**Supplementary material**

**Suppl. Figure 1. Metabolic characteristics and liver parameters of the study population stratified by cluster**

Data are presented as median and interquartile range. Figures depict differences in circulating free fatty acids (panel A), adipose-tissue insulin sensitivity (panel B), whole-body insulin sensitivity (panel C), hepatic insulin sensitivity (panel D), liver fat content (panel E), fatty liver index (panel F), and liver fibrosis indices APRI (panel G) and FiB-4 (panel H). Metabolically healthy humans (CON) are depicted in black, patients with severe autoimmune diabetes (SAID) in indigo, severe insulin deficient diabetes (SIDD) in light blue, severe insulin-resistant diabetes (SIRD) in green, moderate obesity-related diabetes (MOD) in orange and moderate age-related diabetes (MARD) in pink. APRI, AST (aspartate aminotransferase) to Platelet Ratio Index; Adipo-IR, adipose-tissue insulin resistance index; EGP, endogenous glucose production; FLI, fatty liver index. \*, p<0.05.

**Suppl. Figure 2. Metabolic characteristics and liver parameters of the study population stratified by diabetes type and patatin-like phospholipase domain-containing 3 (*PNPLA3*) genotype**

Data are presented as median and interquartile range. Figures depict differences in circulating free fatty acids (panel A), adipose-tissue insulin sensitivity (panel B), whole-body insulin sensitivity (panel C), hepatic insulin sensitivity (panel D), liver fat content (panel E), fatty liver index (panel F), and liver fibrosis indices APRI (panel G) and FiB-4 (panel H) in metabolically healthy humans (CON, circles), patients with Type 1 diabetes (T1DM, triangles) and patients with type 2 diabetes (T2DM, squares). Full shapes represent carriers of the variant (G-allele) while empty shapes represent non-carriers. APRI, AST (aspartate aminotransferase) to Platelet Ratio Index; Adipo-IR, adipose-tissue insulin resistance index; EGP, endogenous glucose production; FLI, fatty liver index. \*, p≤0.05; #, p<0.05 after adjustments for age, sex and BMI.

**Suppl. Figure 3. Targeted lipidomics analysis**

Volcano plots depict the differences in lipid metabolite profiles in the study population. Patients with severe insulin-resistant diabetes (SIRD) were compared to severe autoimmune diabetes (SAID, panel A), severe insulin deficient diabetes (SIDD, panel B), moderate obesity-related diabetes (MOD, panel C), and moderate age-related diabetes (MARD, panel D). Colored dots represent statistically different up- or downregulated lipid metabolites after adjustment for multiple comparison (green, p<0.000098) or unadjusted (blue, p<0.05). The dotted line represents the value for unadjusted statistical significance (p<0.05). Triangles represent metabolites which showed statistically significant differences between SIRD G-allele carriers and non-carriers.

**Suppl. Figure 1. Metabolic characteristics and liver parameters of the study population stratified by cluster**

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**Suppl. Figure 2. Metabolic characteristics and liver parameters of the study population stratified by diabetes type and patatin-like phospholipase domain-containing 3 (*PNPLA3*) genotype**



**Suppl. Figure 3. Targeted lipidomics analysis**



**Supplementary Table 1. Participants’ characteristics stratified by cluster and *PNPLA3* genotype**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CON** | | **SAID** | | **SIDD** | | **SIRD** | | **MOD** | | **MARD** | |
|  | **Non-carriers** | **G-allele carriers** | **Non-carriers** | **G-allele carriers** | **Non-carriers** | **G-allele carriers** | **Non-carriers** | **G-allele carriers** | **Non-carriers** | **G-allele carriers** | **Non-carriers** | **G-allele carriers** |
| N [n] | 54 | 29 | 137 | 117 | 12 | 13 | 22 | 39 | 136 | 104 | 141 | 113 |
| Genotype frequency (CG/GG) [n] |  | 24/5 |  | 105/12 |  | 13/0 |  | 33/6 |  | 91/13 |  | 95/18 |
| Age [years] | 48±14 | 46±13 | 38±12 | 36±12 | 40±15 | 46±9 | 57±9 | 56±10 | 46±10 | 45±10 | 58±8 | 58±7 |
| BMI [kg/m2] | 28.2±6.0 | 28.3±5.2 | 24.7±3.8 | 25.4±4.8 | 26.1±3.1 | 28.0±4.1 | 34.3±3.3 | 34.6±3.8 | 35.4±6.5 | 34.3±6.0 | 27.4±3.6 | 27.4±3.4 |
| WHR | 0.93±0.09 | 0.91±0.08 | 0.88±0.09 | 0.88±0.09 | 0.95±0.06 | 0.93±0.06 | 0.99±0.07 | 1.01±0.07 | 0.98±0.08 | 0.95±0.08\* | 0.96±0.07 | 0.94±0.07 |
| Fasting blood glucose [mg/dl] | 90±8 | 93±22 | 130±42 | 141±50 | 163±44 | 209±66\* | 122±28 | 114±16 | 131±30 | 130±27 | 122±24 | 125±24 |
| HbA1c [%] | 5.3±0.3  34±2 | 5.3±0.2  34±3 | 6.6±1.2  49±13 | 6.7±1.2  49±13 | 8.6±1.3  70±14 | 9.1±1.3  76±14 | 6.4±0.9  46±10 | 6.1±0.5  43±6 | 6.5±0.9  47±9 | 6.5±0.9  47±10 | 6.3±0.7  45±8 | 6.3±0.7  45±8 |
| HOMA-IR [a.u.] | 1.53±0.73 | 1.39±0.29 | 0.91±0.68 | 1.07±1.03 | 1.57±0.86 | 2.34±0.97\* | 4.68±1.52 | 4.36±1.00 | 2.85±1.08 | 2.68±0.89 | 1.92±0.70 | 1.98±0.81 |
| HOMA-B [a.u.] | 124±38 | 118±41 | 47±31 | 45±32 | 38±9 | 40±28 | 164±43 | 173±48 | 98±35 | 98±39 | 84±30 | 82±31 |
| hsCRP [mg/dl] | 0.1 (0.1; 0.2) | 0.1 (0.1; 0.1) | 0.1 (0.1; 0.2) | 0.1 (0.1; 0.2) | 0.1 (0.1; 0.4) | 0.2 (0.1; 0.6) | 0.4 (0.3; 0.6) | 0.4 (0.2; 0.6) | 0.4 (0.2; 0.7) | 0.3 (0.2; 0.7) | 0.2 (0.1; 0.3) | 0.2 (0.1; 0.4) |
| Total cholesterol [mg/dl] | 206±32 | 202±40 | 185±36 | 185±40 | 190±31 | 221±20\* | 193±41 | 199±44 | 201±47 | 204±41 | 198±45 | 204±37 |
| LDL-cholesterol [mg/dl] | 128±32 | 130±35 | 110±31 | 108±36 | 117±31 | 143±22\* | 119±37 | 125±37 | 128±38 | 133±37 | 127±38 | 131±33 |
| HDL-cholesterol [mg/dl] | 62±19 | 59±18 | 62±19 | 62±17 | 55±13 | 48±11 | 40±9 | 42±10 | 44±11 | 46±13 | 51±14 | 51±14 |
| Triglycerides [mg/dl] | 95 (72; 145) | 85 (59; 148) | 69 (53; 104) | 76 (55; 109) | 88 (65; 197) | 155 (138; 217)\* | 192 (134; 283) | 151 (117; 236) | 140 (100; 207) | 141 (92; 181) | 118 (82; 150) | 116 (84; 177) |
| ALT [U/l] | 25±13 | 24±7 | 21±9 | 21±7 | 21±4 | 30±22 | 27±13 | 30±14 | 26±12 | 25±9 | 23±8 | 25±11 |
| AST [U/l] | 28±21 | 27±15 | 23±20 | 24±13 | 26±5 | 41±23 | 42±17 | 42±17 | 37±23 | 37±21 | 27±13 | 32±20\* |
| GGT [U/l] | 26±19 | 26±18 | 19±13 | 25±30 | 31±19 | 41±27 | 53±37 | 47±48 | 54±78 | 36±29\* | 35±38 | 36±24 |

Data are shown as absolute numbers, percentages, mean ± standard deviation or median (interquartile range), as applicable. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CON, control group; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; WHR, waist-to-hip ratio. \*, p<0.05 non-carriers vs. G-allele carriers within the group.

**Supplementary Table 2. Medication of the study population**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **CON** | **SAID** | **SIDD** | **SIRD** | **MOD** | **MARD** |
| Insulin | 0 | 82.7 | 48.0 | 3.3 | 15.0 | 11.0 |
| Metformin | 0 | 6.7 | 36.0 | 60.7 | 40.4 | 34.3 |
| Other glucose-lowering medication | 0 | 2.0 | 4.0 | 3.3 | 3.8 | 5.9 |
| Anti-hypertensive medication | 19.3 | 9.1 | 28.0 | 63.9 | 45.8 | 49.2 |
| Lipid-lowering medication | 2.4 | 1.6 | 12.0 | 31.2 | 11.3 | 21.3 |
| Non-steroidal anti-inflammatory drugs | 16.9 | 4.7 | 12.0 | 24.6 | 17.5 | 19.3 |

Data of the study population are shown as %.