

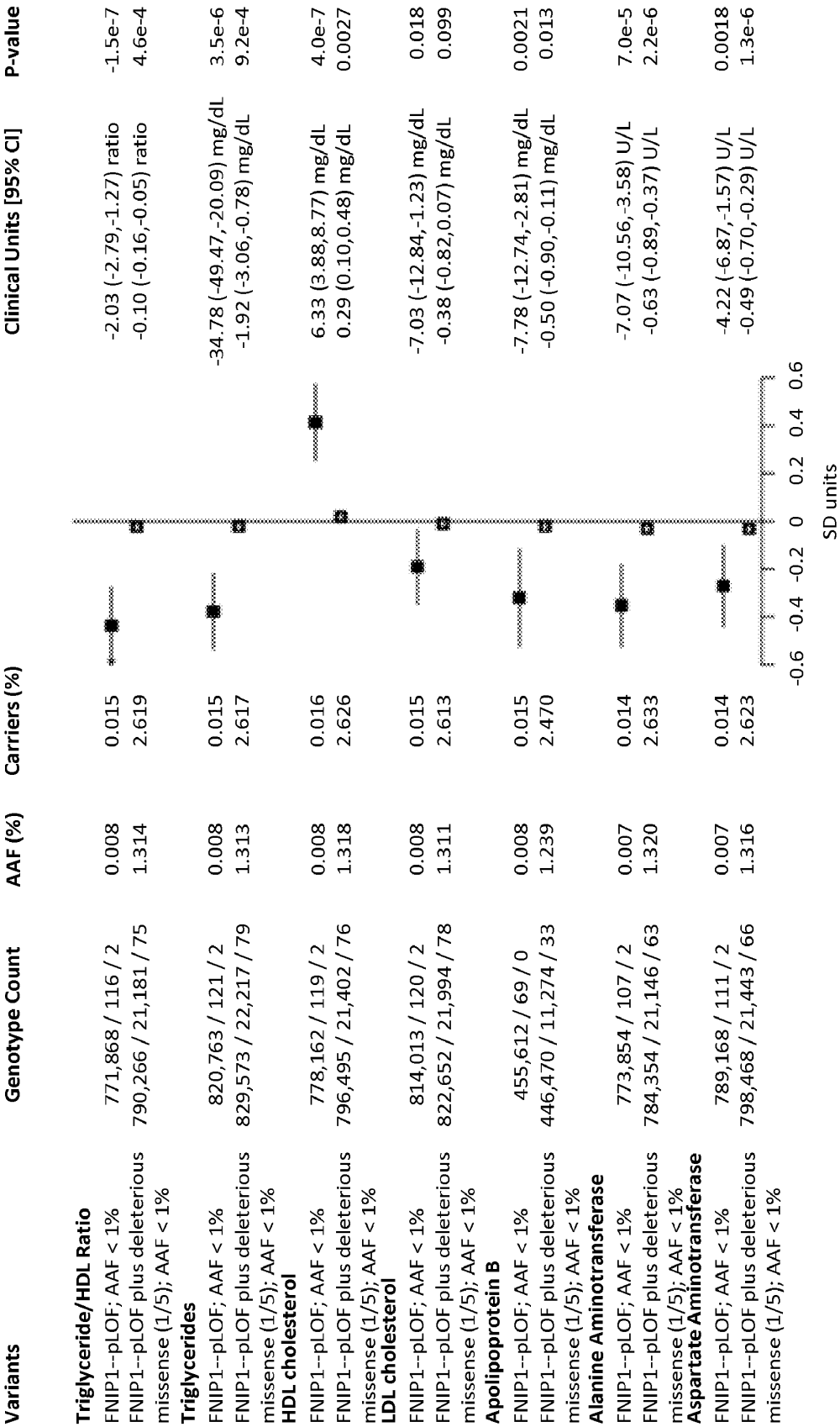


Figure 1

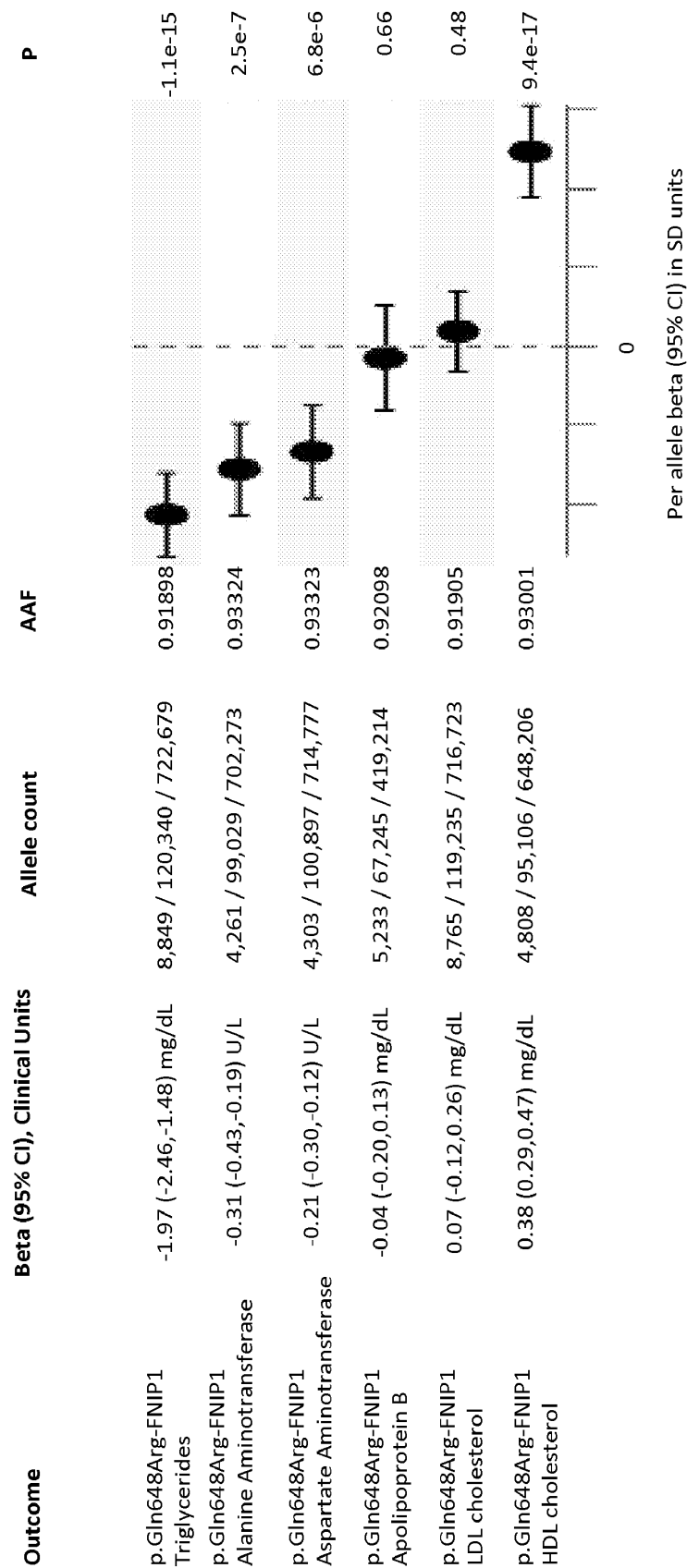


Figure 2

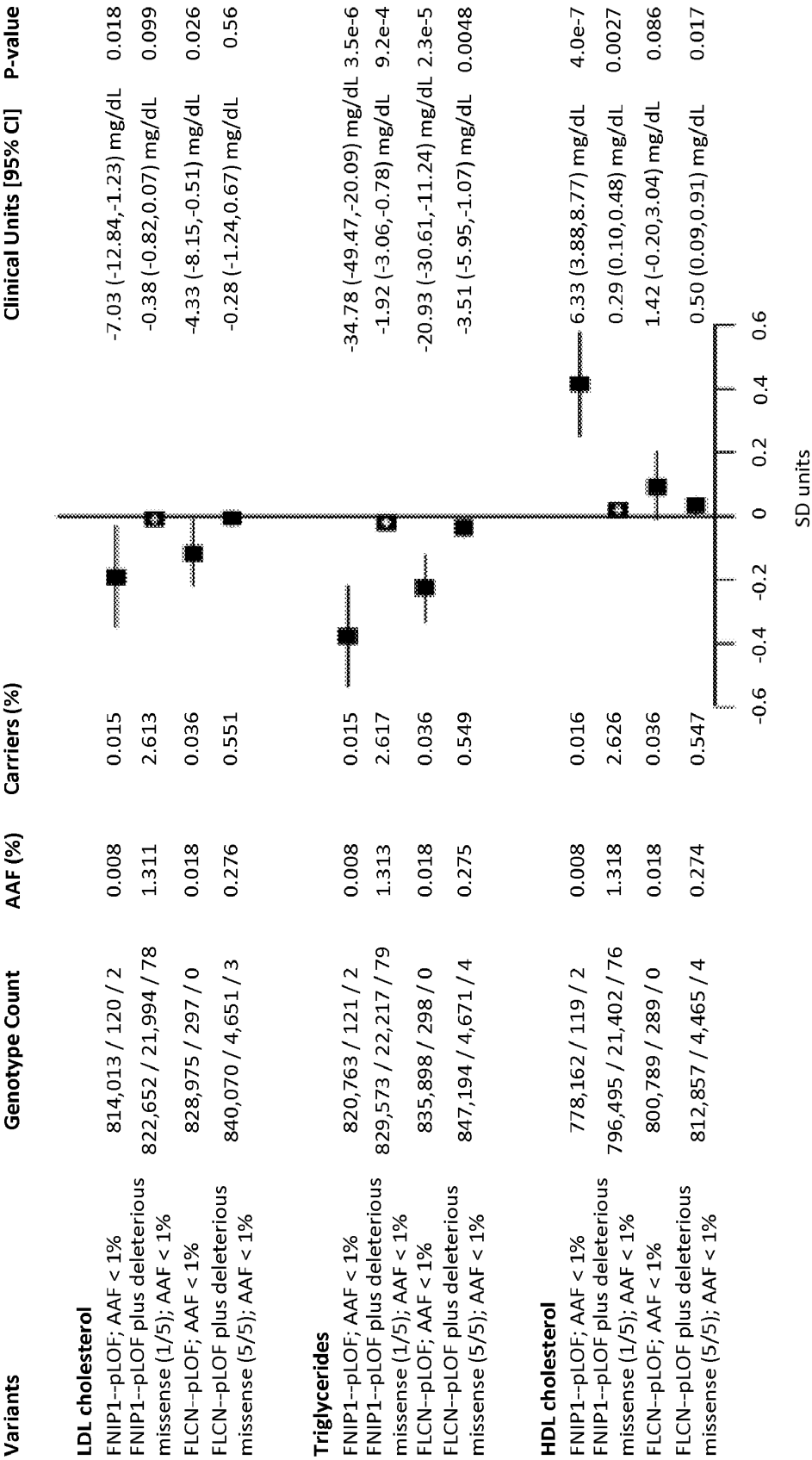


Figure 3

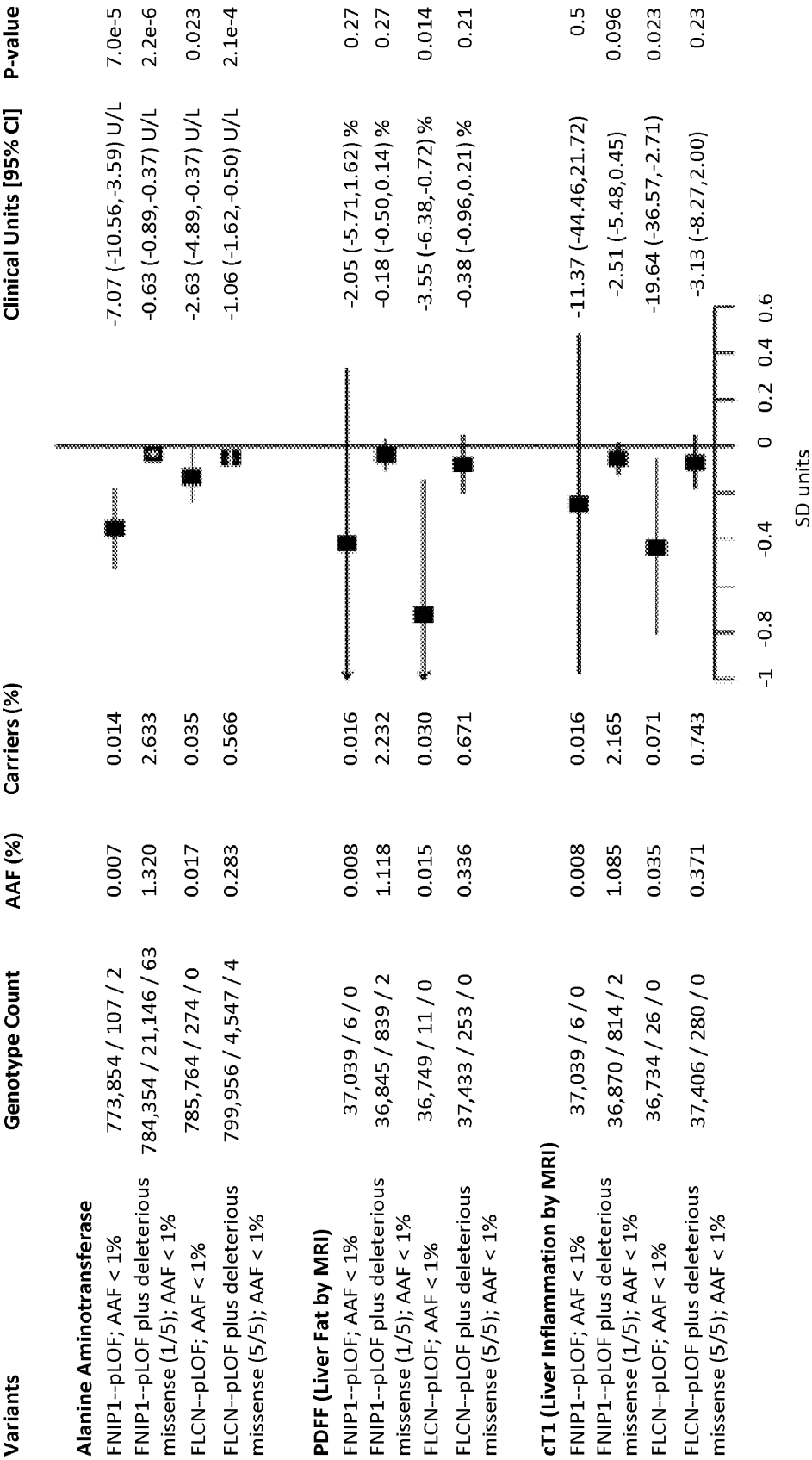


Figure 4

Variants	Genotype Count	AFF (%)	Carriers (%)
PDFF (Liver Fat by MRI)			
FLCN--pLOF; AAF < 1%	36,749 / 11 / 0	0.015	0.030
FNIP1--pLOF; AAF < 1%	37,039 / 6 / 0	0.008	0.016
CIDEB--pLOF; AAF < 1%	37,195 / 53 / 0	0.071	0.142
Alanine Aminotransferase			
FNIP1--pLOF; AAF < 1%	773,854 / 107 / 2	0.007	0.014
FLCN--pLOF; AAF < 1%	785,764 / 274 / 0	0.017	0.035
CIDEB--pLOF; AAF < 1%	801,361 / 1,270 / 1	0.079	0.158

Figure 5

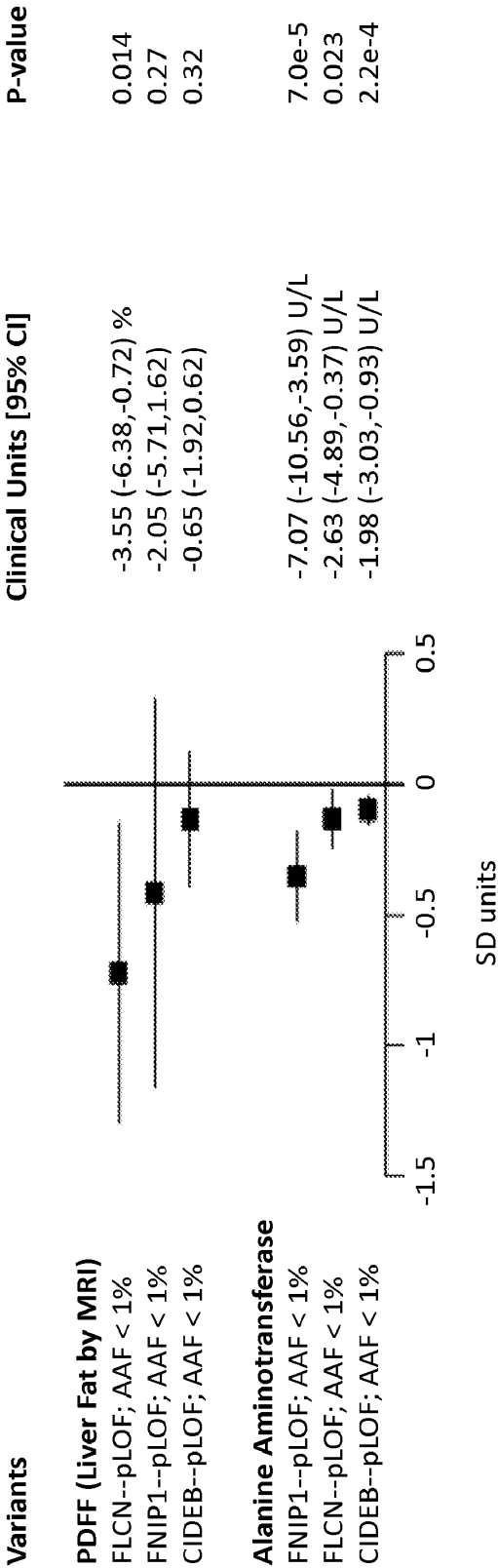


Figure 5 (cont.)

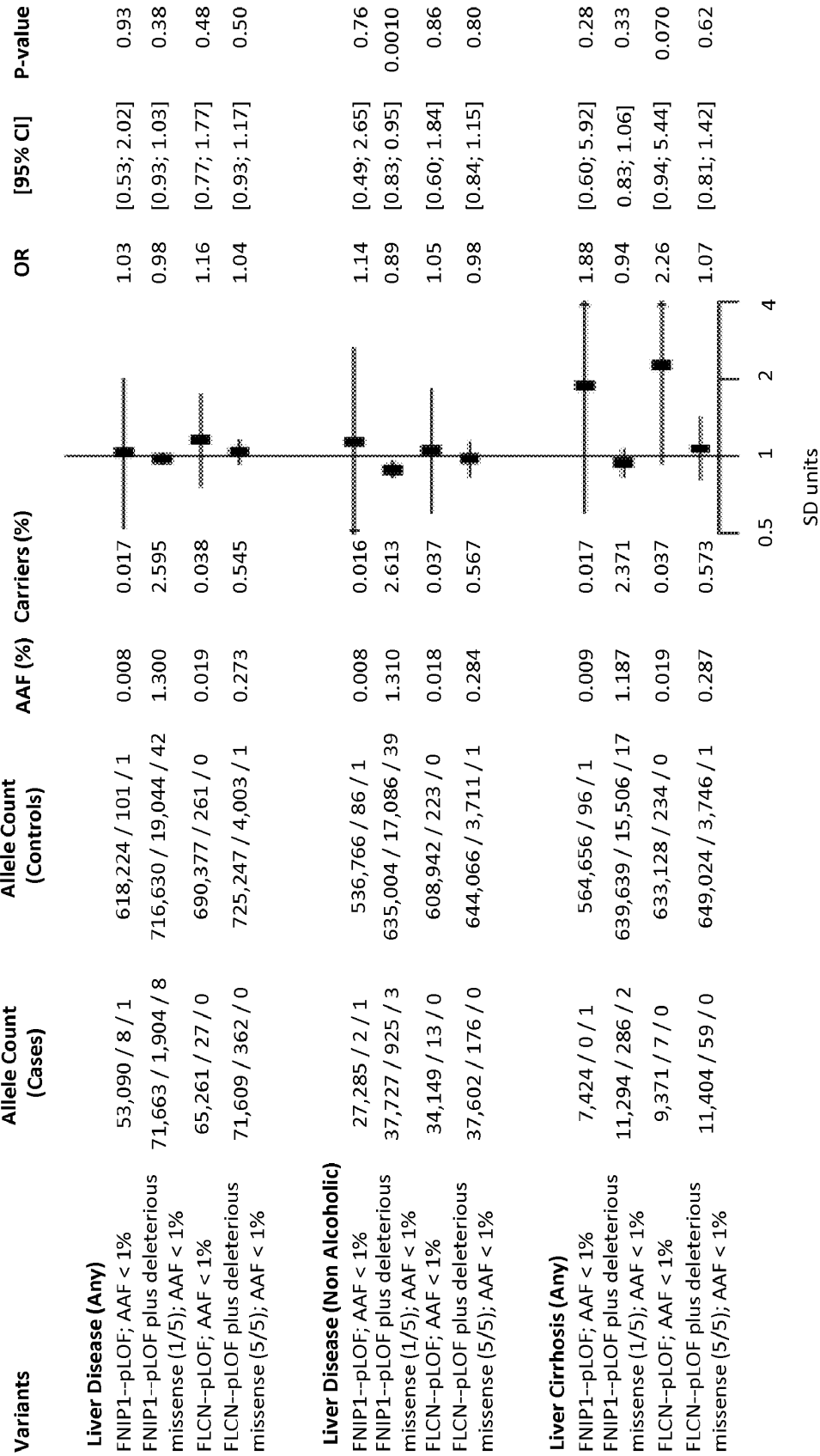


Figure 6

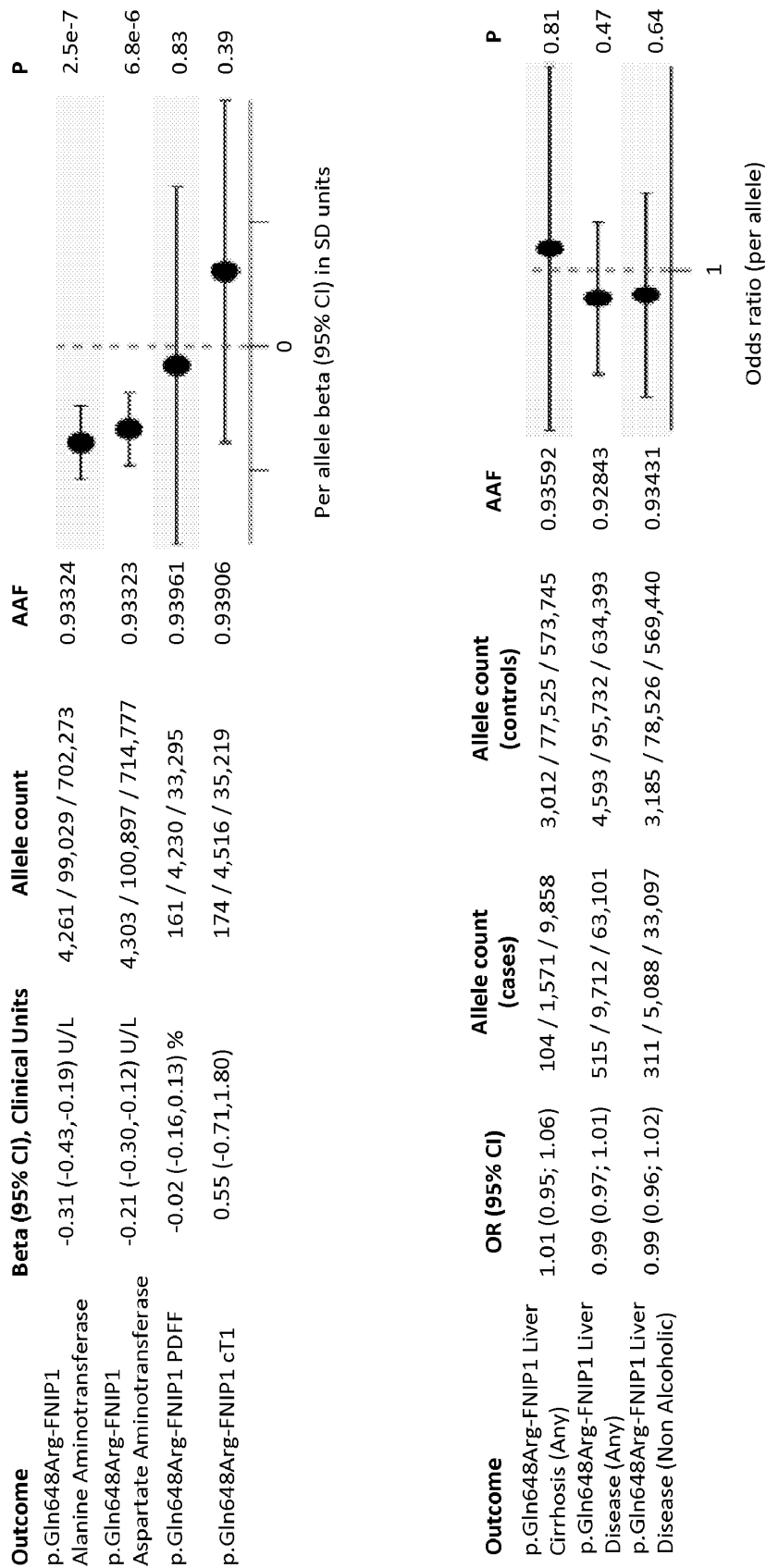
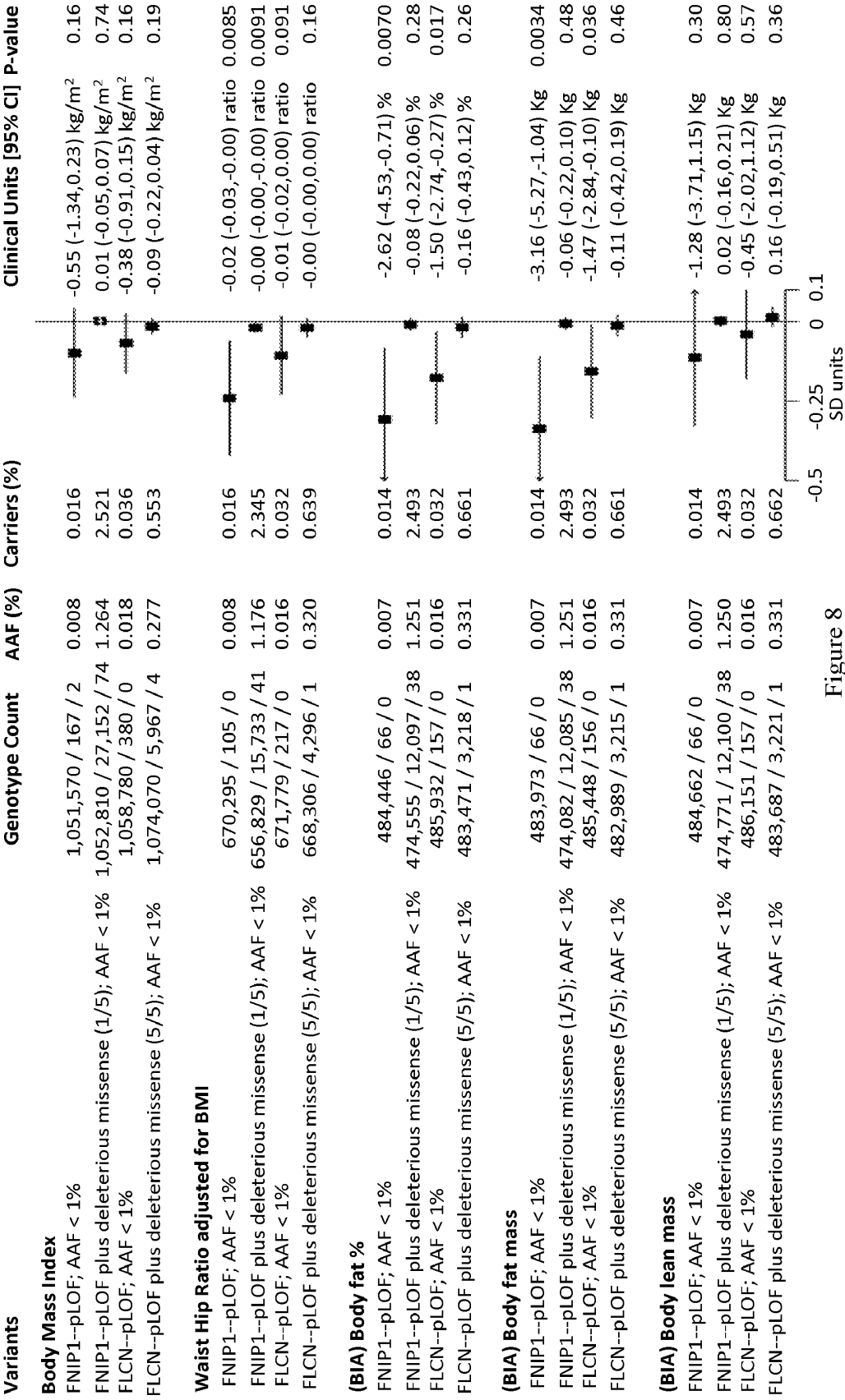


Figure 7



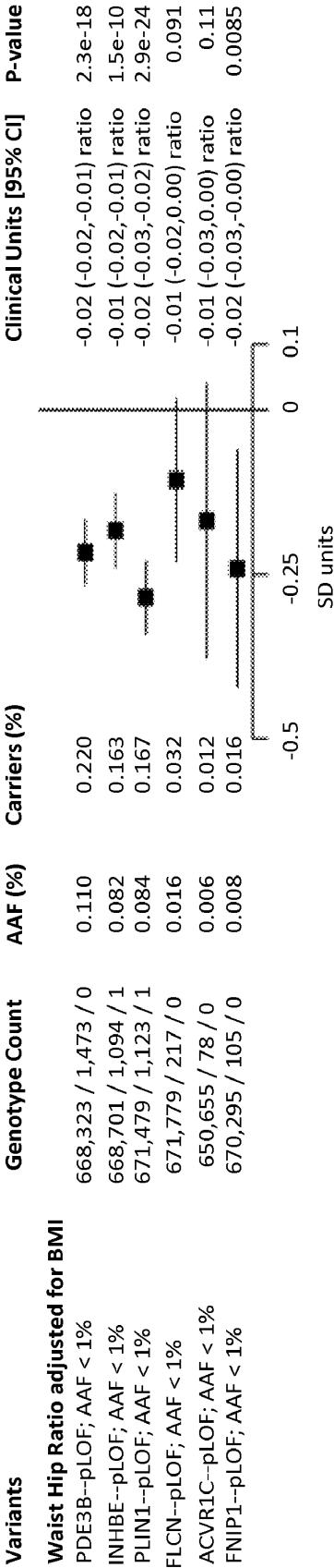


Figure 9

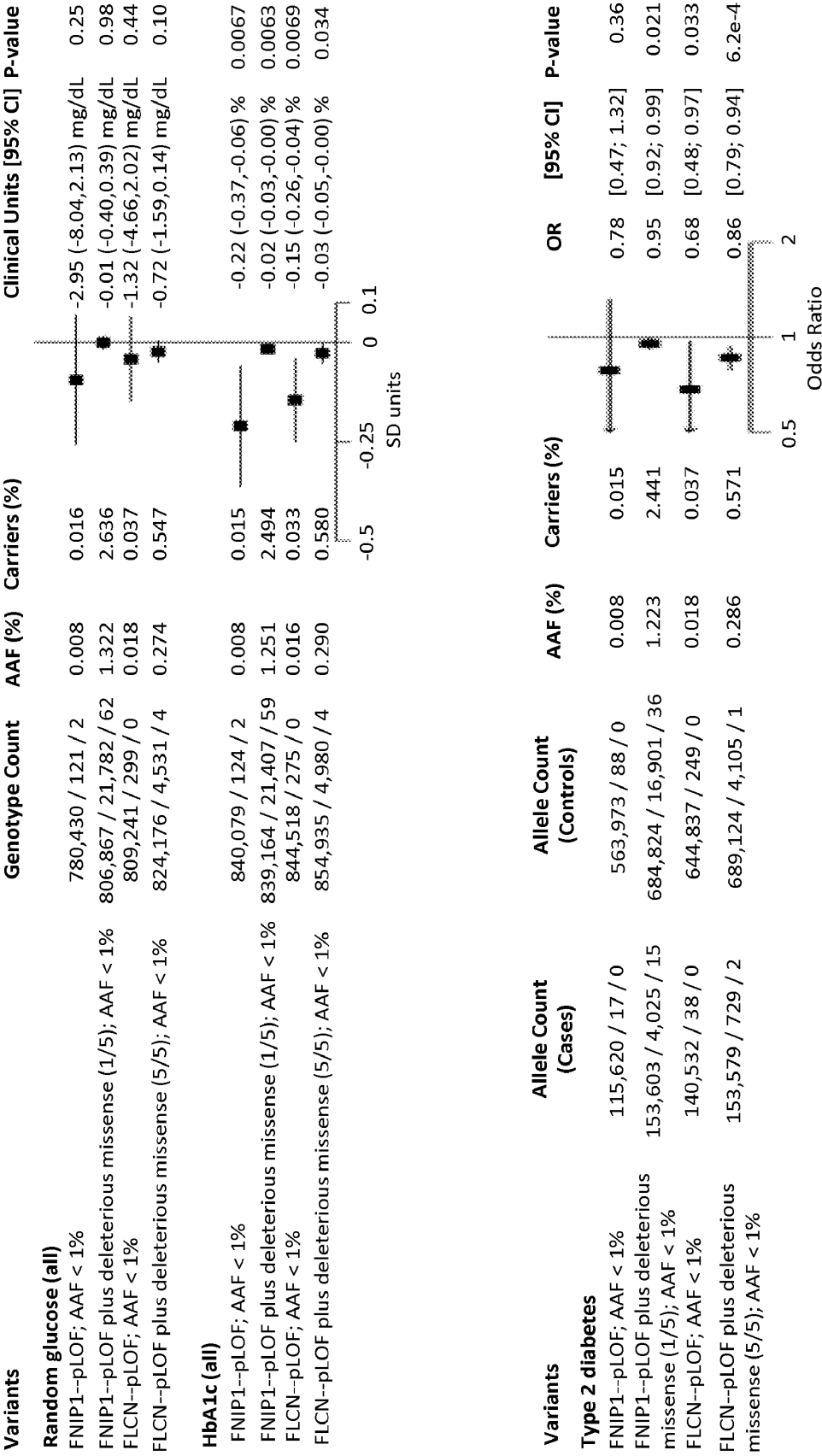


Figure 10

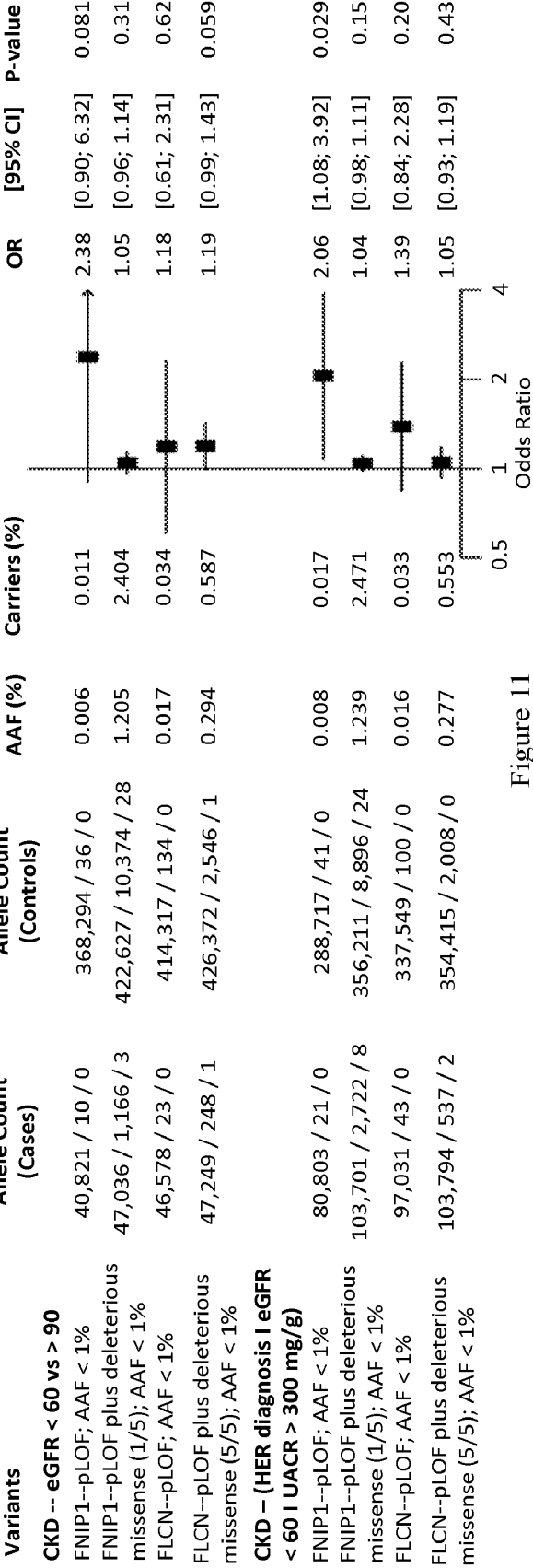
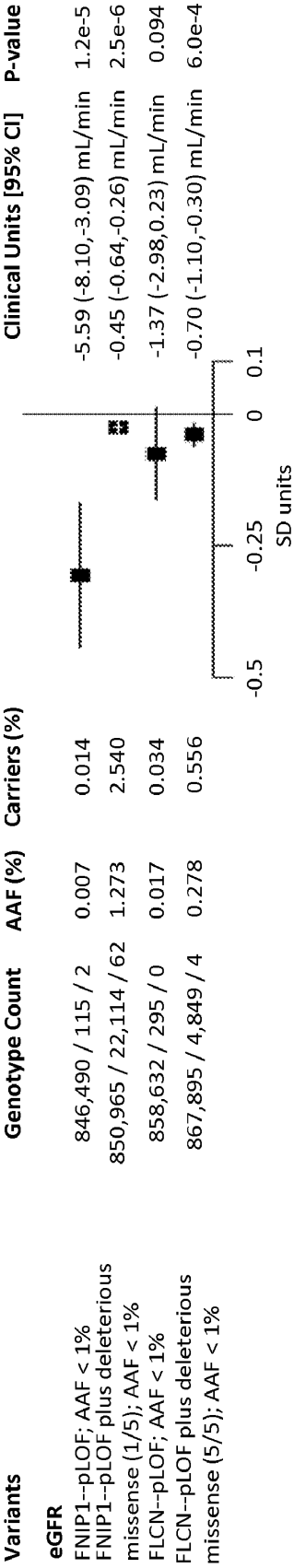


Figure 11

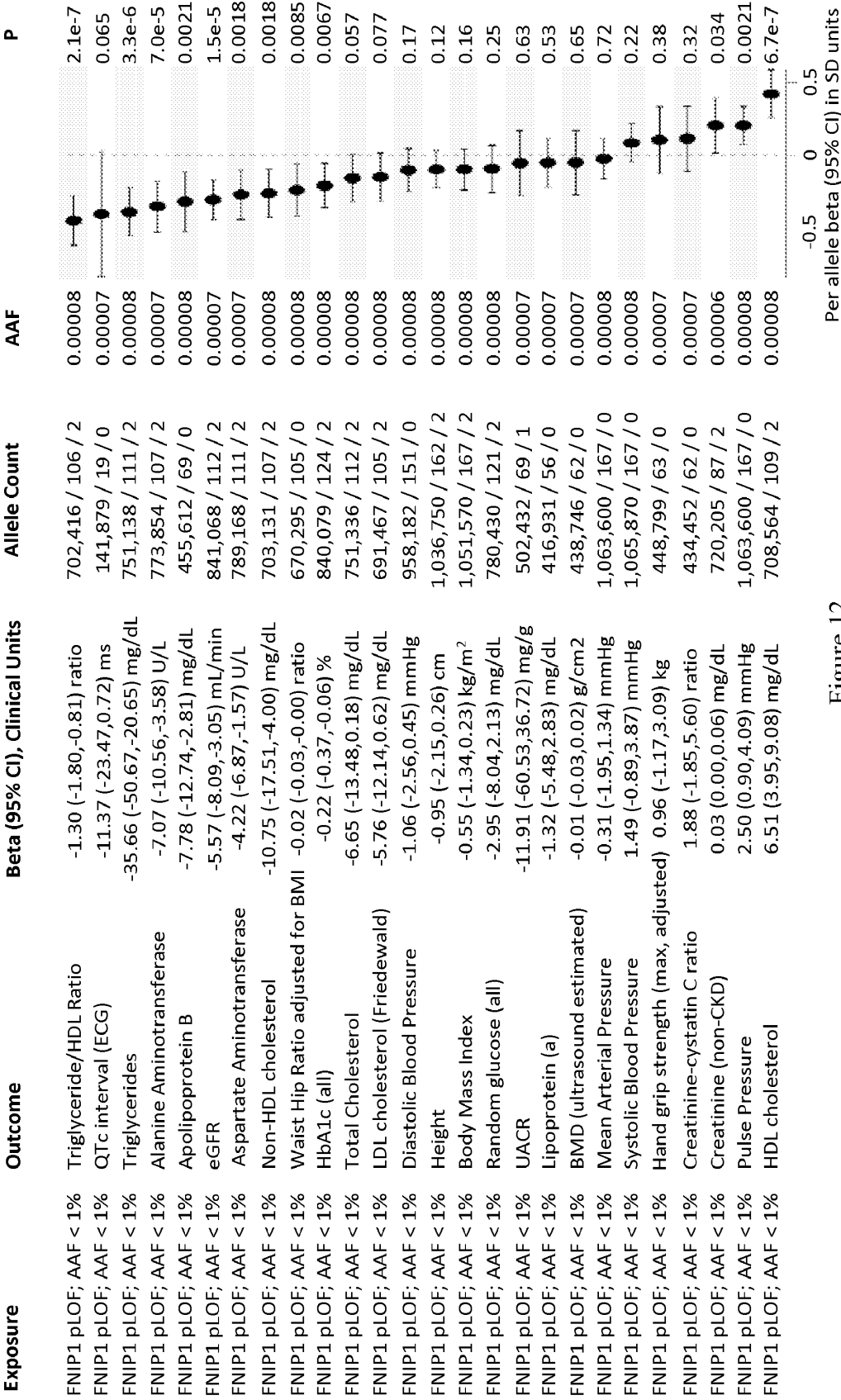


Figure 12

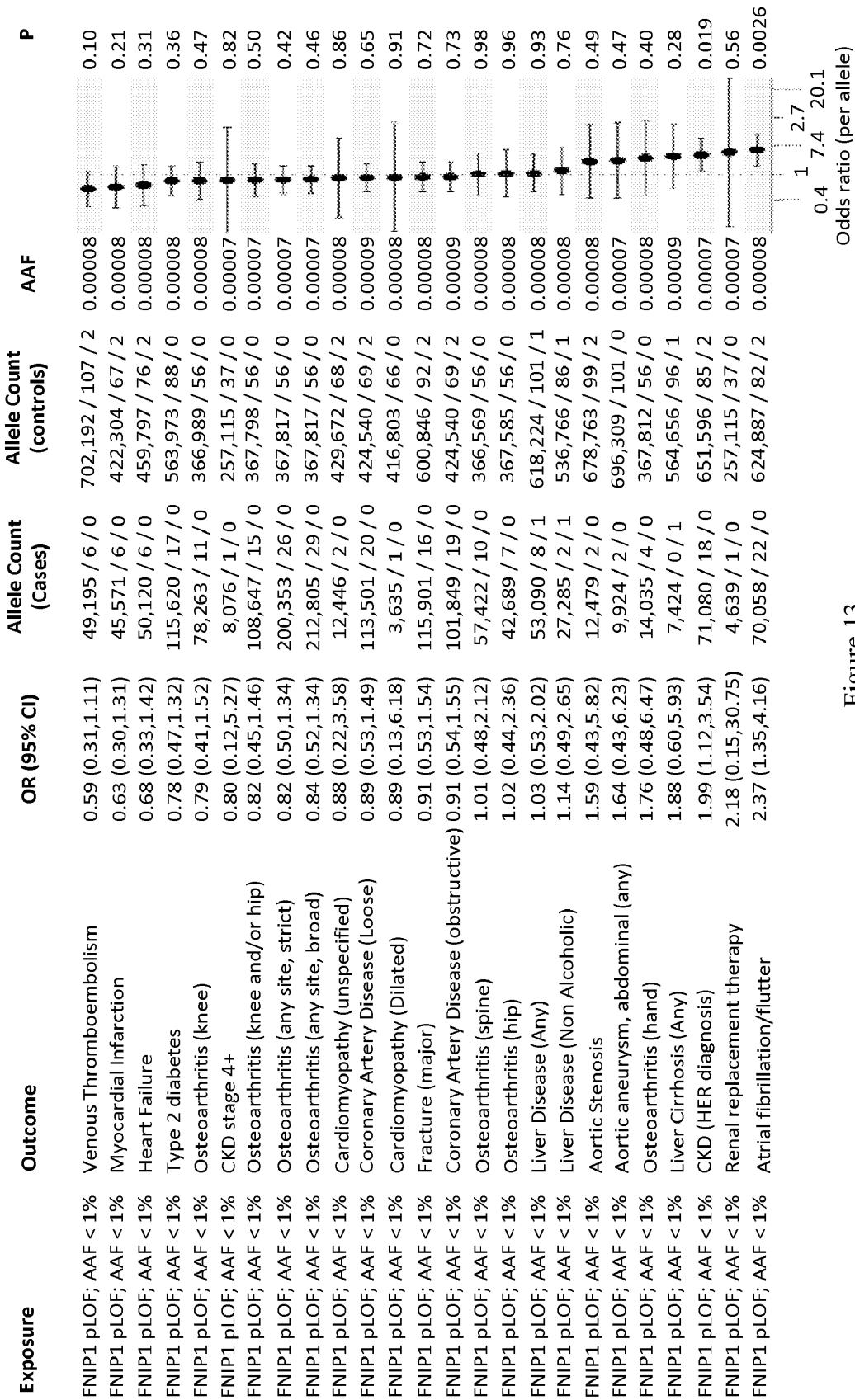


Figure 13

Outcome	Beta (95% CI), Clinical Units	Allele Count	AAF	P
p.Gln648Arg-FNIP1	Triglyceride/HDL Ratio	4,764 / 94,266 / 642,785	0.93004	4.1e-19
p.Gln648Arg-FNIP1	Triglycerides	4,963 / 98,981 / 678,044	0.93037	8.6e-15
p.Gln648Arg-FNIP1	Alanine Aminotransferase	4,261 / 99,029 / 702,273	0.93324	2.5e-7
p.Gln648Arg-FNIP1	Waist Hip Ratio adjusted for BMI	17,104 / 126,900 / 528,598	0.88024	2.4e-9
p.Gln648Arg-FNIP1	Aspartate Aminotransferase	4,303 / 100,897 / 714,777	0.93323	6.8e-6
p.Gln648Arg-FNIP1	UACR	2,136 / 59,603 / 452,291	0.93787	0.0043
p.Gln648Arg-FNIP1	HbA1c (all)	18,433 / 151,655 / 690,541	0.89047	2.8e-5
p.Gln648Arg-FNIP1	eGFR	7,046 / 113,344 / 741,005	0.92603	4.5e-4
p.Gln648Arg-FNIP1	Hand grip strength (max, adjusted)	1,829 / 51,535 / 397,701	0.93882	0.067
p.Gln648Arg-FNIP1	QTc interval (ECG)	591 / 16,884 / 128,632	0.93818	0.52
p.Gln648Arg-FNIP1	Non-HDL cholesterol	4,773 / 94,380 / 643,502	0.93003	0.14
p.Gln648Arg-FNIP1	Random glucose (all)	5,349 / 105,787 / 717,575	0.92972	0.30
p.Gln648Arg-FNIP1	Apolipoprotein B	1,903 / 52,879 / 402,995	0.93809	0.87
p.Gln648Arg-FNIP1	Lipoprotein (a)	1,707 / 47,952 / 369,388	0.93871	0.53
p.Gln648Arg-FNIP1	Pulse Pressure	20,911 / 185,489 / 883,180	0.89569	0.34
p.Gln648Arg-FNIP1	Diastolic Blood Pressure	20,371 / 171,726 / 789,880	0.89182	0.17
p.Gln648Arg-FNIP1	BMD (ultrasound estimated)	1,794 / 50,305 / 388,848	0.93889	0.38
p.Gln648Arg-FNIP1	Systolic Blood Pressure	20,915 / 185,650 / 884,851	0.89578	0.081
p.Gln648Arg-FNIP1	Mean Arterial Pressure	20,911 / 185,489 / 883,180	0.89569	0.085
p.Gln648Arg-FNIP1	Total Cholesterol	4,959 / 99,000 / 678,299	0.93038	0.18
p.Gln648Arg-FNIP1	Creatinine-cystatin C ratio	1,782 / 50,037 / 384,801	0.93862	0.23
p.Gln648Arg-FNIP1	LDL cholesterol (Friedewald)	4,679 / 92,715 / 632,912	0.93012	0.034
p.Gln648Arg-FNIP1	Height	19,727 / 178,527 / 861,614	0.89716	1.4e-6
p.Gln648Arg-FNIP1	Creatinine (non-CKD)	7,230 / 102,717 / 636,962	0.92156	1.7e-4
p.Gln648Arg-FNIP1	Body Mass Index	20,895 / 184,759 / 874,384	0.89512	5.5e-15
p.Gln648Arg-FNIP1	HDL cholesterol	4,808 / 95,106 / 648,206	0.93001	9.4e-17

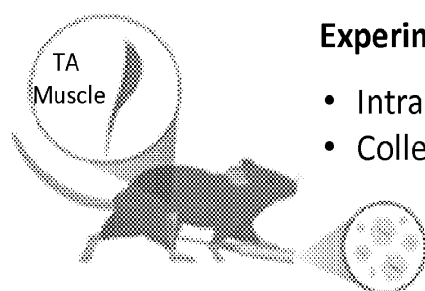
Per allele beta (95% CI) in SD units

Figure 14

Outcome	OR (95% CI)	Allele Count (Cases)	Allele Count (controls)	AAF	P
p.Gln648Arg-FNIP1 Type 2 diabetes	0.96 (0.95,0.98)	4,199 / 29,829 / 117,968	11,794 / 111,488 / 563,880	0.89674	4.0e-7
p.Gln648Arg-FNIP1 Osteoarthritis (hand)	0.97 (0.92,1.01)	71 / 2,047 / 14,300	1,795 / 49,275 / 371,191	0.93725	0.17
p.Gln648Arg-FNIP1 Osteoarthritis (spine)	0.98 (0.96,1.01)	351 / 9,112 / 63,129	2,298 / 55,169 / 396,230	0.93390	0.23
p.Gln648Arg-FNIP1 CKD stage 4+	0.99 (0.95,1.04)	151 / 2,704 / 16,942	1,965 / 44,870 / 319,548	0.93293	0.67
p.Gln648Arg-FNIP1 Osteoarthritis (hip)	0.99 (0.96,1.02)	217 / 5,704 / 42,372	2,035 / 53,162 / 390,660	0.93588	0.55
p.Gln648Arg-FNIP1 Aortic aneurysm, abdominal (any)	0.99 (0.94,1.05)	52 / 1,388 / 10,378	3,009 / 92,101 / 705,483	0.93869	0.76
p.Gln648Arg-FNIP1 Fracture (major)	0.99 (0.97,1.01)	561 / 15,382 / 113,029	3,937 / 91,645 / 648,584	0.93356	0.34
p.Gln648Arg-FNIP1 Liver Disease (Any)	0.99 (0.97,1.01)	515 / 9,712 / 63,101	4,593 / 95,732 / 634,393	0.92843	0.47
p.Gln648Arg-FNIP1 Liver Disease (Non Alcoholic)	0.99 (0.96,1.02)	311 / 5,088 / 33,097	3,185 / 78,526 / 569,440	0.93431	0.64
p.Gln648Arg-FNIP1 Osteoarthritis (any site, broad)	1.00 (0.98,1.02)	1,216 / 30,465 / 221,584	2,401 / 55,403 / 394,419	0.93402	0.96
p.Gln648Arg-FNIP1 Osteoarthritis (knee)	1.00 (0.98,1.02)	423 / 11,005 / 79,780	2,259 / 54,274 / 391,492	0.93450	0.92
p.Gln648Arg-FNIP1 Heart Failure	1.00 (0.98,1.03)	354 / 8,192 / 57,015	3,122 / 72,644 / 509,938	0.93260	0.90
p.Gln648Arg-FNIP1 Osteoarthritis (any site, strict)	1.00 (0.99,1.02)	1,057 / 26,900 / 196,814	2,320 / 53,097 / 379,040	0.93420	0.81
p.Gln648Arg-FNIP1 Osteoarthritis (knee and/or hip)	1.00 (0.98,1.02)	583 / 14,818 / 109,342	2,275 / 53,941 / 388,380	0.93460	0.80
p.Gln648Arg-FNIP1 CKD (HER diagnosis)	1.00 (0.98,1.02)	541 / 11,817 / 78,839	4,734 / 100,046 / 669,091	0.92933	0.80
p.Gln648Arg-FNIP1 Coronary Artery Disease (obstructive)	1.00 (0.98,1.02)	723 / 16,460 / 112,931	4,147 / 80,272 / 511,074	0.92663	0.78
p.Gln648Arg-FNIP1 Cardiomyopathy (unspecified)	1.00 (0.96,1.05)	106 / 2,361 / 16,274	2,567 / 66,044 / 479,836	0.93499	0.90
p.Gln648Arg-FNIP1 Renal replacement therapy	1.00 (0.95,1.06)	116 / 1,654 / 9,997	1,798 / 43,587 / 315,529	0.93417	0.89
p.Gln648Arg-FNIP1 Coronary Artery Disease (Loose)	1.01 (0.99,1.02)	773 / 17,809 / 123,875	4,147 / 80,272 / 511,074	0.92688	0.58
p.Gln648Arg-FNIP1 Liver Cirrhosis (Any)	1.01 (0.95,1.06)	104 / 1,571 / 9,858	3,012 / 77,525 / 573,745	0.93592	0.81
p.Gln648Arg-FNIP1 Aortic Stenosis	1.01 (0.96,1.06)	81 / 1,824 / 13,641	3,388 / 92,951 / 691,591	0.93670	0.67
p.Gln648Arg-FNIP1 Venous Thromboembolism	1.01 (0.99,1.04)	316 / 7,476 / 53,328	4,143 / 102,454 / 737,075	0.93432	0.38
p.Gln648Arg-FNIP1 Myocardial Infarction	1.01 (0.98,1.04)	292 / 6,907 / 48,647	3,839 / 77,305 / 500,844	0.92751	0.41
p.Gln648Arg-FNIP1 Atrial fibrillation/flutter	1.02 (1.00,1.04)	379 / 10,131 / 75,074	3,497 / 89,765 / 650,384	0.93509	0.083
p.Gln648Arg-FNIP1 Cardiomyopathy (Dilated)	1.05 (0.97,1.15)	21 / 586 / 4,200	2,195 / 60,554 / 451,209	0.93680	0.21

1 1.1
Odds ratio (per allele)

Figure 15



Experimental paradigm:

- Intramuscular dose of AAVmyo2A-gRNA pool
- Collect TA muscle after 6 weeks

Dose: 1.5E11 vg/TA muscle

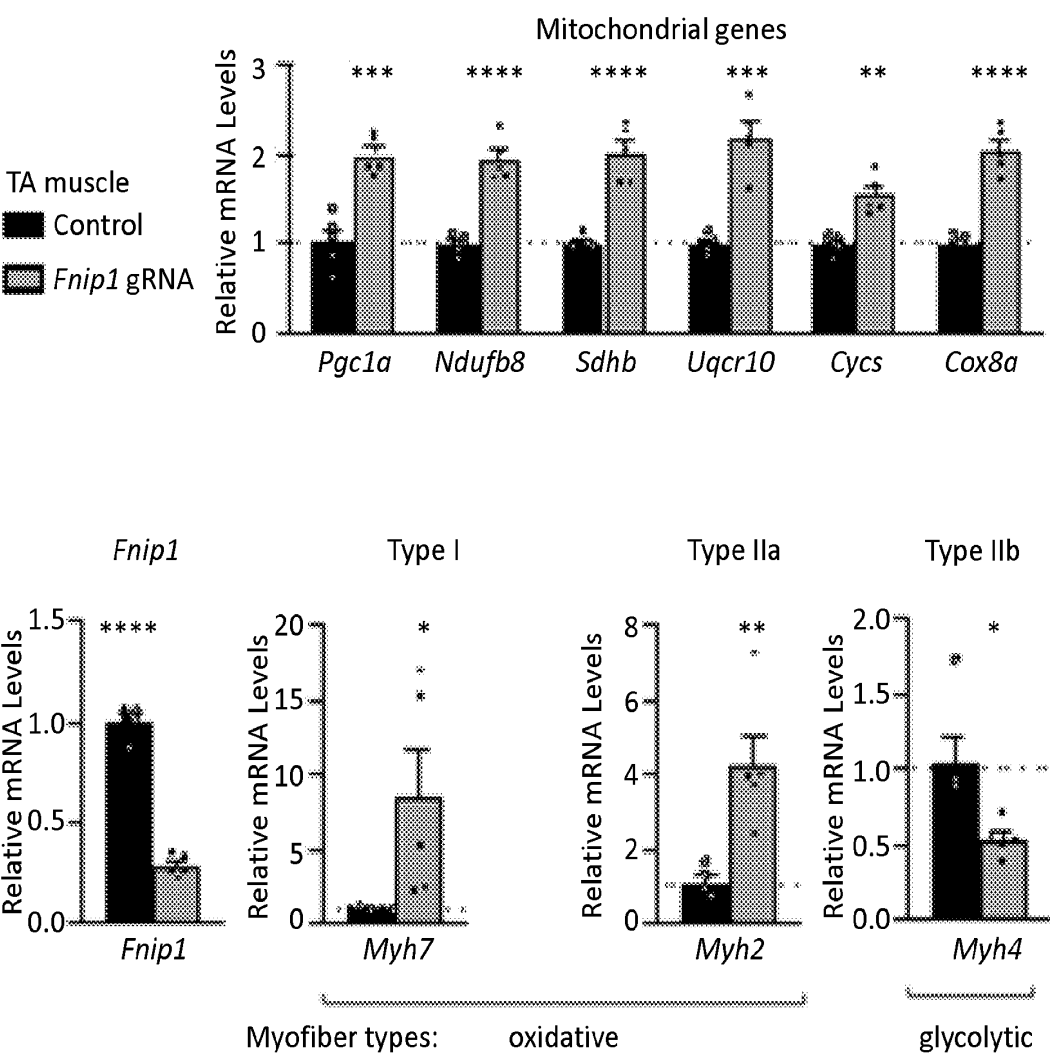


Figure 16

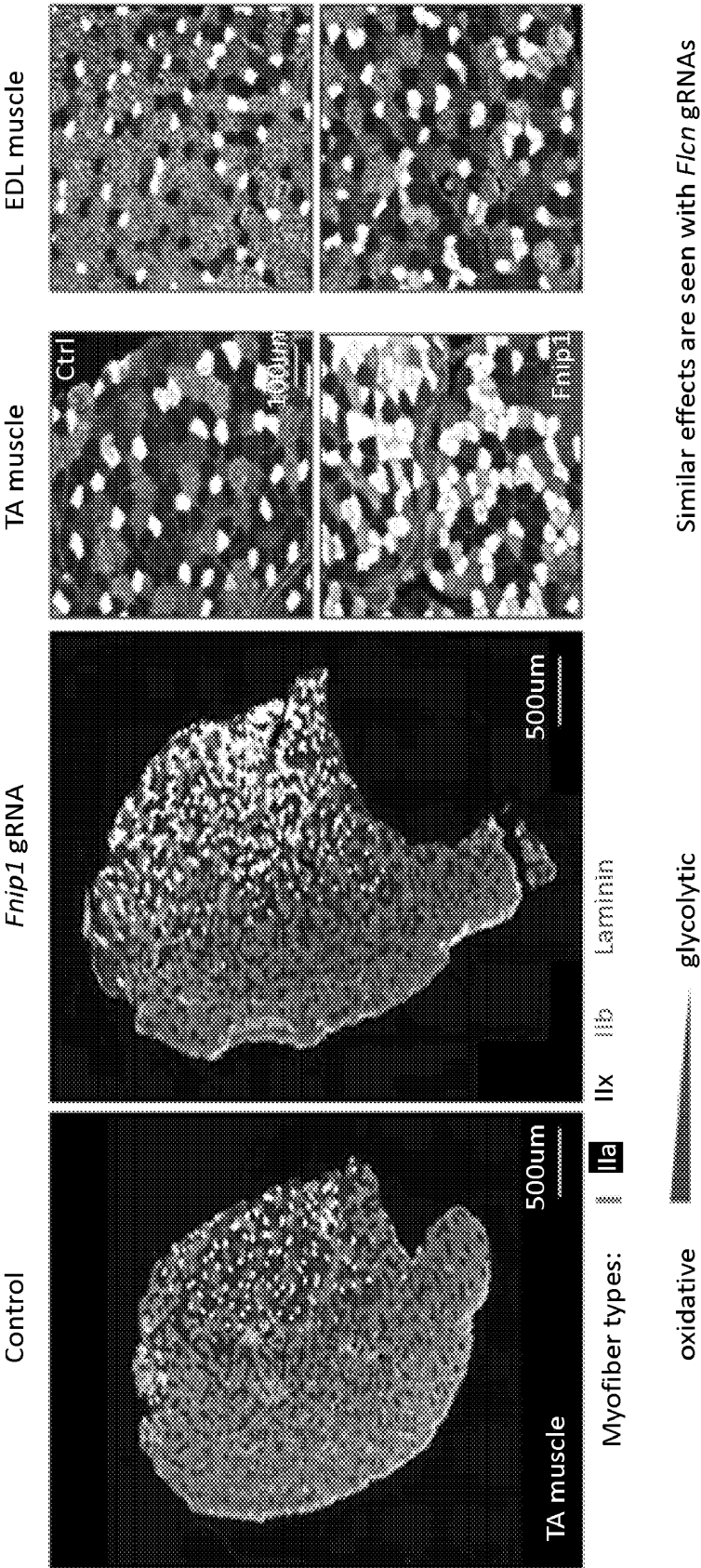


Figure 16 (cont.)

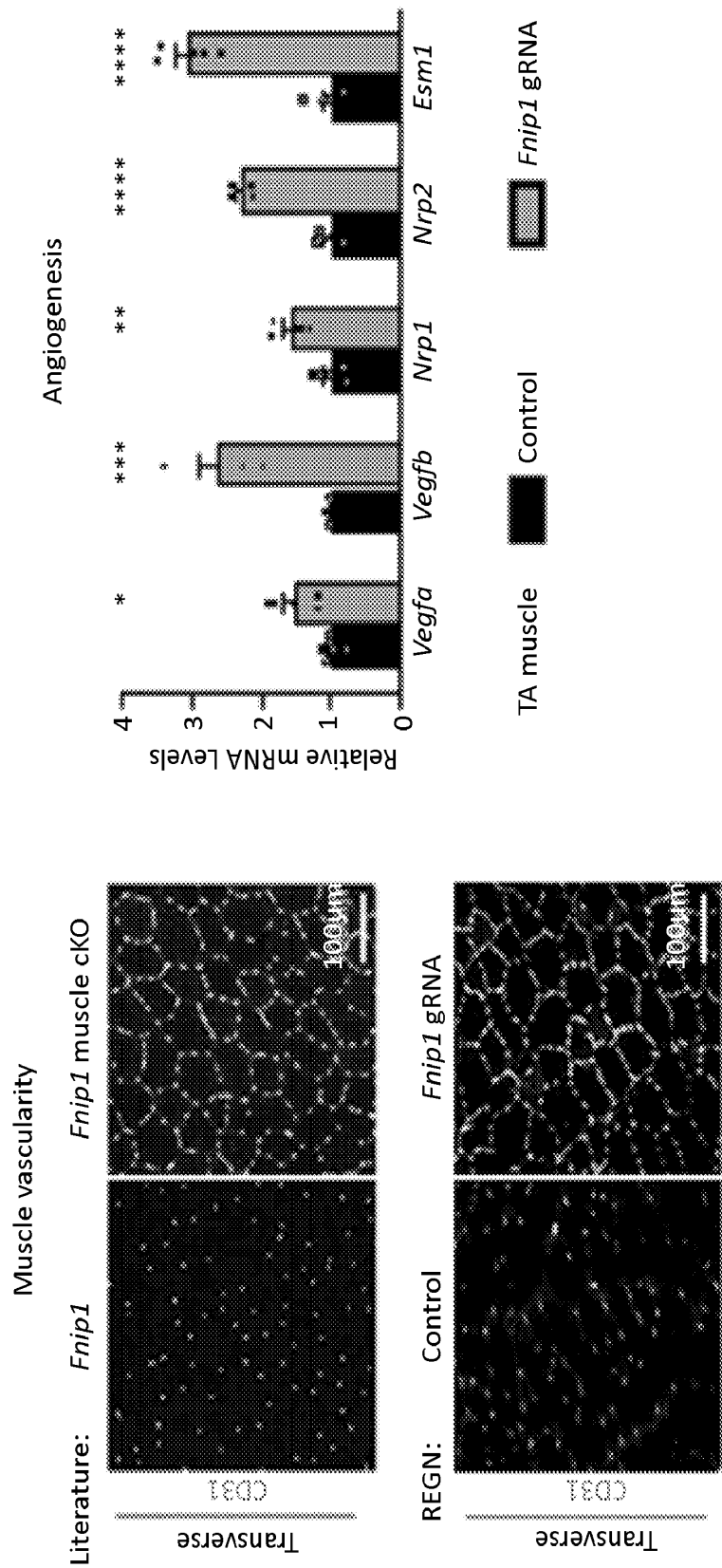


Figure 17

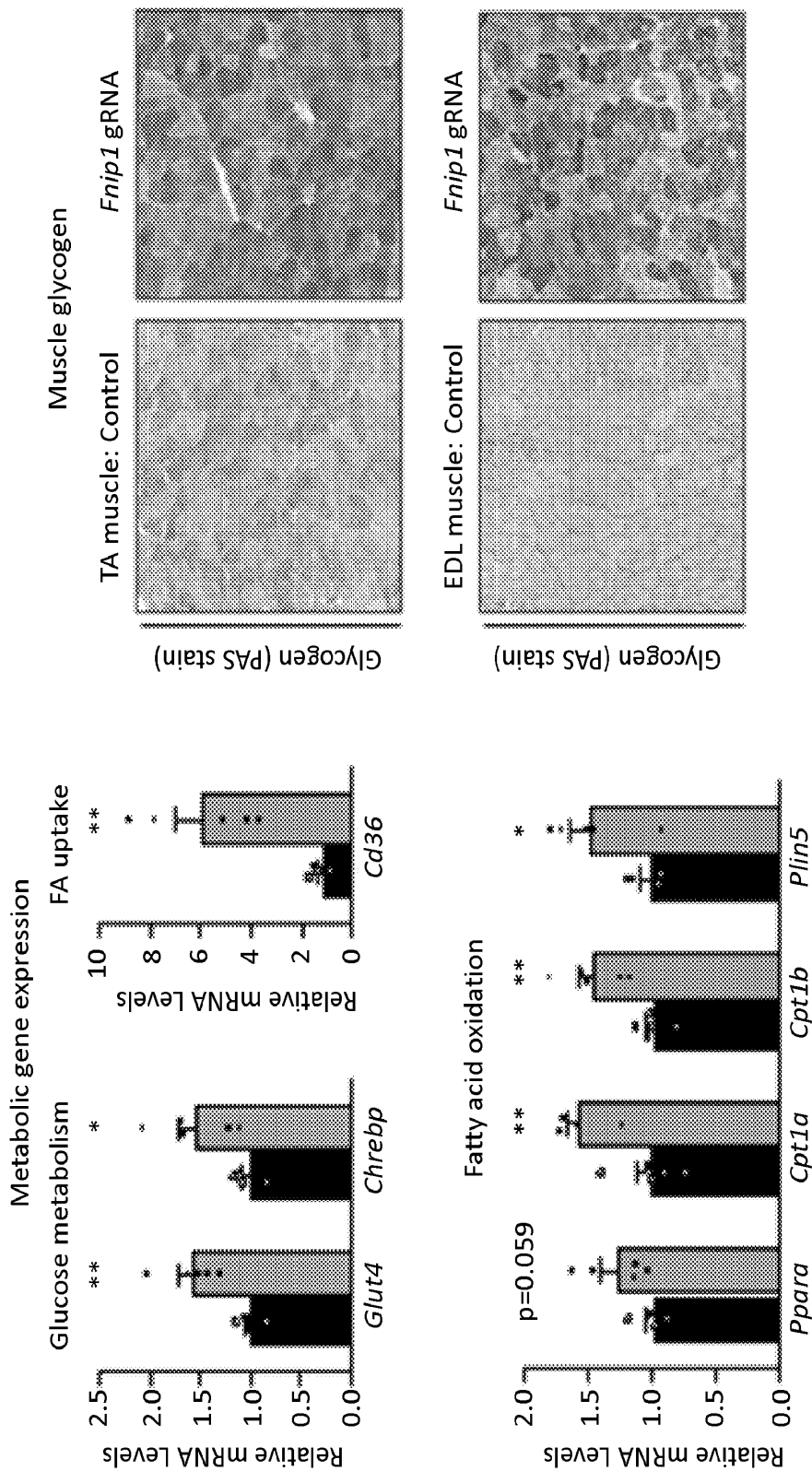
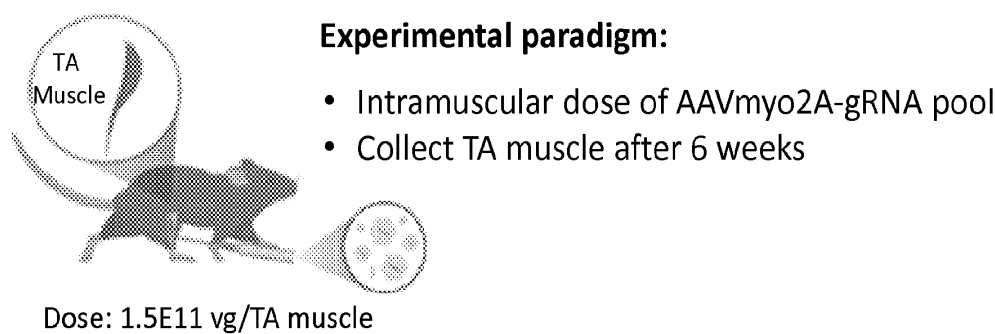


Figure 17 (cont.)



Muscle fiber composition

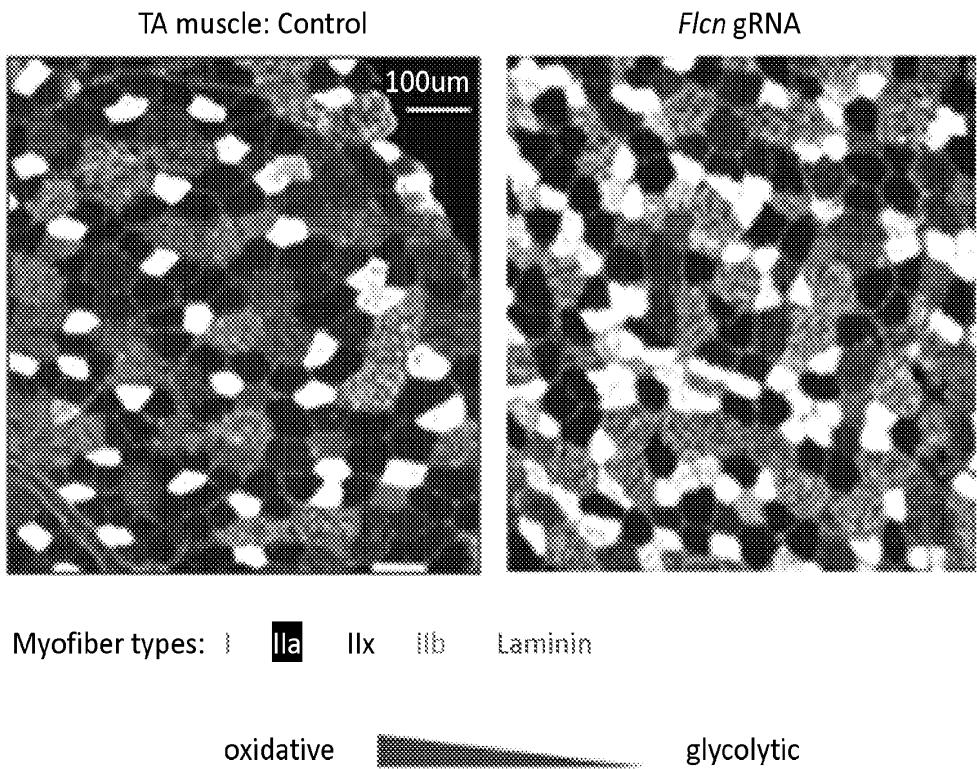


Figure 18

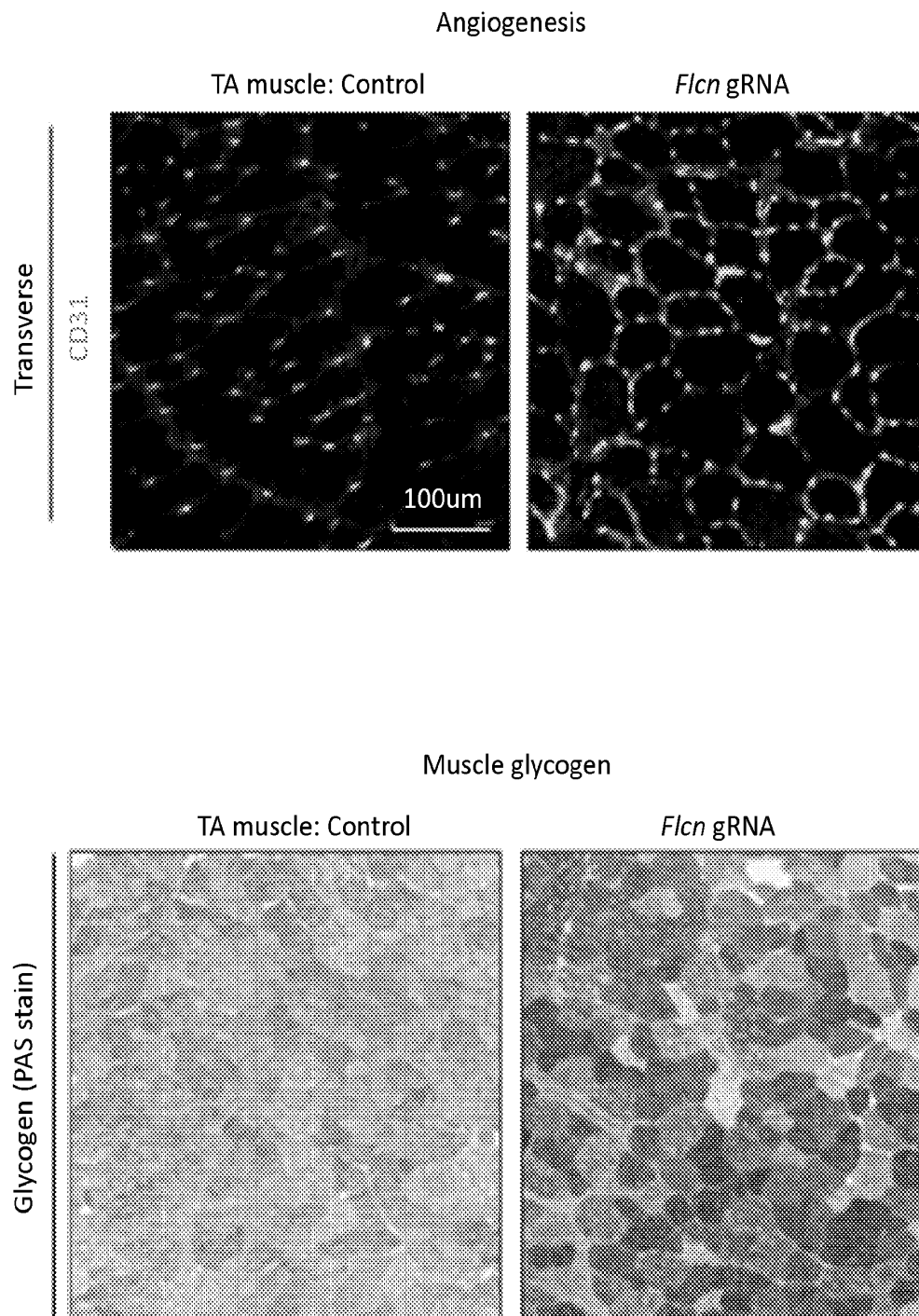


Figure 18 (cont.)