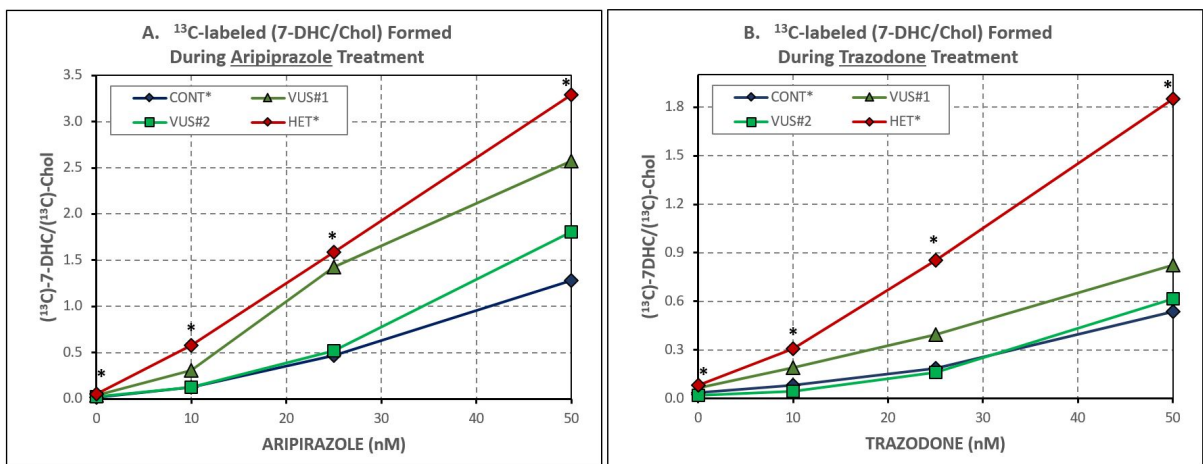


Supplemental material for:

Vulnerability of *DHCR7*^{+/-} mutation carriers to aripiprazole and trazodone exposure

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Aripiprazole

¹³C)-7-DHC/¹³C)-Chol

	DMSO	Aripiprazole (nM)			
	0	10	25	50	
CONT*	0.016	0.123	0.473	1.277	
VUS#2	0.024	0.128	0.518	1.807	
VUS#1	0.041	0.309	1.427	2.571	
HET*	0.051	0.576	1.585	3.286	
*p-val		2.E-03	1.E-07	1.E-08	7.E-10

Trazodone

¹³C)-7-DHC/¹³C)-Chol

	DMSO	Trazodone (nM)			
	0	10	25	50	
CONT*	0.036	0.083	0.188	0.536	
VUS#2	0.019	0.045	0.162	0.617	
VUS#1	0.063	0.191	0.396	0.823	
HET*	0.081	0.306	0.856	1.851	
*p-val		1.E-02	3.E-04	7.E-10	9.E-10

Supplemental Figure S1. Aripiprazole (ARI) or trazodone (TRZ) alter residual cholesterol biosynthesis. Six *DHCR7*-HET, four CTR HF and two fibroblasts having a *DHCR7* variation of unknown significance (VUS) were cultured in the presence of 500 nM ³¹³C-Lan and different concentrations of ARI or TRZ. A and B graphs show the ³¹³C-derived 7-DHC and ³¹³C-derived cholesterol where 7-DHC is normalized to cholesterol for the six *DHCR7*-HET, the four CTR and the individual data for the VUS#1 and VUS#2 cells. The genotyping for each cell is presented in Figure 2 in the manuscript. Stars above bars show p values <0.01 and represents the difference between control and heterozygous samples.

Supplemental Table S1A (Companion to Figure 4). Sterol levels, reported as ng/million cells.

		7-DHC level									
ARIPRAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	284.5	1961.7	3679.9	5049.4	average	81.8	633.3	1549.9	3417.8	
	stdev	155.1	451.5	444.0	672.9	stdev	38.3	253.4	530.0	749.5	
	SEM	36.6	106.4	104.6	158.6	SEM	11.0	73.2	153.0	216.4	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	380.8	1069.6	2370.3	4194.1	average	179.1	328.3	673.4	1584.8	
	stdev	204.4	557.1	586.7	684.3	stdev	61.3	81.7	143.7	291.3	
	SEM	48.2	131.3	138.3	161.3	SEM	17.7	23.6	41.5	84.1	
		Cholesterol level									
ARIPRAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	18356.8	16086.7	14307.2	13385.3	average	23669.0	20891.9	20077.6	18669.8	
	stdev	2154.9	2408.5	1773.3	2226.0	stdev	6151.5	4085.1	3483.7	3856.5	
	SEM	507.9	567.7	418.0	524.7	SEM	1775.8	1179.3	1005.7	1113.3	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	18983.1	17929.5	16165.0	14695.3	average	22457.6	21645.2	20198.5	20066.0	
	stdev	2192.6	3008.3	2599.6	1928.3	stdev	4803.5	3935.9	3161.9	3832.6	
	SEM	516.8	709.1	612.7	454.5	SEM	1386.6	1136.2	912.8	1106.4	
		8-DHC level									
ARIPRAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	359.5	555.8	688.9	836.5	average	246.6	411.5	726.2	831.4	
	stdev	149.8	192.8	244.4	321.4	stdev	177.3	235.5	351.4	317.8	
	SEM	35.3	45.4	57.6	75.8	SEM	51.2	68.0	101.4	91.7	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	433.0	631.0	879.1	986.5	average	374.1	630.3	807.9	877.5	
	stdev	171.7	189.6	300.8	277.5	stdev	142.7	241.0	294.1	367.1	
	SEM	40.5	44.7	70.9	65.4	SEM	41.2	69.6	84.9	106.0	
		Desmosterol level									
ARIPRAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	284.9	228.2	224.3	233.7	average	441.4	315.3	245.3	353.0	
	stdev	125.0	171.1	158.2	169.5	stdev	185.9	187.6	67.0	205.2	
	SEM	29.5	40.3	37.3	40.0	SEM	53.7	54.1	19.3	59.2	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	292.1	261.8	237.4	234.9	average	437.3	334.1	276.8	237.2	
	stdev	182.5	193.1	198.8	182.8	stdev	112.8	101.0	103.0	108.6	
	SEM	43.0	45.5	46.9	43.1	SEM	32.6	29.2	29.7	31.4	
		Lanosterol level									
ARIPRAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	56.2	40.3	48.1	30.4	average	63.4	54.9	56.2	47.0	
	stdev	32.5	28.5	28.9	18.8	stdev	51.7	50.3	44.1	29.3	
	SEM	7.7	6.7	6.8	4.4	SEM	14.9	14.5	12.7	8.5	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	64.0	61.1	63.3	55.4	average	69.3	67.4	59.5	55.2	
	stdev	23.6	24.6	32.3	26.6	stdev	23.8	22.5	18.9	20.3	
	SEM	5.6	5.8	7.6	6.3	SEM	6.9	6.5	5.5	5.9	

Supplemental Table S1B. (Companion to Figure 4). Significance of sterol levels differences.

		7-DHC (significance values)		
		ARI 10	ARI 25	ARI 50
ARIPIRAZOLE	HET ARI vs HET DMSO	1.79E-16	2.41E-26	1.07E-25
	CNT ARI vs CNT DMSO	1.87E-07	2.66E-09	2.90E-13
	CNT ARI vs HET ARI	5.43E-10	1.76E-12	1.02E-06
		TRZ 10	TRZ 25	TRZ 50
TRAZODONE	HET TRZ vs HET DMSO	2.15E-05	2.69E-15	4.29E-22
	CNT TRZ vs CNT DMSO	4.57E-05	2.23E-10	8.50E-14
	CNT TRZ vs HET ARI	9.48E-05	1.60E-10	6.55E-13

		Cholesterol (significance values)		
		ARI 10	ARI 25	ARI 50
ARIPIRAZOLE	HET ARI vs HET DMSO	5.29E-03	5.40E-07	7.85E-08
	CNT ARI vs CNT DMSO	2.06E-01	9.23E-02	2.61E-02
	CNT ARI vs HET ARI	4.00E-04	1.87E-06	5.26E-05
		TRZ 10	TRZ 25	TRZ 50
TRAZODONE	HET TRZ vs HET DMSO	2.38E-01	1.27E-03	4.33E-07
	CNT TRZ vs CNT DMSO	6.55E-01	1.87E-01	1.91E-01
	CNT TRZ vs HET ARI	6.68E-03	6.81E-04	2.19E-05

		8-DHC (significance values)		
		ARI 10	ARI 25	ARI 50
ARIPIRAZOLE	HET ARI vs HET DMSO	1.68E-03	2.49E-05	2.07E-06
	CNT ARI vs CNT DMSO	6.56E-02	3.51E-04	1.35E-05
	CNT ARI vs HET ARI	7.65E-02	7.34E-01	9.66E-01
		TRZ 10	TRZ 25	TRZ 50
TRAZODONE	HET TRZ vs HET DMSO	2.38E-03	4.29E-06	2.51E-08
	CNT TRZ vs CNT DMSO	4.46E-03	1.40E-04	2.12E-04
	CNT TRZ vs HET ARI	9.93E-01	5.27E-01	3.62E-01

		Lanosterol (significance values)		
		ARI 10	ARI 25	ARI 50
ARIPIRAZOLE	HET ARI vs HET DMSO	1.26E-01	4.33E-01	6.13E-03
	CNT ARI vs CNT DMSO	6.87E-01	7.16E-01	3.48E-01
	CNT ARI vs HET ARI	3.17E-01	5.49E-01	6.88E-02
		TRZ 10	TRZ 25	TRZ 50
TRAZODONE	HET TRZ vs HET DMSO	7.21E-01	9.44E-01	3.11E-01
	CNT TRZ vs CNT DMSO	8.41E-01	2.73E-01	1.32E-01
	CNT TRZ vs HET ARI	4.84E-01	7.12E-01	9.84E-01

		Desmosterol (significance values)		
		ARI 10	ARI 25	ARI 50
ARIPIRAZOLE	HET ARI vs HET DMSO	2.64E-01	2.11E-01	3.09E-01
	CNT ARI vs CNT DMSO	1.12E-01	2.34E-03	2.80E-01
	CNT ARI vs HET ARI	1.99E-01	6.69E-01	9.34E-02
		TRZ 10	TRZ 25	TRZ 50
TRAZODONE	HET TRZ vs HET DMSO	6.31E-01	3.96E-01	3.53E-01
	CNT TRZ vs CNT DMSO	2.75E-02	1.45E-03	2.13E-04
	CNT TRZ vs HET ARI	2.45E-01	5.34E-01	9.68E-01

Supplemental Table S2A (Companion to Figure 5). ¹³C-labeled Sterol levels, reported as ng/million cells; 13C 8-DHC could not be determined because of overlapping MS fragments with isotopic internal standards.

		7-DHC level									
ARIPIPAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	44.8	351.0	631.9	914.3	average	14.0	94.5	308.1	625.7	
	stdev	33.3	159.8	200.5	233.4	stdev	15.2	54.2	111.7	161.4	
	SEM	7.9	37.7	47.3	55.0	SEM	4.4	15.6	32.2	46.6	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	89.8	274.6	566.4	856.5	average	41.5	87.8	192.6	430.1	
	stdev	72.9	170.2	197.4	180.9	stdev	20.3	45.0	100.7	170.5	
	SEM	17.2	40.1	46.5	42.6	SEM	5.9	13.0	29.1	49.2	
		Cholesterol level									
ARIPIPAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	853.6	611.8	403.9	288.8	average	872.8	788.0	723.6	521.2	
	stdev	200.6	158.1	89.1	100.1	stdev	248.6	193.0	211.6	159.2	
	SEM	47.3	37.3	21.0	23.6	SEM	71.8	55.7	61.1	46.0	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	1045.5	884.1	658.7	474.5	average	1208.1	1093.6	1050.4	860.7	
	stdev	166.7	105.3	92.6	82.3	stdev	189.6	163.7	126.9	185.6	
	SEM	39.3	24.8	21.8	19.4	SEM	54.7	47.3	36.6	53.6	
		Desmosterol level									
ARIPIPAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	162.9	151.6	178.6	136.1	average	174.5	213.7	159.3	132.7	
	stdev	76.7	87.1	107.3	73.8	stdev	67.1	88.0	58.9	53.7	
	SEM	18.1	20.5	25.3	17.4	SEM	19.4	25.4	17.0	15.5	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	131.3	136.2	114.4	123.9	average	180.0	166.9	144.6	153.8	
	stdev	52.6	68.3	42.3	55.7	stdev	52.7	66.7	35.2	48.0	
	SEM	12.4	16.1	10.0	13.1	SEM	15.2	19.3	10.2	13.8	
		Lanosterol level									
ARIPIPAZOLE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	ARI 10	ARI 25	ARI 50	Sample	DMSO	ARI 10	ARI 25	ARI 50	
	average	1236.8	1414.0	1516.4	1314.7	average	1208.9	1370.9	1359.2	1378.5	
	stdev	500.7	712.4	885.6	483.7	stdev	478.9	674.5	551.6	716.4	
	SEM	118.0	167.9	208.7	114.0	SEM	138.3	194.7	159.2	206.8	
TRAZODONE	HETEROZYGOUS					CONTROL					
	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	Sample	DMSO	TRZ 10	TRZ 25	TRZ 50	
	average	1362.1	1343.5	1351.7	1316.4	average	1459.20	1476.08	1564.50	1346.35	
	stdev	424.6	351.1	411.7	431.6	stdev	294.04	331.33	480.23	287.86	
	SEM	100.1	82.8	97.0	101.7	SEM	84.88	95.65	138.63	83.10	

Supplemental Table S2B (Companion to Figure 5). Significance of sterol level differences.

13C-7-DHC (significance values)				
ARIPIRAZOLE		<i>ARI 10</i>	<i>ARI 25</i>	<i>ARI 50</i>
	HET ARI vs HET DMSO	2.87E-09	5.00E-14	4.23E-17
	CNT ARI vs CNT DMSO	5.84E-05	7.36E-09	7.55E-12
	CNT ARI vs HET ARI	1.12E-05	2.25E-05	8.85E-04
TRAZODONE		<i>TRZ 10</i>	<i>TRZ 25</i>	<i>TRZ 50</i>
	HET TRZ vs HET DMSO	1.65E-04	3.23E-11	6.10E-18
	CNT TRZ vs CNT DMSO	3.68E-03	4.17E-05	8.25E-08
	CNT TRZ vs HET ARI	9.43E-04	1.68E-06	5.22E-07

13C-Cholesterol (significance values)				
ARIPIRAZOLE		<i>ARI 10</i>	<i>ARI 25</i>	<i>ARI 50</i>
	HET ARI vs HET DMSO	3.09E-04	3.72E-10	2.06E-12
	CNT ARI vs CNT DMSO	3.60E-01	1.28E-01	4.43E-04
	CNT ARI vs HET ARI	1.06E-02	3.80E-06	3.43E-05
TRAZODONE		<i>TRZ 10</i>	<i>TRZ 25</i>	<i>TRZ 50</i>
	HET TRZ vs HET DMSO	1.43E-03	4.71E-10	8.95E-15
	CNT TRZ vs CNT DMSO	1.28E-01	2.56E-02	1.63E-04
	CNT TRZ vs HET ARI	1.98E-04	1.54E-10	1.70E-08

13C-Lanosterol (significance values)				
ARIPIRAZOLE		<i>ARI 10</i>	<i>ARI 25</i>	<i>ARI 50</i>
	HET ARI vs HET DMSO	3.94E-01	2.52E-01	6.38E-01
	CNT ARI vs CNT DMSO	5.05E-01	4.84E-01	5.02E-01
	CNT ARI vs HET ARI	8.70E-01	5.89E-01	7.72E-01
TRAZODONE		<i>TRZ 10</i>	<i>TRZ 25</i>	<i>TRZ 50</i>
	HET TRZ vs HET DMSO	8.87E-01	9.41E-01	7.51E-01
	CNT TRZ vs CNT DMSO	8.96E-01	5.24E-01	3.52E-01
	CNT TRZ vs HET ARI	3.09E-01	2.05E-01	8.35E-01

13C-Desmosterol (significance values)				
ARIPIRAZOLE		<i>ARI 10</i>	<i>ARI 25</i>	<i>ARI 50</i>
	HET ARI vs HET DMSO	6.84E-01	6.16E-01	2.94E-01
	CNT ARI vs CNT DMSO	2.32E-01	5.62E-01	1.06E-01
	CNT ARI vs HET ARI	6.71E-02	5.76E-01	8.92E-01
TRAZODONE		<i>TRZ 10</i>	<i>TRZ 25</i>	<i>TRZ 50</i>
	HET TRZ vs HET DMSO	8.10E-01	2.97E-01	6.87E-01
	CNT TRZ vs CNT DMSO	5.98E-01	6.55E-02	2.17E-01
	CNT TRZ vs HET ARI	2.34E-01	5.09E-02	1.40E-01

SUPPLEMENTARY MATERIALS AND METHODS

Cell Cultures. Human control and *DHCR7*-heterozygous human fibroblasts were established from skin biopsy samples. All fibroblasts were maintained in DMEM supplemented with L-glutamine, 10% fetal bovine serum (FBS; Thermo Scientific HyClone, Logan, UT), and penicillin/streptomycin at 37°C and 5% CO₂ and were used between passages 5 and 15. The experiments were performed with fibroblasts grown in 96-well plates. The cells were plated at $5 \times 10^4/\text{cm}^2$ cells per well in regular medium. After overnight incubation in cell culture incubator, the medium was replaced with DMEM containing 10% delipidated serum, 500 nM ³13C-Lan with or without ARI and TRZ at 10, 25 and 50 nM. This medium was changed every two days and the cells were cultured for six days. At the end of experiment, Hoechst dye (10 uL of 40 ng/uL, Molecular Probes) was added to each well and the plates were incubated at 37°C for 30 min. The plates were imaged using an ImageXpress Micro XL (Molecular Devices, Sunnyvale, CA) with 10X objective. After imaging the cells were rinsed two times with PBS (pH 7.4), PBS was removed completely and the plates were frozen at -80°C until analysis. The total number of cells per well was extracted from images and used as a normalizer for sterol values. The whole study was done over the course of two years and we repeated experiments with both ARI and TRZ and different cell lines at least three times. The graphs in the Results section show one example where all twelve fibroblasts (six controls and six *DHCR7*-HET) were grown simultaneously and all samples processed at the same time. Each biological replicate had three technical replicates. Cultures with and without 13C-lanosterol were processed at the same time. Although *DHCR7*-HET fibroblasts have different mutations the level of 7-DHC was similar in all of them and the response to pharmaceutical treatment was similar.

Sterol extraction and LC-MS/MS measurements. To each well in the 96-well plate was added the internal standards (10 μ L of stock solution in MeOH: 0.87 nmol d_7 -Chol, 0.033 nmol d_7 -7-DHC, 0.069 nmol d_7 -8-DHC) and MeOH (100 μ L). The plate was gently shaken on an Orbital shaker for 30 min at room temperature to lyse the cells and extract the sterols. The supernatant was transferred to a PTAD- predeposited 96-well plate (0.2 mg per well). The plates were sealed with Easy Pierce Heat Sealing Foil (ThermoScientific AB-1720) and allowed to react for 30 min at room temperature. The sealed plates were kept in -80 °C until LC-MS analysis. The sealed plates were analyzed on an Acquity UPLC system equipped with ANSI-compliant well plate holder. The sterols (10 μ L injection) were analyzed on an UPLC C18 column (1.7 μ m, 2.1 mm \times 50 mm) with 100% MeOH (0.1% v/v acetic acid) mobile phase at a flow rate of 550 μ L/min and runtime of 1.0 min. A TSQ Quantum Ultra tandem mass spectrometer (ThermoFisher) was used for MS detections, and data were acquired with a Finnigan Xcalibur software package. MS/MS analysis of the PTAD derivatives was acquired in the positive ion mode using atmospheric pressure chemical ionization (APCI) and selected reaction monitoring (SRM). MS parameters were optimized for the 7-DHC-PTAD adduct and were as follows: auxiliary nitrogen gas pressure at 55 psi and sheath gas pressure at 60 psi; discharge current at 22 μ A and vaporizer temperature at 265°C. Collision induced dissociation (CID) was optimized at 12 eV under 1.0 mTorr of argon.

Sterols were analyzed by selective reaction monitoring (SRM) using the following transitions: Chol 369 \rightarrow 369, d_7 -Chol 376 \rightarrow 376, 7-DHC 560 \rightarrow 365, d_7 -7-DHC 567 \rightarrow 372, 8-DHC 558 \rightarrow 363, d_7 -8-DHC 565 \rightarrow 370, Des 592 \rightarrow 560, Lan 634 \rightarrow 602, $^{13}\text{C}_3$ -Chol 372 \rightarrow 372, $^{13}\text{C}_3$ -7-DHC 563 \rightarrow 368, $^{13}\text{C}_3$ -Des 595 \rightarrow 563, and $^{13}\text{C}_3$ -Lan 637 \rightarrow 605. $^{13}\text{C}_3$ -8-DHC could not be analyzed due to interference from the 7-DHC isotope (m/z 561). The values for Lan and Des were calculated

relative to the *d7-7-DHC* standard using response factors of 0.93 and 1.17, respectively. (Kim *et al*, 2016) Final sterol numbers are reported as nmol/million cells.

Total RNA isolation and quantitative RT-PCR. To obtain sufficient amount of material for total RNA isolation, human fibroblasts were grown in 6-well plates under identical conditions as for lipid extraction (six days in delipidated medium with or without aripiprazole). Total RNA was isolated from cultured human fibroblasts using Trizol (Life Technologies, Rockville, MD). Total RNA (500 ng) from each sample was reverse transcribed to cDNA using a High Capacity cDNA Archive kit (Applied Biosystems, Foster City, CA). Real-time PCR was performed with a StepOnePlus™ (ThermoFisher Scientific) (25 µl reaction volume, 2X SYBR green master mix, and gene specific primers). All samples were run in quadruplicate. qPCR dissociation curve of the amplicons was performed after each qPCR run. Primers used were *Dhcr7* (Qiagen QT00074606), *EBP* (Qiagen QT00087570), *Actb* (Qiagen QT00095431), *RPLP0* (Qiagen QT00075012). Data from the PCRs were analyzed using the comparative cycle number determined as threshold (Ct) method (Kurrasch *et al.*, 2004). Differential expression was calculated as $\Delta\Delta Ct$ relative to expression of either *Actb* or *RPLP0* as normalizers. *Actb* and *RPLP0* expression showed no change regardless of the sample type or treatment. The expression of *Dhcr7* and *EBP* mRNAs did not change in response to aripiprazole treatment. The same response was obtained for either control or heterozygous fibroblasts. $\Delta\Delta Ct$ mean \pm SE for *Dhcr7* in *Dhcr*^{+/-} fibroblasts treated with aripiprazole and compared to untreated cells (*Actb* normalizer) = 0.130 \pm 0.049; (*RPLP0* normalizer) = 0.102 \pm 0.046; $\Delta\Delta Ct$ mean \pm SE for *EBP* in *Dhcr*^{+/-} fibroblasts treated with aripiprazole and compared to untreated cells (*Actb* normalizer) = -0.010 \pm 0.142; (*RPLP0* normalizer) = -0.038 \pm 0.147. $\Delta\Delta Ct$ mean \pm SE for *Dhcr7* in control fibroblasts treated with aripiprazole and compared to untreated cells (*Actb* normalizer) = 0.172 \pm 0.051; (*RPLP0*

normalizer) = 0.105 ± 0.043 ; $\Delta\Delta\text{Ct}$ mean \pm SE for EBP in control fibroblasts treated with aripiprazole and compared to untreated cells (Actb normalizer) = 0.091 ± 0.038 ; (RPLP0 normalizer) = 0.024 ± 0.010 .

Kurrasch, D. M., et al., 2004. Quantitative real-time polymerase chain reaction measurement of regulators of G-protein signaling mRNA levels in mouse tissues. *Methods Enzymol.* 389, 3-15.

Statistical Analyses. Final sterol numbers are reported as nmol/million cells. Levels of ^{13}C -labeled sterols were calculated using response factors relative to d7-Chol. All calculations of variability, standard deviation (SD), standard error (SE), and t-test were performed in Microsoft Excel or GraphPad Prism. Results were considered statistically significant if they had $p < 0.01$ using two-sample assuming equal variances and two tail distribution.