

A targeted analysis reveals relevant shifts in the methylation and transcription of genes responsible for bile acid homeostasis and drug metabolism in non-alcoholic fatty liver disease

Supplement

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Additional file 2: Table S2. NAFLD associated methylation changes in genes involved in drug metabolism – significant findings in gene cluster 2 (genes involved in drug transport and metabolism)

Table S2 NAFLD associated methylation changes in genes involved in drug metabolism – significant findings in gene cluster 2

Gene	CpG-sites			Illumina ID	Discovery Group (n=74)**			Validation Cohort (n=54)***			
	Total	Sign.	Sign. (%)*		Healthy vs NAFLD&NASH			Fibrosis stage		Steatosis stage	
					Coef.	p	p (FDR)	Coef.	p	Coef.	p
<i>CYP2C9</i>	2	2	100%	cg24140586	5.67E-02	4.17E-03	1.09E-02	7.95E-02	3.56E-04	-2.66E-02	4.27E-02
				cg09550024	5.46E-02	1.05E-03	4.16E-03	4.70E-02	4.38E-03	-	ns
<i>HNF1A</i>	8	8	100%	cg01341572	4.22E-02	5.69E-04	2.82E-03	5.44E-02	1.69E-03	-	ns
				cg05934698	3.67E-02	1.33E-03	5.00E-03	5.36E-02	1.93E-03	-	ns
				cg25477769	3.19E-02	3.37E-04	2.11E-03	3.60E-02	1.87E-03	-	ns
				cg23661013	5.16E-02	2.67E-04	1.98E-03	4.41E-02	3.53E-03	-	ns
				cg02153339	4.83E-02	6.60E-04	2.94E-03	4.70E-02	4.50E-03	-	ns
				cg01394199	2.28E-02	1.19E-02	2.58E-02	4.39E-02	4.29E-04	-	ns
				cg14996810	5.13E-02	3.39E-04	2.11E-03	4.59E-02	1.95E-02	-	ns
<i>SLCO1B1</i>	1	1	100%	cg00995065	5.47E-02	2.31E-03	6.99E-03	9.38E-02	2.03E-06	-	ns
<i>SLC22A1</i>	3	3	100%	cg13434757	6.82E-02	2.67E-03	7.66E-03	8.57E-02	9.39E-04	-	ns
				cg24864413	4.36E-02	5.92E-04	2.82E-03	4.40E-02	4.78E-03	-	ns
				cg13466809	3.37E-02	1.66E-03	5.64E-03	3.11E-02	1.06E-02	-	ns
<i>SLC22A7</i>	2	2	100%	cg16465769	4.23E-02	1.51E-04	1.68E-03	3.48E-02	1.66E-02	-	ns
				cg03990905	3.60E-02	1.40E-03	5.12E-03	2.86E-02	2.95E-02	-	ns
<i>UGT1A1</i>	2	2	100%	cg19146119	4.66E-02	8.71E-03	1.97E-02	8.02E-02	4.69E-04	-	ns
				cg07823755	-1.34E-02	1.18E-02	2.57E-02	-1.26E-02	1.41E-02	-	ns
<i>NR2A1</i>	18	15	83%	cg27420224	5.55E-02	8.33E-04	3.50E-03	6.45E-02	2.09E-04	-	ns
				cg23792485	5.47E-02	5.16E-04	2.73E-03	6.02E-02	8.44E-04	-	ns
				cg06640637	5.00E-02	6.27E-04	2.84E-03	5.82E-02	1.07E-03	-	ns
				cg20848979	4.53E-02	3.75E-04	2.15E-03	4.82E-02	9.45E-04	-	ns
				cg08314996	4.99E-02	8.35E-04	3.50E-03	4.94E-02	2.97E-03	-	ns
				cg21081369	2.95E-02	4.01E-03	1.05E-02	3.83E-02	3.38E-03	-	ns
				cg19717150	3.37E-02	6.20E-03	1.49E-02	4.21E-02	4.00E-04	-	ns
				cg07006673	4.31E-02	5.52E-03	1.37E-02	5.12E-02	3.50E-03	-	ns
				cg23834593	3.91E-02	2.19E-03	6.76E-03	3.47E-02	7.91E-03	-	ns
				cg03862380	4.20E-02	3.68E-04	2.15E-03	4.07E-02	6.72E-03	-	ns
				cg16221969	3.28E-02	1.63E-03	5.64E-03	3.19E-02	2.42E-02	-	ns
				cg21559386	4.57E-02	5.99E-04	2.82E-03	2.97E-02	3.58E-02	-	ns
				cg06126829	4.47E-02	3.68E-04	2.15E-03	3.47E-02	2.66E-02	-	ns
<i>CYP2E1</i>	7	6	86%	cg21024264	5.72E-02	6.13E-04	2.82E-03	6.43E-02	1.75E-03	-	ns
				cg09208540	5.91E-02	1.94E-03	6.32E-03	7.34E-02	1.37E-03	-	ns
				cg07381788	6.21E-02	3.20E-04	2.09E-03	5.91E-02	2.92E-03	-	ns
				cg01465364	5.18E-02	2.54E-04	1.98E-03	4.89E-02	4.52E-03	-	ns
				cg00436603	3.80E-02	7.16E-03	1.66E-02	4.35E-02	2.67E-03	-	ns
				cg14250048	4.39E-02	2.66E-03	7.66E-03	4.65E-02	1.05E-02	-	ns

UGT1A4	5	4	80%	cg04437648	8.11E-02	5.65E-05	1.63E-03	8.83E-02	2.69E-05	-	ns
				cg05313279	5.12E-02	5.58E-03	1.37E-02	8.79E-02	1.07E-04	-	ns
				cg02234120	-3.48E-02	2.15E-04	1.93E-03	-3.02E-02	1.69E-03	-	ns
				cg05141602	-3.23E-02	3.00E-04	2.09E-03	-2.01E-02	4.28E-02	-	ns
NR1I3	4	3	75%	cg06277277	5.23E-02	1.55E-04	1.68E-03	4.51E-02	2.91E-03	-	ns
				cg25214346	4.26E-02	1.28E-04	1.64E-03	3.49E-02	1.38E-02	-	ns
				cg17028814	4.53E-02	8.58E-04	3.55E-03	3.84E-02	1.19E-02	-	ns
CYP1A2	3	2	67%	cg11473616	6.52E-02	6.09E-04	2.82E-03	7.37E-02	3.87E-04	-	ns
				cg04968473	5.22E-02	1.54E-02	3.22E-02	8.93E-02	8.76E-04	-	ns
CYP2D6	3	2	67%	cg09322432	6.43E-02	8.92E-05	1.63E-03	7.30E-02	1.07E-03	-	ns
				cg04692870	3.63E-02	4.47E-03	1.14E-02	6.37E-02	4.87E-04	-	ns
CYP3A4	3	2	67%	cg23326197	-3.69E-02	1.80E-05	1.63E-03	-3.23E-02	2.36E-04	-	ns
				cg22821554	-1.98E-02	1.68E-03	5.64E-03	-2.50E-02	9.33E-04	-	ns
SLCO2B1	9	6	67%	cg12537437	7.04E-02	9.27E-05	1.63E-03	8.53E-02	3.17E-05	-	ns
				cg25367084	6.36E-02	3.09E-04	2.09E-03	7.40E-02	4.99E-05	-	ns
				cg23577865	3.92E-02	7.32E-04	3.21E-03	4.27E-02	6.23E-04	-	ns
				cg20358275	3.49E-02	6.06E-03	1.47E-02	4.65E-02	5.81E-04	-	ns
				cg15751948	6.04E-02	1.06E-04	1.64E-03	4.73E-02	7.48E-03	-	ns
ABCC2	5	3	60%	cg18589858	-1.81E-02	6.54E-03	1.53E-02	-2.77E-02	3.31E-03	-	ns
				cg17044311	7.22E-02	1.01E-04	1.64E-03	7.84E-02	3.55E-04	-	ns
				cg14947634	7.21E-02	2.19E-04	1.93E-03	7.08E-02	9.22E-04	-	ns
NR1I2	5	3	60%	cg09448875	6.81E-02	1.87E-04	1.88E-03	6.60E-02	1.74E-03	-	ns
				cg22276685	5.57E-02	7.82E-05	1.63E-03	5.25E-02	2.54E-03	-	ns
				cg00836482	-3.51E-02	9.22E-05	1.63E-03	-3.42E-02	1.56E-03	-	ns
CYP2C19	6	3	50%	cg25562664	-2.51E-02	2.43E-03	7.17E-03	-5.21E-02	7.57E-05	-	ns
				cg00051662	8.55E-02	6.29E-03	1.49E-02	1.59E-01	1.06E-05	-	ns
				cg16227251	6.22E-02	5.35E-04	2.73E-03	7.07E-02	6.18E-03	-	ns
NAT2	2	1	50%	cg04189838	7.22E-02	2.41E-02	4.95E-02	1.71E-01	1.02E-05	-	ns
				cg12639234	4.55E-02	2.29E-03	6.99E-03	7.33E-02	3.96E-04	-	ns
UGT2B7	2	1	50%	cg25583503	5.54E-02	3.16E-04	2.09E-03	6.47E-02	1.47E-03	-	ns
NR3A1	47	23	49%	cg07671949	-6.48E-02	2.41E-03	7.17E-03	-1.16E-01	2.72E-07	2.46E-02	4.48E-02
				cg20627916	-7.22E-02	1.24E-03	4.70E-03	-1.23E-01	6.61E-07	2.74E-02	4.47E-02
				cg19411146	-6.70E-02	2.72E-03	7.71E-03	-1.15E-01	4.93E-06	-	ns
				cg21608605	-7.37E-02	3.74E-05	1.63E-03	-9.50E-02	1.21E-08	1.81E-02	3.98E-02
				cg15626350	-2.60E-02	1.53E-02	3.22E-02	-2.22E-02	1.28E-02	1.71E-02	2.26E-03
				cg24900983	-4.91E-02	5.10E-04	2.73E-03	-6.74E-02	1.33E-04	-	ns
				cg23165623	-6.09E-02	3.39E-03	9.16E-03	-1.06E-01	5.78E-06	-	ns
				cg15980539	-3.70E-02	5.57E-05	1.63E-03	-4.47E-02	1.69E-05	-	ns
				cg05171584	-4.20E-02	1.98E-03	6.36E-03	-8.45E-02	4.46E-06	-	ns
				cg01777019	-6.24E-02	8.00E-04	3.46E-03	-1.18E-01	2.96E-07	-	ns
				cg00655307	-7.04E-02	2.37E-04	1.98E-03	-1.05E-01	3.87E-06	-	ns
				cg21950534	-4.79E-02	9.11E-03	2.02E-02	-1.08E-01	2.39E-06	-	ns
				cg00920970	-4.70E-02	2.60E-04	1.98E-03	-4.69E-02	1.03E-03	-	ns
				cg19449067	6.28E-02	1.22E-04	1.64E-03	1.11E-01	8.57E-06	-	ns
				cg07746998	4.93E-02	5.90E-04	2.82E-03	6.93E-02	1.62E-05	-	ns
cg08884395	6.53E-02	7.20E-05	1.63E-03	5.57E-02	3.61E-03	-	ns				

				cg04211581	-6.37E-02	1.47E-04	1.68E-03	-7.35E-02	5.53E-06	-	ns
				cg20253551	-5.08E-02	1.36E-04	1.66E-03	-6.59E-02	1.10E-04	-	ns
				cg18007957	-5.87E-02	1.99E-04	1.93E-03	-6.81E-02	1.00E-05	-	ns
				cg08907436	-1.57E-02	1.91E-03	6.32E-03	-1.60E-02	4.58E-04	-	ns
				cg22157087	-4.72E-02	2.19E-03	6.76E-03	-6.30E-02	4.57E-06	-	ns
				cg02720618	-4.61E-02	2.68E-04	1.98E-03	-3.82E-02	2.36E-03	-	ns
				cg08161546	-3.85E-02	5.60E-03	1.37E-02	-3.53E-02	2.03E-03	-	ns
SULT1A1	7	3	43%	cg01378222	6.76E-02	2.55E-04	1.98E-03	1.13E-01	1.55E-04	-	ns
				cg09685060	4.34E-02	3.10E-03	8.53E-03	5.18E-02	1.14E-04	-	ns
				cg08008286	5.22E-02	2.82E-04	2.03E-03	4.89E-02	2.73E-02	-	ns
SLC47A1	15	6	40%	cg08895056	3.73E-02	3.82E-03	1.01E-02	7.57E-02	2.48E-05	-	ns
				cg10718608	2.85E-02	7.89E-03	1.80E-02	5.52E-02	4.48E-04	-	ns
				cg01530032	5.36E-02	9.66E-04	3.93E-03	1.08E-01	2.37E-06	-	ns
				cg12133118	3.28E-02	1.99E-03	6.36E-03	4.65E-02	4.65E-04	-	ns
				cg24151087	1.52E-02	1.86E-02	3.84E-02	2.03E-02	5.65E-03	-	ns
				cg15014549	6.87E-03	2.15E-03	6.76E-03	1.78E-02	2.40E-02	-	ns
CYP2B6	8	3	38%	cg19756068	5.45E-02	1.20E-04	1.64E-03	4.51E-02	3.04E-03	-	ns
				cg10322876	4.75E-02	1.38E-03	5.10E-03	4.99E-02	1.79E-03	-	ns
				cg08852641	-5.57E-02	2.83E-05	1.63E-03	-5.09E-02	2.58E-04	-	ns
CYP1A1	17	6	35%	cg12101586	6.63E-02	1.92E-05	1.63E-03	1.16E-01	1.62E-06	-	ns
				cg13570656	7.61E-02	3.93E-05	1.63E-03	1.45E-01	9.83E-06	-	ns
				cg00213123	5.41E-02	8.07E-05	1.63E-03	1.01E-01	7.50E-06	-	ns
				cg26516004	7.00E-02	8.42E-05	1.63E-03	1.41E-01	1.19E-06	-	ns
				cg17852385	6.24E-02	9.05E-05	1.63E-03	1.47E-01	9.82E-06	-	ns
				cg11924019	4.63E-02	4.57E-04	2.53E-03	9.71E-02	4.93E-05	-	ns
SLC22A2	10	3	30%	cg04294894	-2.27E-02	1.21E-04	1.64E-03	-3.45E-02	8.33E-05	-	ns
				cg07026448	-3.71E-02	1.08E-03	4.21E-03	-4.78E-02	4.83E-05	-	ns
				cg19627213	-3.83E-02	1.69E-03	5.64E-03	-4.88E-02	1.14E-03	-	ns
SLC01A2	4	1	25%	cg16923485	-4.64E-02	4.59E-04	2.53E-03	-4.34E-02	7.11E-03	-	ns
SLC22A6	4	1	25%	cg04458776	-3.33E-02	1.43E-03	5.15E-03	-3.78E-02	1.04E-02	-	ns
NR3C1	15	2	13%	cg07733851	2.95E-02	2.13E-04	1.93E-03	2.89E-02	3.30E-03	-	ns
				cg08845721	5.29E-02	1.09E-03	4.21E-03	5.19E-02	4.08E-03	-	ns
SLC22A8	8	1	13%	cg15572436	-7.52E-02	3.59E-06	1.01E-03	-1.04E-01	2.72E-06	-	ns
NR2B1	9	1	11%	cg14651936	-2.38E-02	2.95E-03	8.23E-03	-3.25E-02	5.67E-05	-	ns
GSTP1	10	1	10%	cg06928838	-5.34E-02	2.96E-03	8.23E-03	-8.12E-02	3.67E-04	-	ns

Shown are all targets that displayed significantly differentially methylated CpG sites. Listed are the CpG sites that are NAFLD dependently significantly differentially methylated and validated. Targets are ordered according to the percentage of affected CpG sites within the TSS1500 interval.

* Percentage of differentially methylated CpG sites in NAFLD within the TSS1500 interval as confirmed in two cohorts.

** The discovery cohort is composed of liver healthy and NAFLD patients. Performance of multiple linear regression analyses investigating the association between methylation state of gene associated individual CpG sites and hepatic disease state. Listed are raw p-values and false discovery (FDR) corrected p-values.

*** The validation cohort is composed of NAFLD patients with different stages of steatosis and fibrosis. Performance of multiple linear regression analyses investigating the association between methylation state of

gene associated individuals CpG sites and severity of fibrosis and steatosis, respectively. Listed are raw p-values and FDR corrected p-values.

-, no coefficient given for non significant results; n, number; ns, not significant; coef, coefficient; FDR, false discovery rate; sign., significant; total, investigated in total