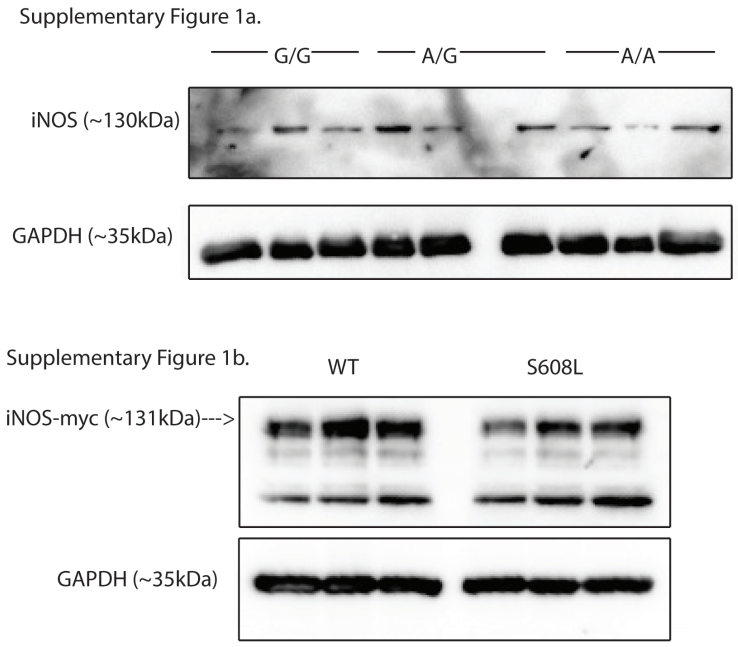
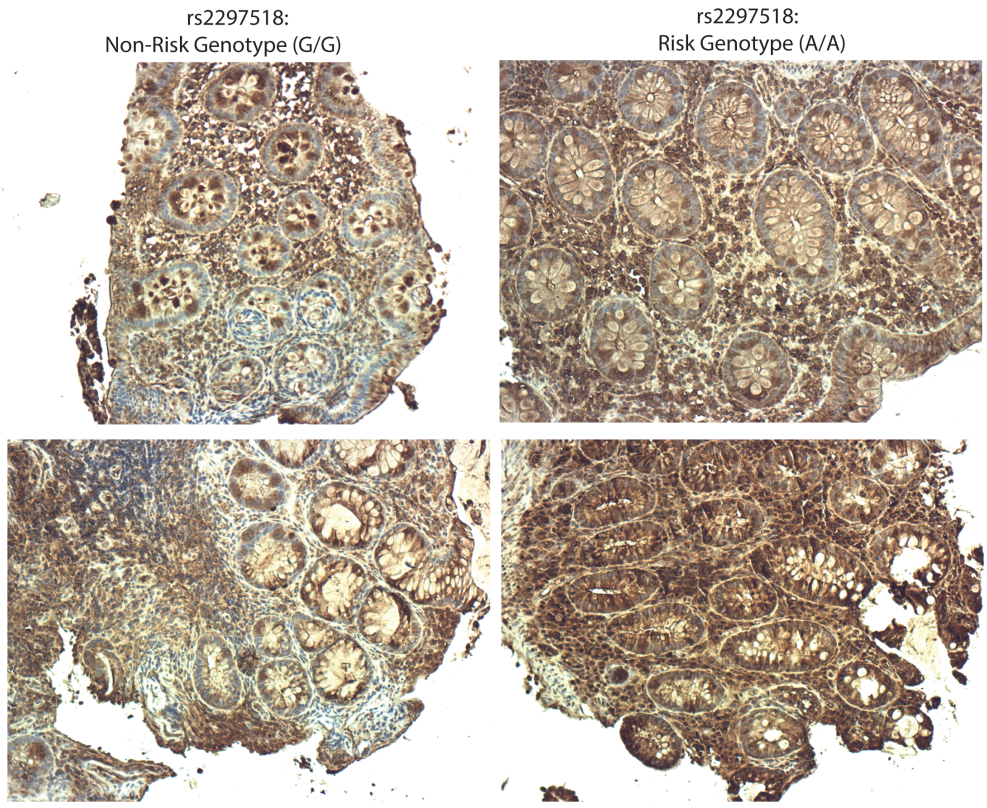
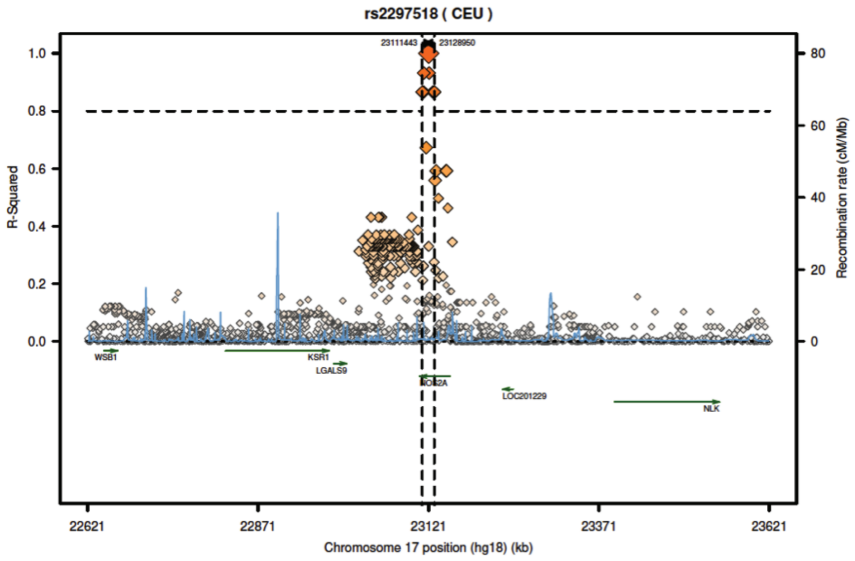
Supplemental Materials



Supplementary Figure 1: iNOS expression in B-lymphoblastoid and transfected Henle-407 cells. 1a. iNOS expression in B-lymphoblastoid cell lines genotyped for the rs2297518 variant were measured at the time of Griess assay. (G/G) is the non-risk genotype, (A/G) is the heterozygous genotype, and (A/A) is the risk genotype. 1b. iNOS-myc expression was measured in three replicates of both variants in transfected Henle-407 cells. (WT) is the wildtype form of iNOS and (S608L) is the risk variant.



Supplementary Figure 2: Immunohistochemistry staining for nitrotyrosine. Immunohistochemistry staining for nitrotyrosine (see Methods) of paraffin-embedded slides of colonic biopsies of VEO-IBD patients from the Hospital for Sick Children genotyped for the rs2297518 SNP. Shown are the non-risk (G/G) and risk genotypes (A/A). Images shown are taken at 10x magnification.



Supplementary Figure 3: Regional LD Plot generated from SNAP. SNP Association and Proxy Search (http://www.broadinstitute.org/mpg/snap/). "SNAP finds proxy SNPs based on linkage disequilibrium, physical distance and/or membership in selected commercial genotyping arrays. Pair-wise linkage disequilibrium is pre-calculated based on phased genotype data from the International HapMap Project. Information about the genotyping arrays is based on data published by the vendors." Figure was generated based on 1000 Genomes Project Database.

Supplementary Table 1: Initial cohort additive and dominant association analyses of 17 NOS2 SNPs with VEO-IBD.

						Additive				Dominant			
Chr.	SNP	Position	MAF	FU	FA	P-Value	OR	P-Value	OR	P-Value	OR	P-Value	OR
17	rs2297518	23120724	0.1822	0.1796	0.2381	$2.96^{10}x10^{-3}$	1.529	$2.9610x10^{-3}$	1.529	$2.9610x10^{-3}$	1.529	$2.9610x10^{-3}$	1.529
17	rs1137933	23130059	0.2176	0.2151	0.2738	$5.5000x10^{-3}$	1.45	$5.5000x10^{-3}$	1.45	$5.5000x10^{-3}$	1.45	$5.5000x10^{-3}$	1.45
17	rs9906835	23113501	0.4295	0.4317	0.381	$6.2200x10^{-2}$	0.7919	$6.2200x10^{-2}$	0.7919	$6.2200x10^{-2}$	0.7919	$6.2200x10^{-2}$	0.7919
17	rs944725	23133698	0.4108	0.4067	0.5	$8.4040x10^{-2}$	1.235	$8.4040x10^{-2}$	1.235	$8.4040x10^{-2}$	1.235	$8.4040x10^{-2}$	1.235
17	rs3730013	23150045	0.3445	0.3466	0.2976	$9.4010x10^{-2}$	0.8	$9.4010x10^{-2}$	0.8	$9.4010x10^{-2}$	0.8	$9.4010x10^{-2}$	0.8
17	rs4795067	23130802	0.3382	0.3375	0.3537	$1.2970x10^{-1}$	1.203	$1.2970x10^{-1}$	1.203	$1.2970x10^{-1}$	1.203	$1.2970x10^{-1}$	1.203
17	rs2297516	23119857	0.423	0.4246	0.3875	$1.6020x10^{-1}$	0.8402	$1.6020x10^{-1}$	0.8402	$1.6020x10^{-1}$	0.8402	$1.6020x10^{-1}$	0.8402
17	rs3794764	23135555	0.2362	0.2372	0.2143	$1.8250x10^{-1}$	0.8194	$1.8250x10^{-1}$	0.8194	$1.8250x10^{-1}$	0.8194	$1.8250x10^{-1}$	0.8194
17	rs8072199	23140975	0.4457	0.4427	0.5119	$1.9670x10^{-1}$	1.173	$1.9670x10^{-1}$	1.173	$1.9670x10^{-1}$	1.173	$1.9670x10^{-1}$	1.173
17	rs10459953	23151645	0.3568	0.3579	0.3333	$2.0050x10^{-1}$	0.8468	$2.0050x10^{-1}$	0.8468	$2.0050x10^{-1}$	0.8468	$2.0050x10^{-1}$	0.8468
17	rs2314809	23119505	0.4017	0.4032	0.369	$2.9420x10^{-1}$	0.8797	$2.9420x10^{-1}$	0.8797	$2.9420x10^{-1}$	0.8797	$2.9420x10^{-1}$	0.8797
17	rs11080344	23128638	0.4613	0.4601	0.4881	$3.1250x10^{-1}$	1.131	$3.1250x10^{-1}$	1.131	$3.1250x10^{-1}$	1.131	$3.1250x10^{-1}$	1.131
17	rs3794756	23110756	0.00835	0.007642	0.02381	$3.7540x10^{-1}$	1.663	$3.7540x10^{-1}$	1.663	$3.7540x10^{-1}$	1.663	$3.7540x10^{-1}$	1.663
17	rs3729508	23133157	0.4013	0.4022	0.381	$4.1340x10^{-1}$	0.9045	$4.1340x10^{-1}$	0.9045	$4.1340x10^{-1}$	0.9045	$4.1340x10^{-1}$	0.9045
17	rs11653716	23108659	0.03239	0.03115	0.05952	$5.1890x10^{-1}$	1.237	$5.1890x10^{-1}$	1.237	$5.1890x10^{-1}$	1.237	$5.1890x10^{-1}$	1.237
17	rs2314810	23128237	0.0466	0.0465	0.04878	$5.8000x10^{-1}$	1.16	$5.8000x10^{-1}$	1.16	$5.8000x10^{-1}$	1.16	$5.8000x10^{-1}$	1.16
17	rs3730017	23133229	0.02086	0.02072	0.02381	$8.8050x10^{-1}$	1.065	$8.8050x10^{-1}$	1.065	$8.8050x10^{-1}$	1.065	$8.8050x10^{-1}$	1.065

The initial cohort consisted of 1075 subjects (159 VEO-IBD, 91 VEO-CD, 68 VEO-UC subjects, 913 healthy controls). P values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism; UC, ulcerative colitis.

Supplementary Table 2: Initial cohort association analyses of 17 NOS2 SNPs with VEO-CD.

						Additive				Dominant				Recessive			
CHR	SNP	position	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	L95	U95	P-Value	OR	L95	U95
17	rs11653716	23,108,659	0.03204	0.03115	0.03333	0.402	1.457	0.6043	3.511	0.402	1.457	0.6043	3.511	NA	NA	NA	NA
17	rs3794756	23,110,756	0.008638	0.007642	0.005495	0.09314	2.974	0.8333	10.61	0.09314	2.974	0.8333	10.61	NA	NA	NA	NA
17	rs9906835	23,113,501	0.4292	0.4317	0.358	0.4176	0.863	0.6043	1.232	0.5973	0.8697	0.518	1.46	0.409	0.7471	0.374	1.492
17	rs2314809	23,119,505	0.3992	0.4032	0.3901	0.2003	0.7926	0.5554	1.131	0.02995	0.5786	0.353	0.9482	0.7011	1.131	0.6034	2.12
17	rs2297516	23,119,857	0.4236	0.4246	0.3596	0.7505	0.9441	0.6624	1.346	0.6772	0.8958	0.5337	1.504	0.9444	0.9772	0.5119	1.866
17	rs2297518	23,120,724	0.1845	0.1796	0.2527	0.04118	1.536	1.017	2.319	0.2821	1.319	0.7963	2.186	0.001285	4.251	1.761	10.26
17	rs2314810	23,128,237	0.04786	0.0465	0.04444	0.3066	1.443	0.7142	2.917	0.2455	1.548	0.7406	3.235	NA	NA	NA	NA
17	rs11080344	23,128,638	0.4639	0.4601	0.4725	0.2166	1.248	0.8784	1.772	0.8606	0.9527	0.5546	1.637	0.02223	1.862	1.093	3.172
17	rs1137933	23,130,059	0.219	0.2151	0.3	0.1301	1.347	0.9159	1.981	0.6149	1.137	0.6891	1.877	0.005399	2.953	1.377	6.33
17	rs4795067	23,130,802	0.3396	0.3375	0.3944	0.4882	1.132	0.7974	1.607	0.8692	1.043	0.6348	1.712	0.2397	1.48	0.77	2.843
17	rs3729508	23,133,157	0.4013	0.4022	0.3681	0.7789	0.9511	0.6702	1.35	0.3034	0.7695	0.4671	1.267	0.4281	1.281	0.6942	2.364
17	rs3730017	23,133,229	0.02132	0.02072	0.01648	0.4959	1.446	0.5003	4.177	0.4959	1.446	0.5003	4.177	NA	NA	NA	NA
17	rs944725	23,133,698	0.4075	0.4067	0.4889	0.7762	1.052	0.7401	1.496	0.5953	0.8715	0.5246	1.448	0.2284	1.445	0.7937	2.632
17	rs3794764	23,135,555	0.234	0.2372	0.2111	0.226	0.7625	0.4917	1.183	0.208	0.7164	0.4262	1.204	0.6367	0.7507	0.2283	2.468
17	rs8072199	23,140,975	0.4426	0.4427	0.511	0.9722	0.9937	0.6951	1.42	0.49	1.217	0.6972	2.123	0.3831	0.7352	0.3684	1.467
17	rs3730013	23,150,045	0.343	0.3466	0.3022	0.2095	0.7813	0.5314	1.149	0.4501	0.8267	0.5045	1.355	0.1538	0.4725	0.1687	1.324
17	rs10459953	23,151,645	0.3576	0.3579	0.2967	0.9065	0.9783	0.6786	1.41	0.436	0.8214	0.5006	1.348	0.3609	1.37	0.6975	2.69

The initial cohort consisted of 1075 subjects (159 VEO-IBD, 91 VEO-CD, 68 VEO-UC subjects, 913 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 3: Initial cohort association analyses of 17 NOS2 SNPs with VEO-UC.

						Additive				Dominant				Recessive			
CHR	SNP	position	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	L95	U95	P-Value	OR	L95	U95
17	rs11653716	23,108,659	0.03204	0.03115	0.04412	0.402	1.457	0.6043	3.511	0.402	1.457	0.6043	3.511	NA	NA	NA	NA
17	rs3794756	23,110,756	0.008638	0.007642	0.02206	0.09314	2.974	0.8333	10.61	0.09314	2.974	0.8333	10.61	NA	NA	NA	NA
17	rs9906835	23,113,501	0.4292	0.4317	0.3955	0.4176	0.863	0.6043	1.232	0.5973	0.8697	0.518	1.46	0.409	0.7471	0.374	1.492
17	rs2314809	23,119,505	0.3992	0.4032	0.3456	0.2003	0.7926	0.5554	1.131	0.02995	0.5786	0.353	0.9482	0.7011	1.131	0.6034	2.12
17	rs2297516	23,119,857	0.4236	0.4246	0.4104	0.7505	0.9441	0.6624	1.346	0.6772	0.8958	0.5337	1.504	0.9444	0.9772	0.5119	1.866
17	rs2297518	23,120,724	0.1845	0.1796	0.25	0.04118	1.536	1.017	2.319	0.2821	1.319	0.7963	2.186	0.001285	4.251	1.761	10.26
17	rs2314810	23,128,237	0.04786	0.0465	0.06618	0.3066	1.443	0.7142	2.917	0.2455	1.548	0.7406	3.235	NA	NA	NA	NA
17	rs11080344	23,128,638	0.4639	0.4601	0.5147	0.2166	1.248	0.8784	1.772	0.8606	0.9527	0.5546	1.637	0.02223	1.862	1.093	3.172
17	rs1137933	23,130,059	0.219	0.2151	0.2721	0.1301	1.347	0.9159	1.981	0.6149	1.137	0.6891	1.877	0.005399	2.953	1.377	6.33
17	rs4795067	23,130,802	0.3396	0.3375	0.3676	0.4882	1.132	0.7974	1.607	0.8692	1.043	0.6348	1.712	0.2397	1.48	0.77	2.843
17	rs3729508	23,133,157	0.4013	0.4022	0.3897	0.7789	0.9511	0.6702	1.35	0.3034	0.7695	0.4671	1.267	0.4281	1.281	0.6942	2.364
17	rs3730017	23,133,229	0.02132	0.02072	0.02941	0.4959	1.446	0.5003	4.177	0.4959	1.446	0.5003	4.177	NA	NA	NA	NA
17	rs944725	23,133,698	0.4075	0.4067	0.4191	0.7762	1.052	0.7401	1.496	0.5953	0.8715	0.5246	1.448	0.2284	1.445	0.7937	2.632
17	rs3794764	23,135,555	0.234	0.2372	0.1912	0.226	0.7625	0.4917	1.183	0.208	0.7164	0.4262	1.204	0.6367	0.7507	0.2283	2.468
17	rs8072199	23,140,975	0.4426	0.4427	0.4412	0.9722	0.9937	0.6951	1.42	0.49	1.217	0.6972	2.123	0.3831	0.7352	0.3684	1.467
17	rs3730013	23,150,045	0.343	0.3466	0.2941	0.2095	0.7813	0.5314	1.149	0.4501	0.8267	0.5045	1.355	0.1538	0.4725	0.1687	1.324
17	rs10459953	23,151,645	0.3576	0.3579	0.3529	0.9065	0.9783	0.6786	1.41	0.436	0.8214	0.5006	1.348	0.3609	1.37	0.6975	2.69

The initial cohort consisted of 1075 subjects (159 VEO-IBD, 91 VEO-CD, 68 VEO-UC subjects, 913 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 4: Initial cohort association analyses of 17 NOS2 SNPs with IBD diagnosed under the age of 6 years.

				Additive						Dominant				Recessive			
CHR	SNP	position	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	L95	U95	P-Value	OR	L95	U95
17	rs2297518	23120724	0.1822	0.1796	0.2516	1.7440E-01	1.435	0.8522	2.415	0.9961	1.002	0.5197	1.931	0.0001861	6.174	2.377	16.04
17	rs1137933	23130059	0.2176	0.2151	0.288	2.1030E-01	1.364	0.8394	2.215	0.5358	1.218	0.6519	2.278	0.05467	2.616	0.9809	6.974
17	rs9906835	23113501	0.4295	0.4317	0.3742	3.6470E-01	0.8139	0.5214	1.27	0.1735	0.6472	0.3459	1.211	0.996	1.002	0.4558	2.203
17	rs944725	23133698	0.4108	0.4067	0.4589	8.9850E-02	1.464	0.9425	2.274	0.1388	1.726	0.8379	3.557	0.2103	1.596	0.768	3.316
17	rs3730013	23150045	0.3445	0.3466	0.2987	3.5120E-01	0.7949	0.4905	1.288	0.7121	0.8896	0.4778	1.656	0.1838	0.378	0.09007	1.587
17	rs4795067	23130802	0.3382	0.3375	0.3829	7.6980E-01	1.069	0.6832	1.673	0.6478	0.8642	0.4621	1.616	0.2049	1.674	0.7548	3.713
17	rs2297516	23119857	0.423	0.4246	0.3814	5.1510E-01	0.8596	0.5451	1.356	0.2326	0.6765	0.3561	1.285	0.7797	1.12	0.5068	2.474
17	rs3794764	23135555	0.2362	0.2372	0.2025	6.3020E-01	0.8776	0.5159	1.493	0.8811	0.9531	0.5076	1.789	0.3656	0.3967	0.05352	2.94
17	rs8072199	23140975	0.4457	0.4427	0.4811	2.0630E-01	1.333	0.8537	2.08	0.1198	1.861	0.8508	4.073	0.6952	1.163	0.5465	2.475
17	rs10459953	23151645	0.3568	0.3579	0.3208	6.4430E-01	0.8961	0.5625	1.427	0.2368	0.6882	0.3706	1.278	0.411	1.419	0.6158	3.272
17	rs2314809	23119505	0.4017	0.4032	0.3711	5.4240E-01	0.8714	0.5595	1.357	0.4164	0.7714	0.4126	1.442	0.9172	0.957	0.4175	2.193
17	rs11080344	23128638	0.4613	0.4601	0.4906	6.1150E-01	1.121	0.7207	1.745	0.7219	0.8855	0.4532	1.73	0.2074	1.557	0.7823	3.1
17	rs3794756	23110756	0.008351	0.007642	0.01258	1.3020E-01	3.221	0.7081	14.66	0.1302	3.221	0.7081	14.66	NA	NA	NA	NA
17	rs3729508	23133157	0.4013	0.4022	0.3774	7.0280E-01	0.9174	0.5892	1.428	0.3966	0.7629	0.408	1.426	0.7082	1.163	0.528	2.56
17	rs11653716	23108659	0.032339	0.03115	0.03797	1.5200E-01	2.034	0.7699	5.374	0.152	2.034	0.7699	5.374	NA	NA	NA	NA
17	rs2314810	23128237	0.0466	0.0465	0.0538	9.2440E-01	1.05	0.3801	2.903	0.8637	1.097	0.3815	3.154	0.999	1.375E-08	0	inf
17	rs3730017	23133229	0.02086	0.02072	0.02201	8.4480E-01	1.157	0.2695	4.964	0.8448	1.157	0.2695	4.964	NA	NA	NA	NA

The cohort for IBD under the age of 6 years analysis consisted of 955 subjects (42 IBD subjects, 913 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 5: Initial cohort association analyses of 17 NOS2 SNPs with IBD diagnosed over the age of 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03275	0.03115	0.03055	0.5858	1.107	0.768	1.596	0.7138	1.073	0.999	NA
17	rs3794756	0.007418	0.007642	0.009165	0.8779	0.9441	0.4533	1.966	0.7182	0.8668	0.9993	NA
17	rs9906835	0.4195	0.4317	0.4173	0.141	0.9075	0.7975	1.033	0.05513	0.8275	0.7259	0.9586
17	rs2314809	0.4001	0.4032	0.39	0.7102	0.9756	0.8566	1.111	0.7362	0.9678	0.7896	0.9672
17	rs2297516	0.4155	0.4246	0.4236	0.2711	0.9296	0.8162	1.059	0.1311	0.8617	0.8759	0.9811
17	rs2297518	0.1905	0.1796	0.1908	0.09095	1.155	0.9772	1.366	0.2135	1.131	0.06308	1.637
17	rs2314810	0.05436	0.0465	0.07245	0.03867	1.353	1.016	1.802	0.04099	1.373	0.4683	1.7
17	rs11080344	0.4699	0.4601	0.4877	0.222	1.087	0.951	1.242	0.1839	1.151	0.5341	1.074
17	rs1137933	0.2182	0.2151	0.2184	0.6463	1.037	0.8875	1.212	0.7077	1.037	0.6884	1.089
17	rs4795067	0.3367	0.3375	0.3299	0.9215	0.9933	0.8685	1.136	0.9952	0.9994	0.8453	0.9727
17	rs3729508	0.4029	0.4022	0.3921	0.9345	1.005	0.8827	1.145	0.8934	0.987	0.7448	1.041
17	rs3730017	0.02309	0.02072	0.01738	0.3442	1.23	0.8007	1.891	0.451	1.186	0.999	NA
17	rs944725	0.4108	0.4067	0.4287	0.6081	1.035	0.9066	1.182	0.64	1.047	0.7212	1.046
17	rs3794764	0.2381	0.2372	0.2546	0.888	1.011	0.868	1.178	0.8229	1.022	0.9129	0.9782
17	rs8072199	0.4293	0.4427	0.4039	0.1025	0.8966	0.7866	1.022	0.03346	0.8083	0.7004	0.9547
17	rs3730013	0.3437	0.3466	0.3411	0.7082	0.9743	0.85	1.117	0.4725	0.9343	0.7486	1.047
17	rs10459953	0.3441	0.3579	0.3357	0.07876	0.885	0.7724	1.014	0.02556	0.8092	0.7994	0.9642

The cohort for IBD over the age of 17 years analysis consisted of 1842 subjects (918 IBD subjects, 419 CD, 499 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 6: Initial cohort association analyses of 17 NOS2 SNPs with CD diagnosed over the age of 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03412	0.03115	0.03468	0.24	1.281	0.8473	1.938	0.3558	1.224	0.999	NA
17	rs3794756	0.007452	0.007642	0.01156	0.8784	0.9341	0.3899	2.238	0.6382	0.7938	0.9993	NA
17	rs9906835	0.4313	0.4317	0.4246	0.957	0.9958	0.8545	1.16	0.359	0.8974	0.3223	1.147
17	rs2314809	0.3974	0.4032	0.396	0.4087	0.9368	0.8024	1.094	0.3132	0.8904	0.7934	0.9617
17	rs2297516	0.4249	0.4246	0.435	0.9692	1.003	0.8593	1.171	0.5891	0.9382	0.4691	1.108
17	rs2297518	0.1835	0.1796	0.1768	0.4599	1.079	0.8819	1.32	0.6523	1.055	0.2758	1.413
17	rs2314810	0.0495	0.0465	0.07514	0.3192	1.194	0.8423	1.693	0.2644	1.231	0.6803	0.621
17	rs11080344	0.4701	0.4601	0.4754	0.1432	1.124	0.961	1.316	0.3597	1.123	0.1359	1.221
17	rs1137933	0.2139	0.2151	0.2124	0.8419	0.981	0.8126	1.184	0.9358	0.9908	0.7169	0.9079
17	rs4795067	0.3323	0.3375	0.3179	0.4324	0.9377	0.7986	1.101	0.4303	0.9153	0.6589	0.9271
17	rs3729508	0.4027	0.4022	0.396	0.9409	1.006	0.8617	1.174	0.7873	0.9692	0.6287	1.074
17	rs3730017	0.02376	0.02072	0.0189	0.1583	1.414	0.8738	2.289	0.2566	1.34	0.999	NA
17	rs944725	0.407	0.4067	0.4292	0.9644	1.004	0.8562	1.176	0.7943	1.031	0.7999	0.9621
17	rs3794764	0.2397	0.2372	0.2616	0.6682	1.04	0.8681	1.247	0.5778	1.065	0.9451	0.9836
17	rs8072199	0.4279	0.4427	0.3899	0.03135	0.8414	0.719	0.9847	0.008319	0.7332	0.4847	0.9033
17	rs3730013	0.3439	0.3466	0.3497	0.6754	0.9658	0.8206	1.137	0.4127	0.9119	0.7023	1.068
17	rs10459953	0.3469	0.3579	0.3232	0.09755	0.8711	0.74	1.026	0.02774	0.7805	0.9221	0.9835

The cohort for IBD over the age of 17 years analysis consisted of 1842 subjects (918 IBD subjects, 419 CD, 499 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 7: Initial cohort association analyses of 17 NOS2 SNPs with UC diagnosed over the age of 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03019	0.03115	0.02069	0.6617	0.8946	0.5432	1.473	0.6617	0.8946	NA	NA
17	rs3794756	0.007536	0.007642	0.003448	0.9245	0.9545	0.3642	2.502	0.9245	0.9545	NA	NA
17	rs9906835	0.4153	0.4317	0.4	0.01159	0.8056	0.6811	0.9528	0.02121	0.7524	0.07463	0.7486
17	rs2314809	0.4051	0.4032	0.3759	0.7699	1.025	0.8688	1.209	0.5753	1.072	0.8674	0.9739
17	rs2297516	0.4119	0.4246	0.3966	0.04898	0.845	0.7146	0.9993	0.04401	0.7799	0.2645	0.8357
17	rs2297518	0.1904	0.1796	0.2241	0.03376	1.253	1.017	1.543	0.09813	1.227	0.03623	1.909
17	rs2314810	0.05408	0.0465	0.06597	0.01243	1.539	1.098	2.158	0.0191	1.548	0.1507	3.007
17	rs11080344	0.4629	0.4601	0.5176	0.6525	1.04	0.8768	1.233	0.2071	1.187	0.524	0.9084
17	rs1137933	0.2206	0.2151	0.2326	0.3122	1.105	0.9103	1.342	0.4591	1.094	0.2867	1.311
17	rs4795067	0.342	0.3375	0.3586	0.4754	1.064	0.898	1.26	0.378	1.112	0.8764	1.028
17	rs3729508	0.4026	0.4022	0.3828	0.9528	1.005	0.8514	1.186	0.9421	1.009	0.9857	1.003
17	rs3730017	0.02074	0.02072	0.01379	0.9916	1.003	0.5593	1.799	0.9916	1.003	NA	NA
17	rs944725	0.412	0.4067	0.4276	0.4023	1.074	0.9087	1.27	0.6048	1.067	0.3696	1.15
17	rs3794764	0.2358	0.2372	0.2379	0.8101	0.9765	0.8044	1.185	0.8092	0.9712	0.9109	0.9716
17	rs8072199	0.44	0.4427	0.4375	0.6805	0.9655	0.817	1.141	0.4715	0.9122	0.907	1.018
17	rs3730013	0.3455	0.3466	0.3207	0.8583	0.9843	0.8272	1.171	0.7461	0.9619	0.8997	1.023
17	rs10459953	0.3506	0.3579	0.3655	0.2345	0.8996	0.7556	1.071	0.1611	0.8453	0.7408	0.9411

The cohort for IBD over the age of 17 years analysis consisted of 1842 subjects (918 IBD subjects, 419 CD, 499 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 8: Initial cohort association analyses of 17 NOS2 SNPs with IBD diagnosed between the ages of 11 and 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03275	0.03115	0.03437	0.9302	0.98	0.6243	1.538	0.8095	0.9449	0.9993	NA
17	rs3794756	0.007418	0.007642	0.00719	0.668	1.203	0.5169	2.8	0.668	1.203	NA	NA
17	rs9906835	0.4195	0.4317	0.407	0.4696	0.9444	0.8087	1.103	0.359	0.8974	0.839	0.9713
17	rs2314809	0.4001	0.4032	0.397	0.504	0.9481	0.811	1.108	0.7607	0.9654	0.386	0.8763
17	rs2297516	0.4155	0.4246	0.4062	0.9609	0.9961	0.8524	1.164	0.8572	0.9789	0.8963	1.019
17	rs2297518	0.1905	0.1796	0.2016	0.4642	1.077	0.8823	1.316	0.8866	1.017	0.06507	1.741
17	rs2314810	0.05436	0.0465	0.06236	0.005388	1.577	1.144	2.174	0.006762	1.607	0.2317	2.499
17	rs11080344	0.4699	0.4601	0.4799	0.1583	1.12	0.9567	1.312	0.2725	1.15	0.2295	1.176
17	rs1137933	0.2182	0.2151	0.2214	0.8401	1.019	0.8454	1.229	0.7467	1.038	0.8554	0.9533
17	rs4795067	0.3367	0.3375	0.3359	0.6913	0.9679	0.824	1.137	0.9226	0.9892	0.4969	0.8889
17	rs3729508	0.4029	0.4022	0.4035	0.6087	0.9602	0.8221	1.122	0.3944	0.9064	0.8948	1.02
17	rs3730017	0.02309	0.02072	0.0255	0.5392	0.8331	0.4652	1.492	0.5392	0.8331	NA	NA
17	rs944725	0.4108	0.4067	0.415	0.2601	1.094	0.9356	1.279	0.5885	1.066	0.1615	1.225
17	rs3794764	0.2381	0.2372	0.2392	0.3074	1.097	0.918	1.312	0.3554	1.11	0.4889	1.172
17	rs8072199	0.4293	0.4427	0.4157	0.0471	0.8517	0.7268	0.9979	0.03493	0.7789	0.3033	0.8592
17	rs3730013	0.3437	0.3466	0.3407	0.7679	0.9754	0.8267	1.151	0.9987	0.9998	0.5381	0.8956
17	rs10459953	0.3441	0.3579	0.33	0.2373	0.9056	0.7683	1.067	0.2027		0.613	0.9158

The cohort for IBD between the ages of 11 and 17 years analysis consisted of 1422 subjects (498 IBD subjects, 351 CD, 147 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 9: Initial cohort association analyses of 17 NOS2 SNPs with CD diagnosed between the ages of 11 and 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03019	0.03115	0.02805	0.6522	1.119	0.6872	1.821	0.7859	1.072	0.9993	NA
17	rs3794756	0.007536	0.007642	0.007299	0.346	1.525	0.634	3.668	0.346	1.525	NA	NA
17	rs9906835	0.4153	0.4317	0.3787	0.7525	0.9722	0.8161	1.158	0.6079	0.9338	0.9633	1.007
17	rs2314809	0.4051	0.4032	0.4093	0.7459	0.9714	0.815	1.158	0.9105	0.9854	0.6421	0.924
17	rs2297516	0.4119	0.4246	0.3833	0.6402	1.043	0.8749	1.243	0.7456	1.045	0.6502	1.076
17	rs2297518	0.1904	0.1796	0.2145	0.8671	0.9803	0.7764	1.238	0.7793	0.963	0.7924	1.106
17	rs2314810	0.05408	0.0465	0.07108	0.005978	1.639	1.152	2.331	0.007536	1.674	0.233	2.656
17	rs11080344	0.4629	0.4601	0.4693	0.4862	1.065	0.8913	1.274	0.4718	1.108	0.6926	1.063
17	rs1137933	0.2206	0.2151	0.2329	0.8852	0.9844	0.7947	1.219	0.7651	1.039	0.2727	0.6954
17	rs4795067	0.342	0.3375	0.3521	0.3618	0.9184	0.7648	1.103	0.5944	0.9348	0.2748	0.8019
17	rs3729508	0.4026	0.4022	0.4034	0.7805	0.9754	0.819	1.162	0.4437	0.9052	0.6472	1.079
17	rs3730017	0.02074	0.02072	0.02078	0.7696	0.9085	0.4779	1.727	0.7696	0.9085	NA	NA
17	rs944725	0.412	0.4067	0.424	0.3052	1.097	0.919	1.31	0.4848	1.098	0.3099	1.181
17	rs3794764	0.2358	0.2372	0.2328	0.2052	1.138	0.9317	1.39	0.2315	1.164	0.4496	1.212
17	rs8072199	0.44	0.4427	0.4341	0.01683	0.8033	0.6713	0.9613	0.008557	0.7068	0.2577	0.8263
17	rs3730013	0.3455	0.3466	0.3431	0.8829	1.014	0.8423	1.221	0.7413	1.043	0.8392	0.9605
17	rs10459953	0.3506	0.3579	0.3341	0.1007	0.8546	0.7085	1.031	0.107	0.8145	0.3485	0.8269

The cohort for IBD between the ages of 11 and 17 years analysis consisted of 1422 subjects (498 IBD subjects, 351 CD, 147 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 10: Initial cohort association analyses of 17 NOS2 SNPs with UC diagnosed between the ages of 11 and 17 years.

					Additive				Dominant		Recessive	
CHR	SNP	MAF	FU	FA	P-Value	OR	L95	U95	P-Value	OR	P-Value	OR
17	rs11653716	0.03412	0.03115	0.03963	0.3258	0.6498	0.2749	1.536	0.3258	0.6498	NA	NA
17	rs3794756	0.007452	0.007642	0.007099	0.4389	0.4474	0.05839	3.428	0.4389	0.4474	NA	NA
17	rs9906835	0.4313	0.4317	0.4306	0.3161	0.8799	0.6852	1.13	0.2792	0.818	0.6112	0.8872
17	rs2314809	0.3974	0.4032	0.3867	0.3863	0.8949	0.6962	1.15	0.6482	0.9195	0.2971	0.7656
17	rs2297516	0.4249	0.4246	0.4254	0.3722	0.8918	0.6936	1.147	0.356	0.8426	0.6209	0.8884
17	rs2297518	0.1835	0.1796	0.1908	0.07071	1.321	0.9767	1.787	0.4415	1.154	0.0009649	3.342
17	rs2314810	0.0495	0.0465	0.0551	0.1639	1.432	0.8637	2.375	0.1807	1.449	0.5155	2.124
17	rs11080344	0.4701	0.4601	0.4888	0.06856	1.266	0.9822	1.631	0.2693	1.261	0.05852	1.474
17	rs1137933	0.2139	0.2151	0.2118	0.5086	1.103	0.8249	1.475	0.8564	1.034	0.1776	1.601
17	rs4795067	0.3323	0.3375	0.3224	0.4926	1.092	0.849	1.405	0.4887	1.133	0.702	1.105
17	rs3729508	0.4027	0.4022	0.4037	0.5358	0.9237	0.7184	1.188	0.6053	0.9093	0.6183	0.8839
17	rs3730017	0.02376	0.02072	0.02941	0.4297	0.6562	0.2307	1.867	0.4297	0.6562	NA	NA
17	rs944725	0.407	0.4067	0.4075	0.5026	1.089	0.8485	1.398	0.9759	0.9944	0.1996	1.332
17	rs3794764	0.2397	0.2372	0.2444	0.9772	1.004	0.752	1.341	0.9529	0.9893	0.8434	1.076
17	rs8072199	0.4279	0.4427	0.4004	0.8674	0.9786	0.7592	1.261	0.9812	0.9954	0.7887	0.9396
17	rs3730013	0.3439	0.3466	0.3387	0.3829	0.8877	0.6794	1.16	0.5765	0.9044	0.3389	0.7446
17	rs10459953	0.3469	0.3579	0.3266	0.8008	1.034	0.7978	1.34	0.9863	1.003	0.6261	1.136
17	rs991804	0.03412	0.03115	0.03963	0.5383	1.087	0.8335	1.417	0.1594	1.288	0.2973	0.697

The cohort for IBD between the ages of 11 and 17 years analysis consisted of 1422 subjects (498 IBD subjects, 351 CD, 147 UC, and 924 healthy controls). p Values are presented as uncorrected. CD, Crohn's disease; MAF, minor allelic frequency; FA, frequency affected; FU, frequency unaffected; IBD, inflammatory bowel disease; L95 and U95, lower and upper 95th confidence interval; SNP, single nucleotide polymorphism.; UC, ulcerative colitis.

Supplementary Table 11: Unpublished 2010 Crohn's Disease meta-analysis statistics for the NOS2 Gene (http://medicine.yale.edu/intmed/ibdgc/index.aspx).

SNP	Chromosome	Position	Allele	P-Value
rs9901734	17	23105156	C	0.8
rs8068149	17	23112982	G	0.33
rs9906835	17	23113501	G	0.74
rs2297515	17	23117460	C	0.64
rs2314809	17	23119505	T	0.21
rs2872753	17	23119689	A	0.22
rs2297516	17	23119857	C	0.32
rs2297518	17	23120724	G	0.74
rs9797244	17	23121258	T	0.77
rs2274894	17	23123298	G	0.35
rs4796052	17	23127161	C	0.88
rs11080344	17	23128638	T	0.34
rs12944039	17	23128891	G	0.68
rs4795067	17	23130802	G	0.38
rs3729508	17	23133157	C	0.89
rs944724	17	23133544	C	0.31
rs3794763	17	23135353	G	0.21
rs3794764	17	23135555	G	0.2
rs8072199	17	23140975	C	0.46
rs3794766	17	23146048	C	0.89

Supplementary Table 12: Unpublished 2011 ulcerative colitis meta-analysis statistics for the NOS2 Gene (http://medicine.yale.edu/intmed/ibdgc/index.aspx).

SNP	Chromosome	Position	Allele	P-Value; OR
rs9901734	17	23105156	C	0.177; 1.04(0.98-1.10)
rs8068149	17	23112982	G	0.889; 1.02(0.78-1.32)
rs9906835	17	23113501	G	0.917; 1.01(0.78-1.32)
rs2297515	17	23117460	C	0.219; 1.32(0.77-2.24)
rs2314809	17	23119505	T	0.025; 1.05(1.00-1.09)
rs2872753	17	23119689	A	0.014; 1.05(1.01-1.10)
rs2297516	17	23119857	C	0.038; 1.05(1.00-1.09)
rs2297518	17	23120724	G	0.271; 1.03(0.97-1.09)
rs9797244	17	23121258	T	0.00355; 1.06(1.02-1.11)
rs2274894	17	23123298	G	0.0032; 1.06(1.02-1.11)
rs4796052	17	23127161	C	0.0183; 1.05(1.01-1.09)
rs11080344	17	23128638	T	0.305; 1.03(0.98-1.08)
rs12944039	17	23128891	G	0.526; 1.02(0.97-1.07)
rs4795067	17	23130802	G	0.00107; 1.07(1.03-1.12)
rs3729508	17	23133157	C	0.923; 1.00(0.95-1.06)
rs944724	17	23133544	C	0.019; 1.05(1.01-1.09)
rs3794763	17	23135353	G	0.0126; 1.06(1.01-1.11)
rs3794764	17	23135555	G	0.559; 1.01(0.97-1.06)
rs8072199	17	23140975	C	0.257; 1.02(0.98-1.07)
rs3794766	17	23146048	C	0.573; 1.05(0.91-1.22)

Proxy	Distance	RSquared	DPrime	Coordinate_HG18	CD Meta-Analysis P-Value	UC Meta-Analysis P-Value; OR
rs9797244	534	0.932	1.000	23121258	0.77	0.526; 1.02(0.97-1.07)
rs28944192	7187	0.932	1.000	23113537	N/A	N/A
rs4796052	6437	0.866	0.931	23127161	0.88	0.923; 1.00(0.95-1.06)
rs4239250	6490	0.866	0.931	23127214	N/A	N/A
rs28944193	7283	0.866	1.000	23113441	N/A	N/A
rs17718148	7393	0.866	0.931	23128117	N/A	N/A
rs28999387	7689	0.866	0.931	23128413	N/A	N/A
rs16966545	8025	0.866	0.931	23128749	N/A	N/A
rs28999385	8135	0.866	0.931	23128859	N/A	N/A
rs28999384	8226	0.866	0.931	23128950	N/A	N/A
rs3729661	9152	0.866	1.000	23111572	N/A	N/A
rs3729727	9281	0.866	1.000	23111443	N/A	N/A

Supplementary Table 13: List of "proxy SNPs based on linkage disequilibrium, physical distance and/or membership in selected commercial genotyping arrays. Pair-wise linkage disequilibrium is pre-calculated based on phased genotype data from the International HapMap Project and the 1000 Genomes Project. Information about the genotyping arrays is based on data published by the vendors." (http://www.broadinstitute.org/mpg/snap/). N/A signifies that the variant was not included in the meta-analyses.

Supplementary Table 14: Gene expression from imputation analysis of rs2297518 (from http://www.sph.umich.edu/csg/liang/imputation/)

Gene	Probe	effect	SE	h2	LOD	Pvalue
ARG2	203945_at	-0.424	0.106	5.12	3.495	6.0e-05
BCAS3	220488_s_at	-0.363	0.106	3.76	2.559	0.00060
EGLN3	219232_s_at	-0.359	0.106	3.69	2.514	0.00067
GLS2	205531_s_at	0.402	0.106	4.64	3.159	1.4e-04
GRK4	241989_at	0.454	0.106	5.88	4.007	1.7e-05
RRAGD	221524_s_at	0.360	0.105	3.73	2.536	0.00063
RRAGD	221523_s_at	0.388	0.105	4.33	2.951	0.00023
TPP1	200743_s_at	0.356	0.106	3.61	2.456	0.00077

"Gene expression in lymphoblastoid cell lines was characterized in a sample of 405 siblings using Affymetrix HG U133 Plus 2.0 chips. Among these individuals, 378 were also genotyped at >300,000 SNPs using the Illumina HumanHap300 arrays, with additional genotypes for SNPs in the Phase II HapMap filled in using imputation. The results summarize the additive association between each SNP and transcripts with estimated heritability > 30% in the sample"