

SUPPLEMENTARY DATA

**Supplementary Table 1. DMVhi and Botnia: Anthropometric and Metabolic Characteristics by Glycemic Status.**

DMVhi	DMVhi				Botnia	Botnia			
	Normal	iIGT	iIFG	IFG&IGT		Normal	iIGT	iIFG	IFG&IGT
n	485	31	104	48	1105	128	938	259	
Women (%)	56	64	43 <sup>§,  </sup>	44	59	60	45 <sup>§,  </sup>	59	
Age (years)	62±8	68±7*	64±8 <sup>¶</sup>	68±7 <sup>‡</sup>	45±13	50±14 <sup>‡</sup>	46±12 <sup>‡,¶</sup>	52±12 <sup>‡</sup>	
BMI (kg/m <sup>2</sup> )	26.3±3.8	26.7±3.6	28.4±4.5 <sup>‡</sup>	28.3±4.6*	25.1±4	27.0±5.0 <sup>‡</sup>	26.±4 <sup>‡,¶</sup>	27.7±4 <sup>‡</sup>	
FFA (mmol/L)	n/a	n/a	n/a	n/a	0.70 (0.26)	0.80 (0.29) <sup>‡</sup>	0.68 (0.26) <sup>#</sup>	0.80 (0.27) <sup>‡</sup>	
Fasting insulin (mU/L)	8.2 (4.0)	9.1 (4.6) <sup>†</sup>	11 (6.1) <sup>‡</sup>	12.0 (8.2) <sup>‡</sup>	6.0 (3.8)	7.8 (5.9) <sup>‡</sup>	7.1 (4.4) <sup>‡</sup>	9.6 (6.8) <sup>‡</sup>	
HbA <sub>1c</sub> (%)	5.54±0.26	5.75±0.24 <sup>‡</sup>	5.79±0.29 <sup>‡</sup>	5.94±0.47 <sup>‡</sup>	n/a	n/a	n/a	n/a	
HbA <sub>1c</sub> (mmol/mol)	37±2	39±2 <sup>‡</sup>	40±2 <sup>‡</sup>	41±3 <sup>‡</sup>	n/a	n/a	n/a	n/a	
2-hr glucose (mg/dl)	94±21	155±14 <sup>‡</sup>	104±22 <sup>‡,¶</sup>	163±15 <sup>‡</sup>	98±19	159±15 <sup>‡</sup>	113±18 <sup>‡,¶</sup>	159±16 <sup>‡</sup>	
Fasting glucose (mg/dL)	90±7	93±5*	107±6 <sup>‡,¶</sup>	110±9 <sup>‡</sup>	92±6	93±6	108±6 <sup>‡,¶</sup>	111±7 <sup>‡</sup>	
M <sup>Q</sup> [29]	5.85±1.6	4.78±0.9*	4.91±1.2 <sup>‡</sup>	4.40±1.6 <sup>‡</sup>	6.61±1.6	5.22±1.3 <sup>‡</sup>	6.16±1.6 <sup>‡,¶</sup>	5.09±1.4 <sup>‡</sup>	
HOMA-IR	1.8±1.0	2.1±0.8 <sup>†</sup>	2.9±1.4 <sup>‡,¶</sup>	3.2±1.5 <sup>‡</sup>	1.6±0.8	2.2±1.4 <sup>‡</sup>	2.2±1.3 <sup>‡</sup>	3.0±1.8 <sup>‡</sup>	

Means ± SD or median (interquartile range); vs normal: † p<0.05, \* p <0.001, ‡ p <0.0001 by Wilcoxon test, § p < 0.05 by  $\chi^2$  test; iIFG vs iIGT: ¶ p<0.05, # p<0.0001 by Wilcoxon test, || p<0.05 by  $\chi^2$  test.

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**Supplementary Table 2. Odds Ratios of iIGT, iIFG, or IFG&IGT vs Normal for Each Metabolite Controlled for Age, Sex, and BMI (RISC)**

Metabolite	iIGT		iIFG		IFG&IGT	
	OR (95% CI)	Adjusted <i>p</i>	OR (95% CI)	Adjusted <i>p</i>	OR (95% CI)	Adjusted <i>p</i>
α-HB	2.54 (1.86-3.48)	5.1E-09	0.99 (0.83-1.18)	0.09	2.28 (1.66-3.14)	4.1E-07
L-GPC	0.48 (0.35-0.66)	4.6E-06	0.82 (0.68-0.98)	0.03	0.46 (0.33-0.64)	3.5E-06
X-12063	1.99 (1.45-2.75)	2.5E-05	1.16 (0.95-1.40)	0.1	1.87 (1.35-2.60)	0.0002
Oleic acid	1.87 (1.38-2.55)	6.4E-05	1.01 (0.85-1.21)	0.9	2.07 (1.49-2.87)	1.3E-05
β-HB	1.75 (1.31-2.34)	0.0001	1.08 (0.92-1.28)	0.4	1.68 (1.25-2.26)	0.0005
Glycine	0.56 (0.42-0.76)	0.0001	1.08 (0.90-1.30)	0.4	0.70 (0.52-0.94)	0.02
Creatine	1.84 (1.33-2.55)	0.0002	1.11 (0.92-1.35)	0.3	1.20 (0.86-1.68)	0.3
2-AAA	1.88 (1.34-2.64)	0.0002	1.37 (1.12-1.67)	0.002	2.38 (1.67-3.40)	1.6E-06
Serine	0.62 (0.46-0.82)	0.0009	1.03 (0.87-1.22)	0.7	0.93 (0.69-1.24)	0.6
3-MOP	1.69 (1.20-2.38)	0.003	0.99 (0.82-1.21)	0.97	1.94 (1.36-2.76)	0.0003
3-MOB	1.49 (1.11-2.01)	0.009	1.45 (1.22-1.74)	4.0E-05	2.15 (1.57-2.94)	1.9E-06
α-KB	1.46 (1.10-1.95)	0.01	1.50 (1.26-1.78)	4.1E-06	2.39 (1.75-3.25)	3.0E-08
3-hydroxyisobutyric acid	1.46 (1.09-1.95)	0.01	1.22 (1.02-1.46)	0.03	2.16 (1.58-2.94)	1.3E-06
Vitamin B5	1.41 (1.06-1.88)	0.02	1.04 (0.87-1.23)	0.7	1.36 (1.01-1.84)	0.04
Tyrosine	0.72 (0.53-0.98)	0.03	1.19 (1.00-1.43)	0.056	1.56 (1.13-2.14)	0.006
4-MOP	1.39 (1.00-1.94)	0.06	1.36 (1.11-1.65)	0.003	2.01 (1.41-2.85)	9.7E-05
Trigonelline	0.78 (0.58-1.04)	0.09	1.14 (0.96-1.36)	0.1	0.93 (0.69-1.26)	0.6
Isoleucine	1.29 (0.91-1.84)	0.2	1.05 (0.85-1.29)	0.7	1.53 (1.07-2.20)	0.02
Hydroxyisovaleroyl carnitine	1.21 (0.91-1.62)	0.2	1.09 (0.92-1.30)	0.3	1.05 (0.78-1.41)	0.7
α-ketoglutarate	1.17 (0.88-1.55)	0.2	0.91 (0.77-1.07)	0.3	1.16 (0.87-1.55)	0.3
Leucine	1.16 (0.81-1.67)	0.4	0.94 (0.75-1.16)	0.5	1.74 (1.19-2.54)	0.005
Phenylalanine	0.92 (0.69-1.25)	0.6	1.10 (0.92-1.31)	0.3	1.58 (1.15-2.16)	0.005
Valine	1.03 (0.70-1.45)	0.9	1.06 (0.86-1.29)	0.6	1.68 (1.19-2.38)	0.003

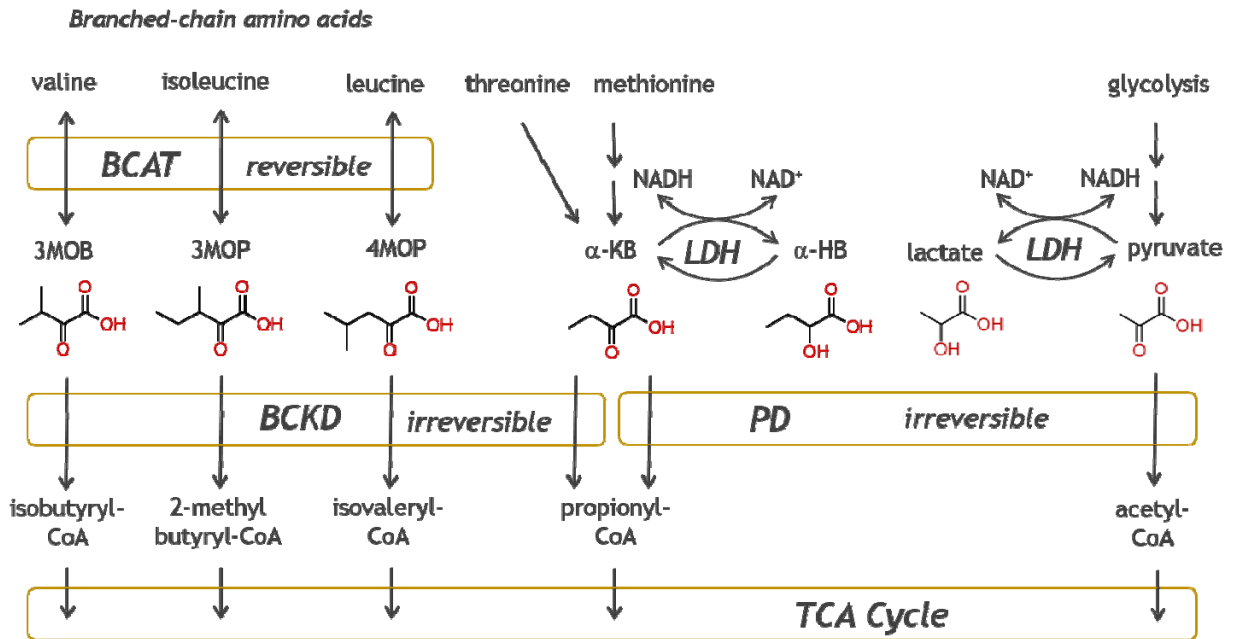
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**Supplementary Table 3. Odds Ratios of iIGT, iIFT, or IFG&IGT for Each Metabolite Controlled for Age, Sex, and BMI (DMVhi).**

	iIGT		iIFG		IFG&IGT	
	OR (95% CI)	adjusted <i>p</i>	OR (95% CI)	adjusted <i>p</i>	OR (95% CI)	adjusted <i>p</i>
$\alpha$ -HB	2.75 (1.81-4.19)	3.6E-05	1.31 (1.04-1.66)	0.05	2.36 (1.66-3.35)	3.0E-05
$\alpha$ -KB	1.93 (1.29-2.89)	0.01	1.52 (1.21-1.93)	0.01	2.58 (1.82-3.66)	<1.0E-5
$\alpha$ -KG	1.81 (1.20-2.73)	0.01	1.49 (1.18-1.89)	0.004	2.61 (1.83-3.73)	<1.0E-5
Oleic acid	1.83 (1.23-2.71)	0.01	1.36 (1.08-1.70)	0.03	1.91 (1.37-2.66)	1.0E-04
Trigonelline	0.57 (0.38-0.84)	0.01	0.93 (0.75-1.16)	0.59	0.73 (0.53-1.01)	0.08
L-GPC	0.55 (0.36-0.84)	0.03	0.97 (0.76-1.24)	0.86	0.45 (0.32-0.64)	1.0E-04
Serine	0.63 (0.43-0.93)	0.04	1.06 (0.85-1.33)	0.67	0.81 (0.59-1.13)	0.28
$\beta$ -HB	1.54 (1.04-2.29)	0.06	1.05 (0.84-1.32)	0.7	1.35 (0.98-1.87)	0.1
Glycine	0.65 (0.43-0.98)	0.07	0.86 (0.68-1.09)	0.28	0.79 (0.56-1.11)	0.25
Vitamin B5	1.48 (1.01-2.17)	0.07	1.03 (0.82-1.28)	0.86	1.32 (0.95-1.82)	0.14
X-12063	1.54 (1.01-2.34)	0.08	1.56 (1.22-1.99)	0.002	1.25 (0.90-1.74)	0.25
3-Hydroxyisobutyric acid	1.37 (0.91-2.08)	0.2	1.42 (1.11-1.81)	0.02	2.11 (1.47-3.02)	4.0E-05
Hydroxyisovaleroyl carnitine	1.32 (0.91-1.93)	0.22	1.01 (0.80-1.26)	0.96	1.41 (1.03-1.94)	0.06
Creatine	1.30 (0.88-1.92)	0.25	1.09 (0.86-1.39)	0.55	1.43 (1.03-1.98)	0.07
3-MOP	1.18 (0.79-1.75)	0.49	1.49 (1.17-1.90)	0.004	1.67 (1.19-2.33)	0.003
3-MOB	1.25 (0.81-1.91)	0.4	1.38 (1.07-1.77)	0.03	1.69 (1.17-2.43)	0.02
2-AAA	1.23 (0.81-1.87)	0.42	1.16 (0.90-1.49)	0.32	1.48 (1.04-2.10)	0.06
Isoleucine	1.25 (0.78-2.00)	0.42	1.40 (1.06-1.85)	0.04	1.66 (1.13-2.44)	0.03
Phenylalanine	1.14 (0.76-1.72)	0.59	1.13 (0.89-1.44)	0.4	1.39 (0.98-1.96)	0.1
Leucine	1.15 (0.72-1.84)	0.63	1.39 (1.05-1.84)	0.04	1.70 (1.14-2.52)	0.03
4-MOP	1.11 (0.71-1.70)	0.71	1.65 (1.26-2.17)	0.001	1.90 (1.30-2.77)	0.004
Valine	1.04 (0.66-1.63)	0.9	1.43 (1.09-1.87)	0.03	1.52 (1.04-2.21)	0.06
Tyrosine	1.02 (0.69-1.52)	0.93	1.28 (1.01-1.62)	0.07	1.27 (0.92-1.77)	0.22

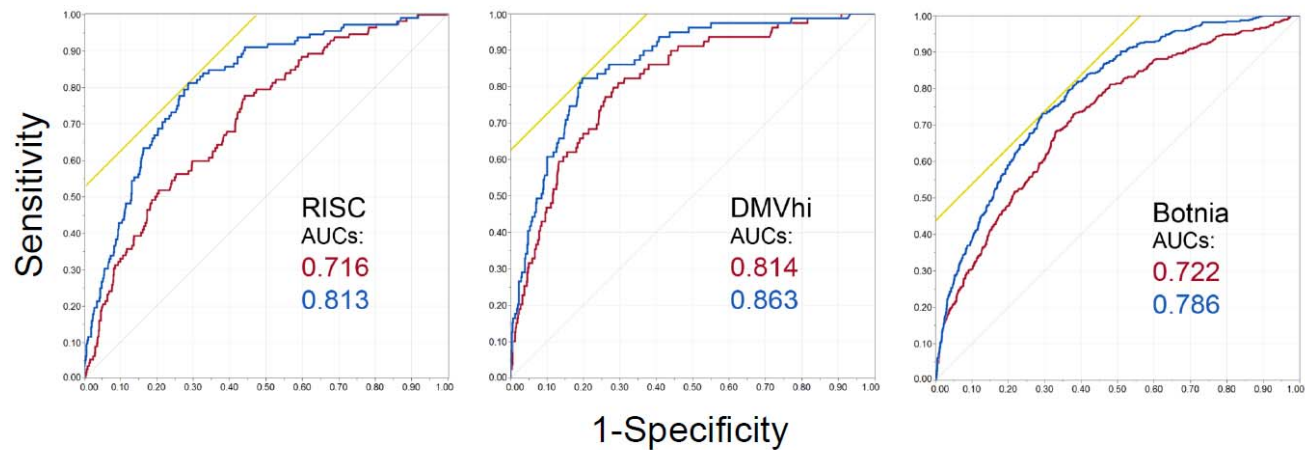
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**Supplementary Figure 1.** Metabolite Flux Through BCKD and PD; BCAT= branched-chain aminotransferase; BCKD = branched-chain  $\alpha$ -ketoacid dehydrogenase complex; LDH = lactate dehydrogenase; PD = pyruvate dehydrogenase complex.



SUPPLEMENTARY DATA

ROC Curves for Prediction of IGT in 3 Cohorts in Non-diabetic Subjects



Model: Age/Sex/BMI/FPG

Model: Age/Sex/BMI/FPG/ $\alpha$ -HB/L-GPC/oleic acid