**Identify Biomarkers for Susceptibility to Both Type 1 Diabetes and Mental Disorders**

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Recent studies show that patients with diabetes have a much higher likelihood of depression than the general population, and young people with type 1 diabetes (T1D) had 11 times the suicide rate. Our goal is to identify genetic signatures in white blood cells that distinguish non-progressor T1D patients and T1D patients that do progress to psychiatric illness.

With the funding received from DRC, we conducted an unbiased search for changes in gene expression in white blood cells from patients with T1D, T1D with depression, and healthy control patients. From UMass Medical Center Biorepository we have obtained blood samples from 60 male patients with T1D (20), T1D with depression (20) and healthy controls (20). We have isolated RNA from all of these samples and constructed and sequenced libraries. Libraries with sequenced depth over 8 million reads were analyzed and successfully mapped to human genome (about 20% efficiency). Out of the 20 libraries each, the sequence libraries with over 8 millions reads included: 17 T1D, 12 T1D with depression and 11 healthy patients. The biometrics for each of these patients is summarized in Table 1. Patients were matched for body mass index (BMI). One of the patients sets: healthy and T1D had statistically significant age difference but not the others. Age of onset of T1D was not different between T1D and T1D with depression.

Table 1.

| ***Health Status*** | ***Subject ID*** | ***Gender*** | ***AGE*** | ***BMI [kg/m2]*** | ***History*** | ***T1D Onset*** |
|---|---|---|---|---|---|---|
| Healthy | 392 | M | 19 | | - | NA |
| Healthy | 775 | M | 24 | 20.3 | Depression | NA |
| Healthy | 613 | M | 26 | 23.7 | - | NA |
| Healthy | 607 | M | 27 | 25.5 | - | NA |
| Healthy | 1716 | M | 40 | 23.0 | Alcohol abuse | NA |
| Healthy | 505 | M | 40 | | - | NA |
| Healthy | 1378 | M | 40 | | - | NA |
| Healthy | 5115 | M | 50 | 28.4 | - | NA |
| Healthy | 2906 | M | 50 | 24.7 | - | NA |
| Healthy | 3475 | M | 50 | 29.9 | - | NA |
| Healthy | 541 | M | 50 | 30.5 | - | NA |
| | | **Average** | **37.82** | **25.75** | | |
| | | **STD** | **11.87** | **3.57** | | |
| | | **St Err** | **3.58** | **1.26** | | |
| T1D | 6740 | M | 26 | - | T1D | 3 |
| T1D | 6525 | M | 26 | 24.3 | T1D | 9 |
| T1D | 6526 | M | 39 | 22.9 | T1D | 22 |
| T1D | 10737 | M | 46 | 37.6 | T1D | 19 |
| T1D | 1025 | M | 48 | 25.4 | T1D | 21 |
| T1D | 1209 | M | 51 | 26.4 | T1D | 14 |

| | | | | | | |
|---|---|---|---|---|---|---|
| T1D | 1229 | M | 51 | 16.5 | T1D | 18 |
| T1D | 6123 | M | 53 | 18.8 | T1D | 40 |
| T1D | 6723 | M | 53 | 27.4 | T1D | 29 |
| T1D | 1630 | M | 56 | 22.9 | T1D | 2 |
| T1D | 2799 | M | 56 | 22.8 | T1D | 14 |
| T1D | 9727 | M | 56 | 24.8 | T1D | 10 |
| T1D | 8952 | M | 56 | 27.7 | T1D | 49 |
| T1D | 5354 | M | 59 | - | T1D | 8 |
| T1D | 3082 | M | 61 | 31.5 | T1D | - |
| T1D | 10586 | M | 62 | 22.0 | T1D | 17 |
| T1D | 6232 | M | 63 | 26.1 | T1D | 25 |
| | | **Average** | **50.71** | **25.12** | | **18.75** |
| | | **STD** | **11.08** | **5.02** | | **12.63** |
| | | **St Err** | **2.69** | **1.30** | | **3.37** |
| **T1D vs Healthy** | | **Ttest** | **0.01** | **-** | | - |
| T1D & Dep | 4828 | M | 20 | 19.5 | Anxiety Disorder | 20 |
| T1D & Dep | 6556 | M | 23 | 23.7 | Anxiety/Depression | 6 |
| T1D & Dep | 5010 | M | 35 | 20.5 | Depression | 15 |
| T1D & Dep | 6602 | M | 42 | 31.7 | Chronic Depression | 26 |
| T1D & Dep | 6048 | M | 46 | 24.2 | Depression | 25 |
| T1D & Dep | 1681 | M | 50 | 24.4 | Depression | 13 |
| T1D & Dep | 1993 | M | 50 | 27.6 | Depression, Suicide ideation | 35 |
| T1D & Dep | 1626 | M | 51 | 29.5 | Anxiety/Depression | 15 |
| T1D & Dep | 8020 | M | 53 | 24.6 | Anxiety disorder, depression | 20 |
| T1D & Dep | 8135 | M | 55 | 29.9 | Anxiety and Depression | 25 |
| T1D & Dep | 512 | M | 57 | 27.0 | Bipolar, Major Depressive Disorder | 38 |
| T1D & Dep | 2333 | M | 61 | 39.0 | Anxiety/Depression | 43 |
| | | **Average** | **45.25** | **26.79** | | **23.42** |
| | | **STD** | **13.03** | **5.32** | | **10.95** |
| | | **St Err** | **3.76** | **1.53** | | **3.16** |
| **T1D Dep vs Healthy** | | **Ttest** | **0.17** | - | | - |
| **T1D vs T1D Dep** | | **Ttest** | **0.24** | - | | **0.32** |

We were able to detect over 21,000 differentially expressed genes from each of the analyzed set: healthy controls vs T1D patients; healthy controls vs T1D patients with depression and T1D vs T1D patients with depression. Unfortunately, there were no significant differentially expressed genes between T1D and T1D with depression. We are currently reanalyzing this data set to make sure this result is accurate. There are 10 significant down regulated genes in common between T1D vs Healthy and T1D with depression vs Healthy (Table 2).

Table 2.

| Gene ID | T1D vs Healthy Fold | P value | T1D Dep vs Healthy Fold | P value |
|---|---|---|---|---|
| RSRP1 | 0.625 | 0.001 | 0.649 | 0.037 |
| S100A8 | 0.169 | 0.007 | 0.141 | 0.008 |
| RPL34 | 0.255 | 0.010 | 0.161 | 2.83 E-08 |
| SNHG10 | 0.503 | 0.022 | 0.431 | 0.002 |
| TXN | 0.435 | 0.023 | 0.397 | 0.031 |
| HMGB2 | 0.501 | 0.028 | 0.443 | 0.019 |
| RPL36A | 0.268 | 0.032 | 0.216 | 0.0004 |
| RPL27 | 0.506 | 0.032 | 0.390 | 1.57 E-06 |
| S100A12 | 0.252 | 0.033 | 0.184 | 0.021 |
| EEF1B2 | 0.496 | 0.041 | 0.437 | 0.025 |

There were 28 significantly up regulated genes and 77 significantly down regulated genes between T1D vs. Healthy (Table 3).

Table 3.

| Gene ID | T1D vs Healthy **Fold Down** | P value | Gene ID | T1D vs Healthy **Fold Up** | P value |
|---|---|---|---|---|---|
| CHRM3 | 0.594 | 0.001 | RBBP7 | 1.477 | 0.004 |
| ITGB2-AS1 | 0.564 | 0.002 | SF3A3 | 1.403 | 0.004 |
| FAM157C | 0.524 | 0.007 | PABPC1 | 1.352 | 0.002 |
| LOC254896 | 0.464 | 0.002 | SLC6A19 | 6.202 | 0.027 |
| LOC441081 | 0.446 | 0.008 | HRASLS5 | 4.018 | 0.049 |
| CSNK1A1L | 0.390 | 0.001 | COL6A3 | 2.515 | 0.048 |
| RPS24 | 0.369 | 0.001 | FOSB | 2.050 | 0.033 |
| C9orf84 | 0.367 | 0.008 | MYADM | 1.699 | 0.013 |
| CASP5 | 0.367 | 0.008 | FAM115A | 1.623 | 0.049 |
| C14orf2 | 0.358 | 0.007 | TAF15 | 1.527 | 0.011 |
| LINC00998 | 0.241 | 0.007 | HTATSF1 | 1.509 | 0.032 |
| CHCHD2 | 0.665 | 0.046 | DDX24 | 1.508 | 0.011 |
| HIST1H2AC | 0.663 | 0.050 | WBP11 | 1.490 | 0.028 |
| PIGH | 0.646 | 0.038 | PARP1 | 1.467 | 0.011 |
| RMRP | 0.633 | 0.023 | PYGB | 1.447 | 0.041 |
| ATP6V1G1 | 0.618 | 0.049 | TAGAP | 1.439 | 0.013 |
| BLOC1S2 | 0.612 | 0.034 | GOLGB1 | 1.422 | 0.010 |
| RPS6 | 0.601 | 0.041 | EZR | 1.398 | 0.048 |
| FAU | 0.598 | 0.028 | PDCD4 | 1.390 | 0.040 |
| SLC8A1 | 0.597 | 0.050 | PBXIP1 | 1.350 | 0.041 |

| | | | | | |
|---|---|---|---|---|---|
| GTF2B | 0.591 | 0.027 | TFIP11 | 1.341 | 0.046 |
| PSMA6 | 0.584 | 0.048 | LUZP1 | 1.319 | 0.048 |
| B2M | 0.577 | 0.033 | HNRNPD | 1.312 | 0.022 |
| GLRX | 0.556 | 0.034 | CSNK2A1 | 1.312 | 0.046 |
| RPS18 | 0.552 | 0.028 | CLINT1 | 1.311 | 0.029 |
| ATP5L | 0.546 | 0.036 | SMARCC1 | 1.288 | 0.016 |
| RPS27A | 0.542 | 0.011 | XRCC6 | 1.288 | 0.022 |
| ATP5J | 0.540 | 0.039 | USP7 | 1.237 | 0.038 |
| HIST1H4F | 0.537 | 0.038 | | | |
| SNORA49 | 0.532 | 0.040 | | | |
| CLEC4A | 0.530 | 0.022 | | | |
| FAM157A | 0.528 | 0.049 | | | |
| AIF1 | 0.520 | 0.021 | | | |
| RPS29 | 0.514 | 0.036 | | | |
| GMFG | 0.512 | 0.023 | | | |
| TUBD1 | 0.510 | 0.046 | | | |
| PTENP1 | 0.510 | 0.027 | | | |
| LINC01094 | 0.495 | 0.032 | | | |
| COX7C | 0.481 | 0.036 | | | |
| MGAM | 0.478 | 0.027 | | | |
| NIPSNAP3A | 0.458 | 0.011 | | | |
| RPS15A | 0.454 | 0.022 | | | |
| TOMM7 | 0.437 | 0.027 | | | |
| SLC8A1-AS1 | 0.434 | 0.016 | | | |
| SCARNA7 | 0.420 | 0.028 | | | |
| NDUFB1 | 0.410 | 0.029 | | | |
| TMA7 | 0.404 | 0.036 | | | |
| RPS17 | 0.393 | 0.029 | | | |
| TP53TG1 | 0.366 | 0.024 | | | |
| RPL23 | 0.347 | 0.048 | | | |
| RPL39 | 0.345 | 0.035 | | | |
| CEP57L1 | 0.337 | 0.023 | | | |
| RPS7 | 0.335 | 0.018 | | | |
| COX7B | 0.311 | 0.033 | | | |
| RPL31 | 0.306 | 0.011 | | | |
| RPL26 | 0.259 | 0.022 | | | |
| AP3B2 | 0.100 | 0.044 | | | |
| CIAO1 | 0.824 | 0.032 | | | |
| UTY | 0.783 | 0.029 | | | |
| PHYKPL | 0.745 | 0.041 | | | |

| | | |
|---|---|---|
| TRIM13 | 0.723 | 0.023 |
| ARGLU1 | 0.717 | 0.028 |
| METTL22 | 0.709 | 0.046 |
| SLC35F5 | 0.701 | 0.011 |
| YIPF4 | 0.699 | 0.011 |
| SMA5 | 0.688 | 0.021 |
| CD48 | 0.669 | 0.041 |

There were 12 significantly down regulated and 6 significantly up regulated genes between T1D with depression vs Healthy (Table 4).

Table 4.

| Gene ID | T1D Dep vs Healthy **Fold Down** | P Value | Gene ID | T1D Dep vs Healthy **Fold Up** | P Value |
|---|---|---|---|---|---|
| RPS20 | 0.514 | 0.0086 | PRAMEF6 | 35.840 | 0.0247 |
| RPL35A | 0.450 | 0.0003 | ZNF334 | 17.060 | 0.0374 |
| RPS21 | 0.441 | 0.0002 | RGMB-AS1 | 12.273 | 0.0317 |
| RPL9 | 0.302 | 0.0000 | CDC42EP1 | 3.675 | 0.0374 |
| NEIL3 | 0.218 | 0.0002 | SIDT2 | 1.557 | 0.0490 |
| ANKRD36BP2 | 0.171 | 0.0069 | RBBP7 | 1.458 | 0.0374 |
| TMBIM4 | 0.615 | 0.0401 | | | |
| SCARNA10 | 0.477 | 0.0490 | | | |
| CLEC4D | 0.353 | 0.0312 | | | |
| VNN1 | 0.328 | 0.0317 | | | |
| SLC35F5 | 0.695 | 0.0401 | | | |
| YIPF4 | 0.675 | 0.0480 | | | |

Our goal of this study was to identify cellular and molecular biomarkers in white blood cells (wbc's) that associate with T1D and major depression in hope to identify at-risk individuals for preventative treatments. We did identify significantly up regulated and down regulated genes between T1D vs healthy and T1D with Depression vs healthy sets and we are currently working to analyze these genes patterns for gene signature that could be used in the clinic. This study preliminary work should be followed with increased sample size that is beyond the scope of this grant. We will continue analyzing these data sets in order to discover genetic biomarkers that identify T1D patients with susceptibility to depression, and vice versa, so that appropriate preventative measures can be taken. Our hope is to find a genetic association linking T1D and depression which will uncover possible novel mechanisms to improve therapies, even preventative ones, to alleviate suffering caused by both illnesses which are very common and extraordinarily costly—both in relation to healthcare, but also in regards to individual quality of life.