | 28.6 (4.8) | 22.7 (1.4) | 26.2 (3.8) | 25.9 (2.7) | 27.9 (3.8) | 20.7 (3.4) |
| Fasting glucose (mmol/L) | 11.1 (3.2) | 5.7 (0.85) | 7.5 (1.8) | 6.6 (1.1) | 11.8 (3.6) | 6.2 (2.2) | 8.2 (2.5) | 6.1 (0.9) |
| HbA1c (mmol/mol) | 88.5 (14.5) | 53.4 (12.6) | 57.5 (13.9) | 41.4 (16.7) | 92.3 (16.6) | 69.6 (6.6) | 57.2 (11.7) | 47.8 (8.7) |
| HOMA2B | 43.7 (25.1) | 224.0 (43.7) | 94.4 (42.2) | 80.1 (34.9) | 37.2 (20.8) | 232.6 (48.6) | 89.9 (42.9) | 73.3 (30.2) |
| Duration of diabetes ≥ 5y (N=472, 66.5%) | | | | | | | | |
| P (SIDD) | 0.001 | 0.501 | 0.067 | 0.067 |
| P (SIRD) | 0.001 | 0.501 | 0.067 | 0.067 |
| P (MOD) | 0.001 | 0.501 | 0.067 | 0.067 |
| P (MARD) | 0.001 | 0.501 | 0.067 | 0.067 |

Note: Values are mean (SD),

*Bonferroni corrected significant p values

p value by ANOVA,

**ESM table 6: Sensitivity Analysis.** Characteristics of participants enrolled in WellGen study by duration of diabetes and clusters, presented separately for men and women.
### ESM Table 7: Characteristics of participants enrolled in WellGen study by clusters generated using de novo k-means clustering, presented separately for men and women.

|                     | Male participants (902) | Female participants (710) | Total (1612) |
|---------------------|-------------------------|---------------------------|--------------|
|                     | 1 (65.4)                | 2 (34.6)                  | 1 (66.6)     |
|                     | 312                     | 227                       | 539          |
| Number (%)          | 590 (65.4)              | 483 (68.0)                | 1073 (66.6)  |
|                     | 312 (34.6)              | 227 (32.0)                | 539 (33.4)   |
| Age at Diagnosis (y)| 36.66 (5.76)            | 35.94 (6.02)              | 36.033 (5.89) |
|                     | 38.76 (4.92)            | 37.59 (5.77)              | 38.27 (5.14)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 10.33 (8.64)            | 10.40 (7.53)              | 10.36 (8.16)  |
|                     | 8.48 (8.21)             | 8.00 (7.69)               | 8.28 (7.16)   |
|                     | 0.0001<sup>a</sup>     | 0.0001<sup>a</sup>       | 0.0001<sup>a</sup>  |
| Duration of diabetes (y) | 24.04 (2.94)             | 25.99 (3.60)              | 24.92 (3.40)  |
|                     | 28.05 (3.69)            | 29.57 (4.54)              | 28.69 (4.14)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 9.51 (3.18)             | 10.37 (3.43)              | 9.90 (3.32)   |
|                     | 8.28 (3.19)             | 7.57 (2.64)               | 7.98 (2.99)   |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
| BMI (Kg/m²)         | 24.04 (2.94)            | 25.99 (3.60)              | 24.92 (3.40)  |
|                     | 28.05 (3.69)            | 29.57 (4.54)              | 28.69 (4.14)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 9.51 (3.18)             | 10.37 (3.43)              | 9.90 (3.32)   |
|                     | 8.28 (3.19)             | 7.57 (2.64)               | 7.98 (2.99)   |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 77.41 (23.27)           | 78.09 (21.31)             | 77.72 (22.41) |
| HbA1c (mmol/mol)    | 65.30 (20.27)           | 57.86 (17.20)             | 62.17 (19.45) |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 77.41 (23.27)           | 78.09 (21.31)             | 77.72 (22.41) |
|                     | 65.30 (20.27)           | 57.86 (17.20)             | 62.17 (19.45) |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
| HbA1c (%)           | 9.2 (4.3)               | 9.3 (4.1)                 | 9.3 (4.2)    |
|                     | 8.1 (4.0)               | 7.4 (3.7)                 | 7.8 (3.9)    |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 9.2 (4.3)               | 9.3 (4.1)                 | 9.3 (4.2)    |
|                     | 8.1 (4.0)               | 7.4 (3.7)                 | 7.8 (3.9)    |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
| Fasting glucose (mmol/l) | 0.55 (0.26)             | 0.59 (0.30)               | 0.57 (0.28)  |
|                     | 1.19 (0.48)             | 1.13 (0.51)               | 1.16 (0.49)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 0.55 (0.26)             | 0.59 (0.30)               | 0.57 (0.28)  |
|                     | 1.19 (0.48)             | 1.13 (0.51)               | 1.16 (0.49)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
| HOMA2B              | 40.87 (22.91)           | 36.94 (19.99)             | 39.10 (21.72) |
|                     | 92.42 (44.29)           | 97.77 (46.21)             | 94.67 (45.14) |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 40.87 (22.91)           | 36.94 (19.99)             | 39.10 (21.72) |
|                     | 92.42 (44.29)           | 97.77 (46.21)             | 94.67 (45.14) |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
| HOMA2IR             | 1.54 (0.80)             | 1.78 (1.02)               | 1.65 (0.91)  |
|                     | 3.19 (1.60)             | 2.91 (1.61)               | 3.07 (1.61)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |
|                     | 1.54 (0.80)             | 1.78 (1.02)               | 1.65 (0.91)  |
|                     | 3.19 (1.60)             | 2.91 (1.61)               | 3.07 (1.61)  |
|                     | <0.0001<sup>a</sup>    | <0.0001<sup>a</sup>      | <0.0001<sup>a</sup>  |

Note: Values are mean (SD), p-value by ANOVA, p1 adjusted for duration of diabetes. Bonferroni corrected significant p-values are indicated with a.
|                          | 1               | 2               | p-value | p1 value |
|--------------------------|-----------------|-----------------|---------|----------|
| Number (%)               | 1073 (66.6)     | 539 (33.4)      |         |          |
| Current Treatment        |                 |                 |         |          |
| Only on Diet             | 68 (6.3)        | 67 (12.4)       | 0.0001* | 0.0001*  |
| Only on OHA (SUs+Metofrmin+/Glitazones) | 605 (56.4)  | 374 (69.4)      |         |          |
| Only on Insulin          | 72 (6.7)        | 13 (2.4)        |         |          |
| Both OHA+ Insulin        | 328 (30.6)      | 85 (15.8)       |         |          |
| Complications            |                 |                 |         |          |
| Cardiovascular disease   |                 |                 | 0.436   | 0.050    |
| Coronary Events          | 63 (5.9)        | 37 (6.9)        |         |          |
| Stroke                   | 17 (1.6)        | 9 (1.7)         |         |          |
| Nephropathy (Macroalbuminuria and / or CKD) (n=1612) | 406 (37.8) | 155 (28.8)      | 0.0001* | 0.076    |
| Macroalbuminuria b       | 165 (16.0)      | 85 (16.5)       | 0.813   | 0.271    |
| CKD: e-Glomerular Filtration Rate d (n=1471) | 316 (32.7) | 97 (19.2)       | 0.0001* | 0.0001*  |
| Early CKD (60-90)        | 249 (25.8)      | 81 (16.0)       |         |          |
| Moderate (30-60)         | 62 (6.4)        | 12 (2.4)        |         |          |
| Severe (<30)             | 5 (0.6)         | 4 (0.8)         |         |          |
| Diabetic Retinopathy n=657 e | 144 (32.1) (n=448) | 36 (17.2) (n=209) | 0.0001* | 0.013    |
| NPDR                     | 135 (30.1)      | 32 (15.3)       |         |          |
| PDR                      | 9 (2.0)         | 4 (1.9)         |         |          |
| Neuropathy f             | 449 (43.0)      | 261 (49.2)      | 0.020   | 0.697    |

Values are number (%). p-value by Chi-square test.

a Bonferroni corrected significant p-values
b N=1020 for WellGen.
c Based on MDRD formula.
d N=1039 for WellGen.
e N=441 for WellGen.
f N=1031, diagnosed using biothesiometry for WellGen

ESM table 8: Treatment and complications by cluster in the WellGen by clusters generated using de novo k-means clustering.
|          | Beta | SE  | Z    | P     |
|----------|------|-----|------|-------|
|          | WellGen |      |      |       |
| T1D vs controls (positive control) | 15.43 | 1.24 | 12.47 | <2e-16$^a$ |
| SIDD vs controls           | -1.38 | 1.07 | -1.29 | 0.197 |
| MOD vs controls           | -0.90 | 1.08 | -0.83 | 0.40  |
| T1D vs SIDD                | 14.30 | 1.33 | 10.73 | <2e-16$^a$ |
| T1D vs MOD                 | 13.01 | 1.31 | 9.93  | <2e-16$^a$ |

*Bonferroni corrected significant p-values are indicated with a.*

**ESM table 9.** Association of type 1 diabetes genetic risk scores with T1D (as positive control), SIDD, and MOD clusters.
### DIREVA

#### All (420)

| Cluster   | SIDD       | SIRD       | MOD        | MARD        | p         | p1         |
|-----------|------------|------------|------------|-------------|-----------|------------|
| Number (%)| 99 (23.57) | 1 (3.0)    | 297 (70.7) | 23 (5.47)   |           |            |
| Age at Diagnosis (y) | 34.30 (7.70) | 41.20 (0)  | 36.99 (6.88) | 41.94 (2.16) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.08 |
| Duration of diabetes (y) | 20.48 (13.26) | 0.35 (6.46) | 12.39 (11.06) | 14.54 (12.54) |           |            |
| BMI (Kg/m²)       | 27.03 (3.97) | 37.80 (0)  | 33.65 (6.42) | 25.00 (1.97) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |
| Fasting glucose (mmol/L) | 11.10 (3.7)  | 5.9 (0)    | 8.42 (2.65) | 7.66 (2.09) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.69 |
| HbA1c (mmol/mol)   | 75.31 (16.74) | 38 (0)     | 53.47 (13.24) | 45.25 (6.43) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |
| Fasting C-Peptide (nmol/L) | 9.0 (3.7)    | 5.6 (0)    | 7.0 (3.3)   | 6.3 (2.7)   | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |
| HOMA2B      | 24.22 (15.64) | 219.3 (0)  | 58.21 (33.85) | 41.64 (18.63) |           |            |
| HOMA2IR     | 1.23 (0.96)  | 5.23 (0)   | 1.89 (1.27) | 0.97 (0.47) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |            |

### WellGen vs DIREVA

#### p: SIDD vs MOD

### Male participants (243)

| Cluster   | SIDD       | SIRD       | MOD        | MARD        | p         | p1         |
|-----------|------------|------------|------------|-------------|-----------|------------|
| Number (%)| 77 (31.69) | -          | 148 (60.91) | 18 (7.4)    |           |            |
| Age at Diagnosis (y) | 33.94 (7.86) | -          | 37.66 (6.76) | 48.21 (3.76) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.09 |
| Duration of diabetes (y) | 20.77 (13.62) | -          | 11.74 (10.20) | 13.64 (8.61) |           |            |
| BMI (Kg/m²)       | 26.85 (3.53) | -          | 34.85 (6.11) | 32.30 (10.42) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |
| Fasting glucose (mmol/L) | 10.59 (3.55) | -          | 8.63 (2.60) | 9.08 (3.14) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.45        | 0.0002<sup>a</sup> |
| HbA1c (mmol/mol)   | 72.47 (16.55) | -          | 54.18 (13.61) | 45.35 (6.09) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.0001<sup>a</sup> |
| HbA1c (%)      | 8.8 (3.7)   | -          | 7.1 (3.4)   | 6.3 (2.7)   | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> | 0.0001<sup>a</sup> |
| Fasting C-Peptide (nmol/L) | 0.32 (0.28)  | -          | 0.78 (0.54) | 0.65 (0.39) | <0.0001<sup>a</sup> | <0.0001<sup>a</sup> |            |
### Characteristics of participants enrolled in the DIREVA study by clusters for all participants, men and women.

**Note:** Values are mean (SD), p-value by ANOVA, p1 adjusted for duration of diabetes. P: SIDD and P: MOD= p values for SIDD group and MOD group comparisons between WellGen and DIREVA respectively. Bonferroni corrected significant p-values are indicated with a.

**ESM table 10:** Characteristics of participants enrolled in the DIREVA study by clusters for all participants, men and women.
### Ahmedabad

| Cluster       | SIDD       | SIRD       | MOD       | MARD       | p           |
|---------------|------------|------------|-----------|------------|-------------|
| **Number (%)** | 106 (56.68) | 0 (0)      | 62 (33.15)| 19 (10.16) |             |
| Age at Diagnosis (y) | 37.05(6.66) | 34.84 (6.79) | 42.05(3.34) | <0.0001*<br> <br> |<br> | 25.06(2.68) |
| BMI (Kg/m²)   | 26.76(3.34) | 29.99 (3.79) | 25.06(2.68) | <0.0001*<br> <br> |<br> | 29.99 (3.79) |
| Fasting glucose ( mmol/L) | 13.03 (4.53) | 8.48 (3.26) | 6.66 (2.13) | <0.0001*<br> <br> |<br> | 8.48 (3.26) |
| HbA1c (mmol)  | 88.25(22.94) | 53.6 (11.18) | 48.29(8.91) | <0.0001*<br> <br> |<br> | 53.6 (11.18) |
| HbA1c (%)     | 10.2 (4.3)  | 7.1 (3.2)  | 6.5 (2.9) | <0.0001*<br> <br> |<br> | 7.1 (3.2) |
| Fasting C-Peptide (nmol/L) | 0.43 (0.20) | 0.48 (0.18) | 0.44 (0.20) | 0.282  |<br> | 0.44 (0.20) |
| HOMA2B        | 22.83(18.63) | 48.48 (30.84) | 64.38(39.32) | <0.0001*<br> <br> |<br> | 48.48 (30.84) |
| HOMA2IR       | 1.66(1.22)  | 1.34(0.86)  | 1.06(0.52) | 0.032  |<br> | 1.34(0.86) |

### Ahmedabad: Male participants (138)

| Cluster       | SIDD       | SIRD       | MOD       | MARD       | p           |
|---------------|------------|------------|-----------|------------|-------------|
| **Number**    | 85 (61.59) | 0 (0)      | 36 (26.08)| 17 (12.32) |             |
| Age at Diagnosis (y) | 36.63(6.85) | 34.11(6.44) | 41.71(3.37) | <0.0001*<br> <br> |<br> | 41.71(3.37) |
| BMI (Kg/m²)   | 26.5(3.32) | 30.66 (2.97) | 25.33(2.68) | <0.0001*<br> <br> |<br> | 30.66 (2.97) |
| Fasting glucose ( mmol/L) | 12.66 (4.45) | 8.05 (3.24) | 6.50 (1.71) | <0.0001*<br> <br> |<br> | 8.05 (3.24) |
| HbA1c (mmol)  | 86.38(23.16) | 52.09 (12.55) | 47.22(8.79) | <0.0001*<br> <br> |<br> | 52.09 (12.55) |
| HbA1c (%)     | 10.4 (4.3)  | 6.9 (3.3)  | 6.5 (3.0) | <0.0001*<br> <br> |<br> | 6.9 (3.3) |
| Fasting C-Peptide (nmol/L) | 0.43 (0.22) | 0.51 (0.18) | 0.45 (0.21) | 0.218  |<br> | 0.51 (0.18) |
| HOMA2B        | 24.17(19.34) | 56.15 (35.34) | 63.91(36.8) | <0.0001*<br> <br> |<br> | 56.15 (35.34) |
| HOMA2IR       | 1.62(1.23)  | 1.4 (0.91)  | 1.10(0.54) | 0.168  |<br> | 1.4 (0.91) |
### Ahmedabad: Female participants (49)

| Cluster    | SIDD     | SIRD     | MOD      | MARD     | p       |
|------------|----------|----------|----------|----------|---------|
| Number (%) | 21 (42.86) | 0 (0)    | 26 (53.06) | 2 (4.10) | 0.084   |
| Age at Diagnosis (y) | 38.76 (5.66) | 35.85 (7.24) | 45 (0) | 0.093 |
| BMI (Kg/m²) | 27.83 (3.31) | 29.07 (4.59) | 22.76 (1.68) | 0.084 |
| Fasting glucose (mmol/L) | 14.53 (4.66) | 8.89 (3.34) | 7.99 (5.57) | 0.093 |
| HbA1c (mmol) | 95.79 (20.86) | 55.63 (9.05) | 57.38 (3.09) | 0.093 |
| HbA1c (%) | 10.9 (4.1) | 7.3 (3.0) | 7.5 (2.4) | 0.093 |
| Fasting C-Peptide (nmol/L) | 0.40 (0.14) | 0.44 (0.18) | 0.31 (0.05) | 0.480 |
| HOMA2B | 17.41 (14.6) | 37.87 (19.23) | 68.35 (78.28) | 0.093 |
| HOMA2IR | 1.82 (1.19) | 1.25 (0.8) | 0.75 (0.06) | 0.094 |

Note: Values are mean (SD), p-value by ANOVA. Bonferroni corrected significant p-values are indicated in bold.

**ESM table 11.** Characteristics of participants enrolled in the Ahmedabad study by clusters for all participants, for men and women
### Assam

| Cluster | SIDD | SIRD | MOD | MARD | p  | p1  |
|---------|------|------|-----|------|----|-----|
| Number (%) | 138 (66.66) | 3 (1.40) | 48 (23.20) | 16 (7.72) |    |     |
| Age at Diagnosis (y) | 32.14 (5.3) | 34 (6.56) | 31.48 (5.44) | 35.38 (3.1) | 0.069 | 0.112 |
| Duration of diabetes (y) | 3.66 (3.83) | 4.26 (5.04) | 3.01 (3.15) | 1.81 (2.00) | 0.209 | - |
| BMI (Kg/m²) | 22.68 (3.43) | 17.6 (3.5) | 26.25 (3.44) | 21.79 (2.95) | <0.0001* | <0.0001* |
| Fasting glucose (mmol/L) | 11.89 (4.14) | 29.11 (3.32) | 6.84 (2.08) | 6.18 (1.27) | <0.0001* | <0.0001* |
| HbA1c (mmol) | 97.06 (26.51) | 105.46 (52.95) | 52.44 (13.91) | 39.62 (7.9) | <0.0001* | <0.0001* |
| HbA1c (%) | 11.0 (4.6) | 11.8 (7.0) | 6.9 (3.4) | 5.8 (2.8) | <0.0001* | <0.0001* |
| Fasting C-Peptide (nmol/L) | 0.38 (0.32) | 0.07 (0.01) | 0.57 (0.39) | 0.33 (0.25) | 0.002* | 0.002* |
| HOMA2B | 24.26 (18.7) | 3.2 (0) | 71.03 (39.28) | 58.6 (31.49) | <0.0001* | <0.0001* |
| HOMA2IR | 1.4 (1.19) | 30.3 (0) | 1.45 (0.92) | 0.88 (0.52) | <0.0001* | <0.0001* |

### Assam: Male participants (135)

| Cluster | SIDD | SIRD | MOD | MARD | p  | p1  |
|---------|------|------|-----|------|----|-----|
| Number (%) | 99 (73.33) | 1 (0.74) | 21 (15.55) | 14 (10.37) |    |     |
| Age at Diagnosis (y) | 32.53 (4.93) | 40 (NA) | 32.86 (4.96) | 35.36 (3.32) | 0.096 | 0.225 |
| Duration of diabetes (y) | 3.20 (3.57) | 0.15 (NA) | 2.23 (3.06) | 1.72 (1.96) | 0.267 | - |
| BMI (Kg/m²) | 22.73(3.53) | 15.35 (NA) | 28.03(2.44) | 22.39(2.52) | <0.0001* | <0.0001* |
| Fasting glucose (mmol/L) | 11.59 (4.35) | 31.97 (NA) | 5.98 (1.30) | 6.29 (1.29) | <0.0001* | <0.0001* |
| HbA1c (mmol) | 94.72(27.32) | 163.39 (NA) | 48.22(13.56) | 39.81(8.46) | <0.0001* | <0.0001* |
| HbA1c (%) | 10.8 (4.6) | 17.1 (NA) | 6.5 (3.4) | 5.8 (2.9) | <0.0001* | <0.0001* |
| Fasting C-Peptide (nmol/L) | 0.36 (0.28) | 0.08 (NA) | 0.64 (0.40) | 0.35 (0.26) | 0.001* | 0.001* |
| HOMA2B | 25.32(19.57) | 3.2 (NA) | 91.66(39.73) | 58.89(33.75) | <0.0001* | <0.0001* |
| Cluster | SIDD | SIRD | MOD | MARD | p  | p1 |
|---------|------|------|-----|------|----|----|
| Number (%) | 39 (54.16) | 2 (2.77) | 27 (37.5) | 2 (2.77) |    |    |
| Age at Diagnosis (y) | 31.15 (6.1) | 31 (5.66) | 30.41 (5.65) | 35.5 (0.71) | 0.689 | 0.562 |
| Duration of diabetes (y) | 4.82 (4.27) | 6.32 (5.04) | 3.61 (3.14) | 2.44 (3.02) | 0.467 | - |
| BMI (Kg/m²) | 22.58 (3.19) | 18.73 (4.11) | 24.86 (3.49) | 17.61 (2.79) | 0.001* | 0.002* |
| Fasting glucose (mmol/L) | 12.68 (3.50) | 27.69 (3.13) | 7.50 (2.34) | 5.41 (1.06) | <0.0001* | <0.0001* |
| HbA1c (mmol) | 103 (23.61) | 76.5 (23.96) | 55.72 (13.52) | 38.25 (0.77) | <0.0001* | <0.0001* |
| HbA1c (%) | 11.6 (4.3) | 9.2 (4.3) | 7.3 (3.4) | 5.6 (2.2) | <0.0001* | <0.0001* |
| Fasting C-Peptide (nmol/L) | 0.44 (0.40) | 0.07 (0) | 0.51 (0.38) | 0.21 (0.18) | 0.333 | 0.381 |
| HOMA2B | 21.56 (16.2) | 3.2 (0) | 54.99 (31.04) | 56.55 (7.28) | <0.0001* | <0.0001* |
| HOMA2IR | 1.53 (1.32) | 30.3 (0) | 1.37 (0.95) | 0.62 (0.26) | <0.0001* | <0.0001* |

Note: Values are mean (SD), p-value by ANOVA, p1 adjusted for duration of diabetes. Bonferroni corrected significant p-values are indicated with a.

**ESM Table 12.** Characteristics of participants enrolled in the Assam study by clusters for all participants, men and women.
**ESM Figure 1:** Flowchart for the WellGen cohort.
ESM figure 2. 2a. Silhouette plot showing optimal number of clusters in the WellGen cohort. 2b. Nearest centroid vs k-means clustering: Overlap of distribution of patients in the two largest clusters derived using two methods. De novo k-means clustering showed two clusters, with patients in cluster 1 showing as 88.8% overlap with those in SIDD (ALL: 88.88%, Men: 86.8%, Women: 92.4%) whereas patients in cluster 2 patients showed a 62.5% overlap with MOD (ALL: 62.5%, Men: 83.9% and Women: 49.5%).
ESM figure 3. Density plot of genetic risk score distributions in T1D, SIDD, MOD and controls in the WellGen study.
ESM figure 4. Patient distribution in various predefined clusters. (a) Distribution of DIREVA patients (n = 424) (b) distribution of men with diabetes from the DIREVA study (n = 243) (c) distribution of women with diabetes from the DIREVA study (n = 177). (d) Box plots of cluster characteristics of patients in the DIREVA study. Distribution of age at diagnosis, BMI, HbA1c, HOMA2-B and HOMA2-IR in the DIREVA study for each cluster. The central line within the box represents the median and the upper and lower limits of the box represent the interquartile range. The whiskers are the most extreme values within 1.5 × the interquartile range from the first and second quartiles. k-means clustering was done separately for men and women; data is shown for each sex separately. SIDD = severe insulin-deficient diabetes, SIRD = resistant diabetes, MOD = mild obesity-related-related diabetes, MARD = mild age-related diabetes. HOMA2-B = homeostatic model assessment 2 estimates of beta cell function. HOMA2-B = homeostatic model assessment 2 estimates insulin resistance.
ESM figure 5. Distribution of participants from the Ahmedabad study in the predefined clusters. (a) Distribution of patients (n =) (b) distribution of women with diabetes (n =) (c) distribution of men with diabetes (n =) (d) Box plots of cluster characteristics in the Ahmedabad cohort. Distribution of age at diagnosis, BMI, HbA1c, HOMA2-B and HOMA2-IR in the Ahmedabad study for each cluster. The central line within the box represents the median and the upper and lower limits of the box represent the interquartile range. The whiskers are the most extreme values within 1.5× the interquartile range from the first and second quartiles. k-means clustering was done separately for men and women; data is shown for each sex separately. SIDD = severe insulin-deficient diabetes, SIRD = resistant diabetes, MOD = mild obesity-related-related diabetes, MARD = mild age-related diabetes. HOMA2-B = homeostatic model assessment 2 estimates of beta cell function. HOMA2-IR = homeostatic model assessment 2 estimates insulin resistance.
ESM Figure 6. Distribution of participants from the Assam study in the predefined clusters. (a) Distribution of patients (n =) (b) distribution of women with diabetes (n =) (c) distribution of men with diabetes (n =) (d) Box plots of cluster characteristics in the Assam cohort. Distribution of age at diagnosis, BMI, HbA1c, HOMA2-B and HOMA2-IR in the Assam study for each cluster. The central line within the box represents the median and the upper and lower limits of the box represent the interquartile range. The whiskers are the most extreme values within 1.5× the interquartile range. k-means clustering was done separately for men and women; data is shown for each sex separately. SIDD = severe insulin-deficient diabetes, SIRD = resistant diabetes, MOD = mild obesity-related diabetes, MARD = mild age-related diabetes. HOMA2-B = homeostatic model assessment 2 estimates of beta cell function. HOMA2-B = homeostatic model assessment 2 estimates insulin resistance.