

Table S1. Quantitative analysis of ADCY plasma levels in the study subjects according to gender and age classification.

ADCY Isoforms	Total Population					
	Gender		<i>p</i> -value	Age		<i>p</i> -value
	Male	Female		<46 years	≥46 years	
ADCY1 ng/ml	8.19 ± 1.33 (72)	8.27 ± 1.63 (106)	0.715	8.61 ± 1.58 (61)	8.04 ± 1.45 (117)	0.020
ADCY3 ng/ml	8.71 ± 2.70 (53)	8.78 ± 3.58 (75)	0.936	8.39 ± 3.39 (52)	9.00 ± 3.12 (76)	0.412
ADCY8 ng/ml	12.33 ± 1.70 (76)	12.35 ± 1.68 (109)	0.931	12.11 ± 1.46 (65)	12.47 ± 1.79 (120)	0.142

Data are presented as mean ± SD. Differences in the expression level were tested using Mann Whitney U test for ADCY3 and unequal variance t-test for ADCY1 and ADCY8. ADCY, adenylate cyclase. Statistically significant *p*-values are in bold font.

Table S2. Correlation between plasma levels of ADCY isoforms and biochemical variables.

Phenotype	Unadjusted			Adjusted for Age & Gender *		
	ADCY1			ADCY1		
	r	<i>p</i> -value	N	r	<i>p</i> -value	N
FPG (mmol/L)	-0.10	0.899	175	0.044	0.586	171
Insulin (U/L)	0.242	0.008	119	0.287	0.002	115
TGL (mmol/L)	0.201	0.008	174	0.247	0.001	170
BMI (Kg/m ²)	-0.014	0.852	178	0.021	0.781	174
HbA1C (%)	-0.063	0.414	172	-0.007	0.933	168
Phenotype	ADCY3			ADCY3#		
	r	<i>p</i> -value	N	r	<i>p</i> -value	N
FPG (mmol/L)	0.022	0.803	126	-0.038	0.679	122
Insulin (U/L)	0.062	0.571	85	0.042	0.704	81
TGL (mmol/L)	-0.017	0.853	125	-0.050	0.582	121
BMI (Kg/m ²)	-0.154	0.082	128	-0.183	0.040	124
HbA1C (%)	-0.038	0.680	123	-0.106	0.248	119
Phenotype	ADCY8			ADCY8		
	r	<i>p</i> -value	N	r	<i>p</i> -value	N
FPG (mmol/L)	0.115	0.123	183	0.098	0.189	179
Insulin (U/L)	-0.004	0.963	125	-0.018	0.841	121
TGL (mmol/L)	0.057	0.447	182	0.045	0.551	178
BMI (Kg/m ²)	0.151	0.040	185	0.139	0.060	181
HbA1c (%)	0.188	0.012	180	0.174	0.020	176

Correlation coefficients (r) were calculated using Pearson's correlation test unless otherwise specified.

* Indicates partial correlation adjusted for age and gender. # indicates non-parametric partial correlation adjusted for age. ADCY, adenylate cyclase; FPG: Fasting Plasma glucose, BMI, body mass index; HbA1c, glycated hemoglobin; r, correlation coefficient; TGL, triglycerides. Statistically significant *p*-values are in bold font.

Table S3. Correlation between plasma levels of ADCY isoforms and biochemical variables based on diabetes and obesity status.

Category	Phenotype	ADCY1			ADCY3*			ADCY8		
		r	p-value	N	r	p-value	N	r	p-value	N
Non-T2D	Age (Years)	-0.301	0.004	90	0.258	0.018	83	0.070	0.501	96
	FPG (mmol/L)	0.045	0.679	88	0.238	0.032	81	-0.023	0.829	94
	Insulin (U/L)	0.207	0.137	53	0.119	0.419	48	-0.023	0.863	57
	TGL (mmol/L)	0.102	0.342	88	0.028	0.807	81	0.091	0.384	94
	BMI (Kg/m ²)	0.044	0.677	90	-0.117	0.293	83	-0.021	0.841	96
	HbA1C (%)	-0.164	0.130	86	0.069	0.543	79	-0.003	0.978	92
T2D	Age (Years)	0.068	0.531	88	0.041	0.791	45	-0.090	0.402	89
	FPG (mmol/L)	0.016	0.884	87	0.210	0.166	45	0.029	0.786	89
	Insulin (U/L)	0.326	0.007	66	0.060	0.722	37	-0.103	0.404	68
	TGL (mmol/L)	0.326	0.002	86	0.098	0.529	44	-0.034	0.756	88
	BMI (Kg/m ²)	-0.078	0.473	88	-0.115	0.453	45	0.294	0.005	89
	HbA1C (%)	-0.032	0.771	86	0.253	0.098	44	0.151	0.161	88
Non-obese	Age (Years)	-0.243	0.024	86	0.157	0.215	64	0.094	0.379	89
	FPG (mmol/L)	-0.057	0.606	83	0.106	0.411	62	0.007	0.947	87
	Insulin (U/L)	0.139	0.281	62	0.133	0.383	45	-0.002	0.988	65
	TGL (mmol/L)	0.160	0.150	83	0.002	0.989	62	0.040	0.715	87
	BMI (Kg/m ²)	0.004	0.974	86	-0.069	0.587	64	0.170	0.111	89
	HbA1C (%)	-0.041	0.719	80	0.132	0.318	59	-0.092	0.406	84
Obese	Age (Years)	-0.086	0.413	92	0.106	0.403	64	0.030	0.769	96
	FPG (mmol/L)	0.044	0.677	92	0.056	0.658	64	0.146	0.156	96
	Insulin (U/L)	0.357	0.006	57	0.036	0.826	40	-0.041	0.757	60
	TGL (mmol/L)	0.247	0.018	91	0.005	0.970	63	0.051	0.624	95
	BMI (Kg/m ²)	0.127	0.228	92	-0.32	0.010	64	0.107	0.301	96
	HbA1c (%)	-0.052	0.623	92	-0.083	0.514	64	0.306	0.002	96

Correlation coefficients (r) for ADCY1 and ADCY8 were assessed using Pearson's correlation test and ADCY3* using Spearman correlation test. ADCY, adenylate cyclase; FBG, Fasting Blood Glucose; BMI, body mass index; HbA1c, glycated hemoglobin; r, correlation coefficient; TGL, triglycerides. Statistically significant *p*-values are in bold font.

Table S4. Normality test.

ADCY Isoforms	Total Population			Non-Diabetic			Diabetic		
	Statistic	df	p-value	Statistic	df	p-value	Statistic	df	p-value
ADCY1, ng/mL	0.983	120	0.140	0.984	77	0.47	0.965	43	0.210
ADCY3, ng/mL	0.921	120	<0.001	0.979	77	0.23	0.969	43	0.301
ADCY8, ng/mL	0.993	120	0.773	0.991	77	0.84	0.994	43	0.997