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(54) **METHODS OF DETERMINING RESPONSIVENESS TO ANTI-TNF ALPHA THERAPY IN INFLAMMATORY BOWEL DISEASE**

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(57) **ABSTRACT**

The present invention relates to methods of prognosing responsiveness to anti-TNFα therapy by determining the presence or absence of risk factors in the individual. In one embodiment, the risk factors are genetic markers, serological markers and/or clinical phenotypes associated with non-responsiveness to treatment with anti-TNFα therapy in an individual diagnosed with IBD.

Figure 1

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs4855535	3	69017124	G	0.5714	0.05556	T	6.987E-06	22.67	5.1557093	FAM19A4
rs17048128	3	69028502	A	0.5714	0.05556	G	6.987E-06	22.67	5.1557093	FAM19A4
rs17048129	3	69031452	A	0.5714	0.05556	G	6.987E-06	22.67	5.1557093	FAM19A4
rs17039556	4	161545059	A	0.7143	0.1296	G	8.744E-06	16.79	5.0582899	
rs2983478	14	94433843	C	1	0.4167	T	1.555E-05		4.8082696	
rs12640159	4	161586073	A	0.7857	0.1944	G	1.882E-05	15.19	4.7253804	
rs13079040	3	68988334	C	0.7143	0.1574	T	3.361E-05	13.38	4.4735315	FAM19A4
rs880330	7	67842575	T	0.7857	0.213	C	3.927E-05	13.55	4.4059391	
rs4776127	15	51373815	G	0.7857	0.213	A	3.927E-05	13.55	4.4059391	
rs2057917	7	67867804	C	0.8571	0.2778	T	4.331E-05	15.6	4.3634118	
rs4936810	11	122843102	G	0.8571	0.2778	T	4.331E-05	15.6	4.3634118	
rs13077937	3	88620181	G	0.6429	0.1204	A	0.0000469	13.15	4.3288272	
rs4960945	8	88868301	G	0.6429	0.1204	T	0.0000469	13.15	4.3288272	
rs4859033	3	88601013	G	0.7143	0.1667	A	5.032E-05	12.5	4.2982594	
rs969774	14	19631920	T	0.7143	0.1667	C	5.032E-05	12.5	4.2982594	
rs11071331	15	55621184	T	0.7143	0.1667	C	5.032E-05	12.5	4.2982594	CGNL1
rs3764584	19	2471716	T	0	0.5648	C	5.265E-05	0	4.2786016	GNG7
rs13103431	4	161589079	T	0.7857	0.2222	G	5.552E-05	12.83	4.2555505	
rs919329	5	28009510	G	0.5	0.05556	T	6.294E-05	17	4.2010733	
rs12856567	23	39572159	G	0.6667	0.1098	A	7.274E-05	16.22	4.1382267	
rs11768422	7	67807659	T	0.7857	0.2315	C	7.749E-05	12.17	4.1107543	
rs2723829	12	11819364	A	0.8571	0.2963	G	7.893E-05	14.25	4.1027579	ETV6
rs10785007	12	71799725	C	0	0.5192	T	9.794E-05	0	4.0090399	
rs10107666	8	14741501	T	0.8571	0.3056	C	0.0001052	13.64	3.9779843	SGCZ
rs10104703	8	14741552	A	0.8571	0.3056	C	0.0001052	13.64	3.9779843	SGCZ
rs13092167	3	59747382	G	0.7857	0.2407	A	0.0001068	11.56	3.9714287	FHIT
rs11700340	20	59707924	C	0.7857	0.2407	A	0.0001068	11.56	3.9714287	CDH4
rs464557	16	82385954	G	0.6429	0.1389	A	0.0001126	11.16	3.9484616	CDH13
rs254343	16	82393257	C	0.6429	0.1389	T	0.0001126	11.16	3.9484616	
rs7960773	12	125627131	G	0.2857	0	T	0.000114		3.9430951	
rs11058720	12	125629813	A	0.2857	0	G	0.000114		3.9430951	
rs17699529	8	94345308	C	0.5	0.06481	T	0.0001189	14.43	3.9248181	
rs5752585	22	26266871	A	0.5	0.06481	C	0.0001189	14.43	3.9248181	
rs9866579	3	118096151	A	0.4286	0.03704	G	0.000122	19.5	3.9136402	
rs6777752	3	118106511	G	0.4286	0.03704	A	0.000122	19.5	3.9136402	
rs11061121	12	129791564	T	0.4286	0.03704	C	0.000122	19.5	3.9136402	LOC729014
rs2318480	14	19661054	A	0.4286	0.03704	G	0.000122	19.5	3.9136402	
rs12635949	3	69029799	C	0.5714	0.1019	T	0.0001363	11.76	3.8655041	FAM19A4
rs4557199	3	77151956	C	0.5714	0.1019	T	0.0001363	11.76	3.8655041	
rs4947404	7	52263829	A	0.5714	0.1019	G	0.0001363	11.76	3.8655041	
rs6466213	7	77892967	A	0.5714	0.1019	C	0.0001363	11.76	3.8655041	MAGI2
rs984071	9	112178851	T	0.8571	0.3148	C	0.000139	13.06	3.8569852	SVEP1
rs6425838	1	34027003	T	0.7857	0.25	C	0.0001457	11	3.8365404	CSMD2
rs603688	8	2872872	T	0.7143	0.1944	C	0.0001513	10.36	3.8201611	CSMD1
rs10014285	4	161527422	A	0.6429	0.1481	G	0.000168	10.35	3.7746907	
rs12896479	14	75768562	T	0.6429	0.1481	G	0.000168	10.35	3.7746907	
rs11734574	4	131343294	C	0.8571	0.3208	T	0.0001686	12.71	3.7731424	

rs12407980	1	48993224	G	0.8571	0.3241	A	0.0001823	12.51	3.7392133	AGBL4, C1orf165
rs1323690	11	34457263	T	0.8571	0.3241	C	0.0001823	12.51	3.7392133	ELF5
rs10144441	14	58388714	G	0.8571	0.3241	A	0.0001823	12.51	3.7392133	
rs13168690	5	7202777	T	0.6429	0.1509	C	0.0001933	10.13	3.7137681	
rs2200520	15	51372185	T	0.7857	0.2593	C	0.0001965	10.48	3.7066374	
rs12439607	15	51381505	G	0.7857	0.2593	T	0.0001965	10.48	3.7066374	
rs681478	22	24226979	T	0.8333	0.2685	C	0.0002086	13.62	3.6806857	
rs7003556	8	5213929	T	0.5	0.07407	C	0.0002105	12.5	3.6767479	
rs4974227	3	60723766	G	0.7143	0.2037	A	0.0002116	9.773	3.6744843	FHIT
rs1023793	3	59302501	G	0.5714	0.1111	A	0.0002157	10.67	3.6661499	
rs820082	6	35139419	A	0.5714	0.1111	G	0.0002157	10.67	3.6661499	ANKS1A
rs1917716	7	45430747	A	0.5714	0.1111	C	0.0002157	10.67	3.6661499	
rs704014	10	80502780	A	0.5714	0.1111	G	0.0002157	10.67	3.6661499	
rs3758947	11	17457786	T	0.5714	0.1111	C	0.0002157	10.67	3.6661499	
rs12797160	11	134108466	A	0.3571	0.01961	G	0.0002278	27.78	3.6424463	LOC729893
rs10159239	1	245673675	A	1	0.4907	G	0.0002332		3.6322715	NLRP3
rs10152918	15	88152578	A	0	0.5	G	0.000236	0	3.627088	
rs7559777	2	121312086	T	0.8571	0.3333	G	0.0002373	12	3.6247023	GLI2
rs1489636	2	163734443	C	0.9286	0.3981	T	0.0002432	19.65	3.6140364	
rs1821942	3	61091049	G	0.6429	0.1574	A	0.0002453	9.635	3.6103025	FHIT
rs1194707	10	53870134	A	0.6429	0.1574	G	0.0002453	9.635	3.6103025	
rs1561662	10	53910718	A	0.6429	0.1574	G	0.0002453	9.635	3.6103025	
rs11677188	2	98112642	T	0	0.4907	C	0.0002515	0	3.599462	VWA3B
rs13396689	2	98125279	G	0	0.4907	A	0.0002515	0	3.599462	VWA3B
rs17819978	18	70569789	C	0.4286	0.0463	T	0.0002521	15.45	3.5984272	ZNF407
rs4408289	11	6667523	A	0.7857	0.2685	G	0.0002623	9.989	3.5812017	
rs1207592	22	24227330	A	0.7857	0.2685	C	0.0002623	9.989	3.5812017	
rs1387588	2	163723934	C	0.07143	0.5926	T	0.0002664	0.05288	3.5744658	
rs1979771	18	14557390	G	0.07143	0.5926	T	0.0002664	0.05288	3.5744658	
rs11100264	4	140902337	C	0	0.4815	T	0.00028	0	3.552842	MAML3
rs1586030	8	3496385	C	0	0.4815	T	0.00028	0	3.552842	CSMD1
rs3745101	19	57777625	C	0	0.4815	T	0.00028	0	3.552842	ZNF701
rs17507263	20	9933041	G	0	0.4815	A	0.00028	0	3.552842	
rs1340704	13	75404658	G	0.07143	0.5849	A	0.0002978	0.05459	3.5260753	
rs2189439	7	29413667	A	0.9286	0.4167	G	0.000304	18.2	3.5171264	CHN2
rs2189440	7	29413794	T	0.9286	0.4167	C	0.000304	18.2	3.5171264	CHN2
rs4287512	15	62997194	T	0.07143	0.5833	C	0.000304	0.05495	3.5171264	
rs6756742	2	98066320	T	0.8571	0.3426	C	0.0003068	11.51	3.5131446	
rs6543280	2	98067475	C	0.8571	0.3426	T	0.0003068	11.51	3.5131446	
rs2062365	2	151544236	T	0.8571	0.3426	C	0.0003068	11.51	3.5131446	
rs1905744	2	151544451	T	0.8571	0.3426	G	0.0003068	11.51	3.5131446	
rs6100556	20	57701043	T	0.8571	0.3426	G	0.0003068	11.51	3.5131446	PHACTR3
rs272456	5	6537012	A	0	0.4722	G	0.0003226	0	3.4913356	FLJ25076
rs6868112	5	40851764	C	0	0.4722	A	0.0003226	0	3.4913356	
rs7725810	5	40863064	C	0	0.4722	T	0.0003226	0	3.4913356	
rs2349682	2	5405625	C	0.5714	0.1204	T	0.0003306	9.744	3.4806972	
rs4974241	3	60750500	T	0.5714	0.1204	C	0.0003306	9.744	3.4806972	FHIT

rs923512	3	68995221	G	0.5714	0.1204	A	0.0003306	9.744	3.4806972	FAM19A4
rs1761628	6	118781084	T	0.5714	0.1204	G	0.0003306	9.744	3.4806972	
rs1761630	6	118782630	C	0.5714	0.1204	T	0.0003306	9.744	3.4806972	
rs12910328	15	29159268	T	0.5714	0.1204	C	0.0003306	9.744	3.4806972	TRPM1
rs1898618	4	118199183	C	0	0.4706	T	0.000338	0	3.4710833	
rs1811264	12	97027466	C	0.7857	0.2778	T	0.0003469	9.533	3.4597957	
rs2200522	15	51362944	C	0.7857	0.2778	A	0.0003469	9.533	3.4597957	
rs7214248	17	25598303	A	0.7857	0.2778	G	0.0003469	9.533	3.4597957	BLMH
rs1050565	17	25600202	G	0.7857	0.2778	A	0.0003469	9.533	3.4597957	BLMH
rs9811499	3	59300424	T	0.6429	0.1667	C	0.0003512	9	3.4544455	
rs11782013	8	88720153	G	0.6429	0.1667	A	0.0003512	9	3.4544455	
rs6993181	8	88755036	G	0.6429	0.1667	A	0.0003512	9	3.4544455	
rs7828921	8	88816298	G	0.6429	0.1667	A	0.0003512	9	3.4544455	
rs1194649	10	53839390	T	0.6429	0.1667	C	0.0003512	9	3.4544455	
rs1045653	2	225338679	A	0.5	0.08333	G	0.0003531	11	3.4521023	DOCK10
rs11712727	3	64685061	A	0.5	0.08333	C	0.0003531	11	3.4521023	LOC730057
rs10504973	8	98481327	A	0.5	0.08333	G	0.0003531	11	3.4521023	
rs13129968	4	186742187	A	0.07143	0.5741	G	0.0003575	0.05707	3.446724	SORBS2
rs1157669	11	34374446	A	0.9286	0.4259	G	0.0003575	17.52	3.446724	
rs2191351	17	25783161	T	0.9286	0.4259	C	0.0003575	17.52	3.446724	CPD
rs1720545	3	64927793	G	0	0.463	T	0.0003804	0	3.4197595	
rs10496839	2	140766339	T	0.5	0.08491	C	0.0003938	10.78	3.4047243	LRP1B
rs2369476	1	158388112	A	0.7143	0.2222	C	0.0003968	8.75	3.4014283	ATP1A4
rs12649063	4	186707415	T	0.07143	0.5648	C	0.0004289	0.05927	3.367644	
rs216476	17	25890772	T	0.9286	0.4352	C	0.0004289	16.87	3.367644	
rs216484	17	25895301	A	0.9286	0.4352	G	0.0004289	16.87	3.367644	
rs17667217	14	81894043	A	0.3571	0.02778	G	0.0004429	19.44	3.3536943	
rs10520094	15	36690462	A	0.3571	0.02778	G	0.0004429	19.44	3.3536943	
rs7272567	20	40219855	T	0.3571	0.02778	C	0.0004429	19.44	3.3536943	PTPRT
rs2631731	4	8480717	T	0.7857	0.287	C	0.0004546	9.108	3.3423706	ACOX3
rs1949733	4	8554259	A	0.7857	0.287	G	0.0004546	9.108	3.3423706	
rs4361657	7	67822769	T	0.7857	0.287	C	0.0004546	9.108	3.3423706	
rs755804	19	60941257	T	0.7857	0.287	C	0.0004546	9.108	3.3423706	NLRP9
rs6027558	20	58381559	A	0.7857	0.287	G	0.0004546	9.108	3.3423706	
rs6427504	1	158391499	G	0.7143	0.2264	A	0.0004628	8.542	3.3346066	ATP1A4
rs17079099	8	2866477	T	0.6429	0.1731	C	0.0004641	8.6	3.3333884	CSMD1
rs7616813	3	118140859	T	0.4286	0.05556	C	0.0004734	12.75	3.3247717	
rs1051970	5	121866811	G	0.4286	0.05556	A	0.0004734	12.75	3.3247717	
rs11087974	12	115218570	C	0.4286	0.05556	T	0.0004734	12.75	3.3247717	
rs7623995	3	68905991	G	0.5714	0.1296	A	0.0004927	8.952	3.3074174	FAM19A4
rs9388278	6	124026860	A	0.5714	0.1296	G	0.0004927	8.952	3.3074174	
rs13090878	3	59294515	C	0.6429	0.1759	T	0.0004937	8.432	3.3065369	
rs9871910	3	69054550	G	0.6429	0.1759	A	0.0004937	8.432	3.3065369	FAM19A4
rs9814149	3	88621706	T	0.6429	0.1759	G	0.0004937	8.432	3.3065369	
rs1336974	6	117179344	A	0.6429	0.1759	C	0.0004937	8.432	3.3065369	C6orf189
rs4762485	12	97302491	T	0.6429	0.1759	C	0.0004937	8.432	3.3065369	
rs10131515	14	58384905	C	0.6429	0.1759	A	0.0004937	8.432	3.3065369	
rs719988	23	85035022	T	0.75	0.2195	C	0.0005111	10.67	3.2914941	CHM

rs869896	1	44220697	T	0.2857	0.009259	C	0.0005312	42.8	3.2747419	B4GALT2
rs9360459	6	72309728	T	0.2857	0.009259	C	0.0005312	42.8	3.2747419	
rs6927647	6	72346372	G	0.2857	0.009259	A	0.0005312	42.8	3.2747419	
rs4416886	9	73923515	T	0.2857	0.009259	C	0.0005312	42.8	3.2747419	
rs6040544	20	11261614	G	0.2857	0.009259	A	0.0005312	42.8	3.2747419	
rs575633	1	84237624	A	0.7143	0.2315	C	0.0005334	8.3	3.272947	TTLL7
rs1693232	1	231802517	A	0.7143	0.2315	G	0.0005334	8.3	3.272947	
rs7634255	3	161843390	T	0.7143	0.2315	C	0.0005334	8.3	3.272947	
rs6766478	3	192769221	A	0.7143	0.2315	G	0.0005334	8.3	3.272947	
rs11134466	5	166972188	T	0.7143	0.2315	C	0.0005334	8.3	3.272947	ODZ2
rs10485886	7	77895776	T	0.7143	0.2315	C	0.0005334	8.3	3.272947	MAGI2
rs2399685	11	92934982	C	0.7143	0.2315	T	0.0005334	8.3	3.272947	
rs35693	12	99503643	T	0.7143	0.2315	C	0.0005334	8.3	3.272947	GAS2L3
rs405478	16	82389805	A	0.7143	0.2315	C	0.0005334	8.3	3.272947	
rs6730278	2	44290721	A	0.5	0.09259	G	0.0005662	9.8	3.2470301	PPM1B
rs933984	2	204707718	T	0.5	0.09259	G	0.0005662	9.8	3.2470301	
rs9805984	14	51201493	T	0.5	0.09259	G	0.0005662	9.8	3.2470301	FRMD6
rs10141001	14	51201951	A	0.5	0.09259	G	0.0005662	9.8	3.2470301	FRMD6
rs682133	8	2871989	T	0.6429	0.1792	C	0.0005664	8.242	3.2468768	CSMD1
rs4851462	2	97723595	C	0.7857	0.2963	T	0.0005907	8.708	3.228633	
rs940136	4	8499892	G	0.7857	0.2963	A	0.0005907	8.708	3.228633	
rs10942722	5	74219900	G	0.7857	0.2963	T	0.0005907	8.708	3.228633	
rs10788478	10	87797370	A	0.7857	0.2963	G	0.0005907	8.708	3.228633	GRID1
rs1006920	17	52604886	A	0.7857	0.2963	G	0.0005907	8.708	3.228633	
rs11672145	19	12361149	G	0.7857	0.2963	T	0.0005907	8.708	3.228633	ZNF799
rs967023	8	88721133	A	0.6667	0.1731	G	0.0006369	9.556	3.1959288	
rs323928	7	34700776	T	0	0.4565	C	0.0006795	0	3.1678105	AAA1, NPSR1
rs1898866	4	161529827	C	0.6429	0.1852	T	0.0006826	7.92	3.1658337	
rs7677076	4	161530598	A	0.6429	0.1852	G	0.0006826	7.92	3.1658337	
rs12526079	6	99671936	A	0.6429	0.1852	G	0.0006826	7.92	3.1658337	
rs11261084	1	19032244	A	0.7143	0.2407	G	0.0007087	7.885	3.1495376	
rs11265329	1	158362070	T	0.7143	0.2407	C	0.0007087	7.885	3.1495376	ATP1A2
rs6744417	2	98131355	C	0.7143	0.2407	T	0.0007087	7.885	3.1495376	VWA3B
rs7603077	2	151593802	G	0.7143	0.2407	A	0.0007087	7.885	3.1495376	
rs11204005	8	12895576	G	0.7143	0.2407	A	0.0007087	7.885	3.1495376	
rs10888160	8	12896188	T	0.7143	0.2407	C	0.0007087	7.885	3.1495376	
rs3098360	10	58495356	C	0.7143	0.2407	T	0.0007087	7.885	3.1495376	
rs1504568	12	97017215	A	0.7143	0.2407	C	0.0007087	7.885	3.1495376	
rs3751335	13	28753822	T	0.7143	0.2407	C	0.0007087	7.885	3.1495376	KIAA0774
rs2069334	14	58368941	A	0.7143	0.2407	G	0.0007087	7.885	3.1495376	
rs10130841	14	58390147	G	0.7143	0.2407	A	0.0007087	7.885	3.1495376	
rs4668565	2	5404548	C	0.5714	0.1389	T	0.0007161	8.267	3.1450263	
rs4735211	8	94367360	T	0.5714	0.1389	C	0.0007161	8.267	3.1450263	
rs3758280	9	33439952	T	0.5714	0.1389	C	0.0007161	8.267	3.1450263	
rs11217593	11	119327504	A	0.5714	0.1389	G	0.0007161	8.267	3.1450263	
rs6630695	23	14539311	G	0.75	0.2317	A	0.0007238	9.947	3.1403814	GLRA2
rs12130711	1	245674265	T	0	0.4537	C	0.0007391	0	3.1312968	NLRP3

rs11191839	10	105624885	A	0	0.4537	G	0.0007391	0	3.1312968	
rs12889741	14	69955785	A	0	0.4537	C	0.0007391	0	3.1312968	
rs8088963	18	57198294	G	0	0.4537	A	0.0007391	0	3.1312968	
rs7005262	8	14903851	A	0.8571	0.3519	G	0.0007433	11.05	3.1288359	SGCZ
rs13251017	8	14912887	C	0.8571	0.3519	T	0.0007433	11.05	3.1288359	SGCZ
rs13251961	8	14913179	C	0.8571	0.3519	T	0.0007433	11.05	3.1288359	SGCZ
rs12550462	8	14913506	C	0.8571	0.3519	T	0.0007433	11.05	3.1288359	SGCZ
rs2840649	23	121345910	G	0.3333	0.0122	A	0.0007539	40.5	3.1226863	
rs7053253	23	39774364	T	0.6667	0.1707	C	0.0007546	9.714	3.1222832	
rs6549392	3	71621386	T	0.7857	0.3056	G	0.0007612	8.333	3.1185012	FOXP1
rs4696828	4	8506504	A	0.7857	0.3056	G	0.0007612	8.333	3.1185012	C4orf23
rs4762486	12	97302567	T	0.7857	0.3056	C	0.0007612	8.333	3.1185012	
rs6761283	2	209990576	C	0.8571	0.3585	T	0.0007652	10.74	3.116225	
rs2469389	8	3500873	T	0	0.4444	C	0.0007706	0	3.113171	CSMD1
rs1683163	12	25124885	C	0	0.4444	T	0.0007706	0	3.113171	LRMP
rs3859301	18	13440234	C	0	0.4444	T	0.0007706	0	3.113171	C18orf1
rs1965402	1	15190986	G	0.8571	0.3611	A	0.0007839	10.62	3.1057393	KIAA1026
rs1446596	2	209993773	G	0.8571	0.3611	A	0.0007839	10.62	3.1057393	
rs10005281	4	161583013	A	0.8571	0.3611	G	0.0007839	10.62	3.1057393	
rs10794008	10	127227908	G	0.8571	0.3611	A	0.0007839	10.62	3.1057393	
rs2311789	23	115546167	G	0.3333	0.0125	A	0.0008214	39.5	3.0854453	
rs12677379	8	12894120	G	0.7143	0.2453	A	0.000825	7.692	3.0835461	
rs16866089	2	225213336	C	0.4286	0.06481	T	0.0008253	10.82	3.0833882	
rs7710100	5	134796228	G	0.4286	0.06481	A	0.0008253	10.82	3.0833882	
rs17078724	13	22894197	C	0.4286	0.06481	A	0.0008253	10.82	3.0833882	
rs279955	8	94092322	A	0.7857	0.3077	G	0.0008314	8.25	3.08019	
rs1584783	4	140879842	T	0	0.4352	C	0.0008379	0	3.0768078	MAML3
rs7678266	4	140887824	T	0	0.4352	C	0.0008379	0	3.0768078	MAML3
rs4242300	6	156658003	C	0	0.4352	T	0.0008379	0	3.0768078	
rs1034716	7	29400969	G	0	0.4352	A	0.0008379	0	3.0768078	CHN2
rs10846765	12	123940680	A	0	0.4352	G	0.0008379	0	3.0768078	
rs8022575	14	34217176	A	0	0.4352	C	0.0008379	0	3.0768078	
rs2725627	15	51979784	A	0	0.4352	G	0.0008379	0	3.0768078	
rs1862892	2	45385870	T	0.8571	0.3704	C	0.0008629	10.2	3.0640395	LOC730059
rs7042161	9	112237084	T	0.8571	0.3704	C	0.0008629	10.2	3.0640395	SVEP1
rs7043404	9	112241097	G	0.8571	0.3704	T	0.0008629	10.2	3.0640395	SVEP1
rs7314409	12	31803830	G	0.8571	0.3704	A	0.0008629	10.2	3.0640395	
rs11146953	12	131665980	T	0.8571	0.3704	C	0.0008629	10.2	3.0640395	KIAA1545
rs994859	3	63155203	T	0.5	0.1019	C	0.0008737	8.818	3.0586377	
rs6770731	3	63156168	T	0.5	0.1019	C	0.0008737	8.818	3.0586377	
rs2367763	3	63188675	A	0.5	0.1019	G	0.0008737	8.818	3.0586377	
rs3733665	5	149213748	G	0.5	0.1019	A	0.0008737	8.818	3.0586377	
rs1743242	6	118771801	A	0.5	0.1019	C	0.0008737	8.818	3.0586377	
rs6942609	7	100682200	A	0.5	0.1019	G	0.0008737	8.818	3.0586377	
rs16910063	10	58474305	A	0.5	0.1019	G	0.0008737	8.818	3.0586377	
rs10998921	10	71125879	C	0.5	0.1019	T	0.0008737	8.818	3.0586377	
rs12430711	13	42324586	G	0.5	0.1019	A	0.0008737	8.818	3.0586377	
rs12902840	15	29140275	T	0.5	0.1019	C	0.0008737	8.818	3.0586377	TRPM1

rs8039189	15	29146495	T	0.5	0.1019	G	0.0008737	8.818	3.0586377	TRPM1
rs2820229	6	35184054	G	0.7143	0.2449	A	0.0008763	7.708	3.0573472	
rs5935714	23	14073189	G	0.5833	0.122	A	0.0008774	10.08	3.0568024	
rs7060021	23	14077199	A	0.5833	0.122	C	0.0008774	10.08	3.0568024	
rs6690040	1	90833710	G	0.5714	0.1442	A	0.0009148	7.911	3.0386738	
rs5988206	23	113541942	C	0	0.5	T	0.0009259	0	3.0334359	
rs17421247	1	4624817	T	0.6429	0.1944	C	0.0009294	7.457	3.0317973	AJAP1
rs1507894	8	88855893	G	0.6429	0.1944	T	0.0009294	7.457	3.0317973	
rs835808	11	44831214	A	0.6429	0.1944	G	0.0009294	7.457	3.0317973	
rs588030	19	7788551	G	0.6429	0.1944	A	0.0009294	7.457	3.0317973	
rs780242	1	231752014	A	0.7143	0.25	G	0.0009316	7.5	3.0307705	
rs317588	3	4021691	A	0.7143	0.25	G	0.0009316	7.5	3.0307705	
rs2367209	3	161881579	A	0.7143	0.25	C	0.0009316	7.5	3.0307705	
rs6810359	3	189992908	T	0.3571	0.03704	G	0.0009316	14.44	3.0307705	LPP
rs11984112	7	137469409	C	0.3571	0.03704	T	0.0009316	14.44	3.0307705	
rs1317274	13	94372419	C	0.3571	0.03704	T	0.0009316	14.44	3.0307705	
rs10405167	19	6218757	G	0.7143	0.25	A	0.0009316	7.5	3.0307705	MLLT1
rs576895	22	24261580	C	0.7143	0.25	T	0.0009316	7.5	3.0307705	
rs984070	9	112178391	T	0.75	0.25	C	0.0009398	9	3.0269646	SVEP1
rs7791836	7	87899093	G	0	0.4259	A	0.0009427	0	3.0256265	
rs2469407	8	3493770	G	0	0.4259	A	0.0009427	0	3.0256265	CSMD1
rs6468833	8	103593637	G	0	0.4259	A	0.0009427	0	3.0256265	
rs10842458	12	25118569	C	0	0.4259	T	0.0009427	0	3.0256265	LRMP
rs6431936	2	8424878	A	0	0.4245	G	0.0009652	0	3.0153827	
rs2278700	2	97793814	C	0.7857	0.3148	T	0.0009735	7.98	3.011664	TMEM131
rs16863792	2	176990201	A	0.7857	0.3148	G	0.0009735	7.98	3.011664	
rs1525922	3	192745333	C	0.7857	0.3148	T	0.0009735	7.98	3.011664	
rs1583732	4	161539927	A	0.7857	0.3148	C	0.0009735	7.98	3.011664	
rs6453083	5	74111114	A	0.7857	0.3148	G	0.0009735	7.98	3.011664	
rs2515032	8	119563481	C	0.7857	0.3148	T	0.0009735	7.98	3.011664	SAMD12
rs1487971	17	25596879	A	0.7857	0.3148	G	0.0009735	7.98	3.011664	
rs11034493	11	4861778	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	
rs1945443	11	21365895	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	NELL1
rs747250	11	129776888	G	0.8571	0.3796	T	0.0009834	9.805	3.0072698	FLJ34521
rs10879571	12	71837819	A	0.8571	0.3796	G	0.0009834	9.805	3.0072698	
rs5001655	13	96394772	A	0.8571	0.3796	G	0.0009834	9.805	3.0072698	
rs11867581	17	25646354	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	
rs8073378	17	25653889	A	0.8571	0.3796	G	0.0009834	9.805	3.0072698	
rs9959914	18	48946456	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	DCC
rs2163854	19	61444704	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	
rs2032327	21	44441756	G	0.8571	0.3796	A	0.0009834	9.805	3.0072698	
rs33998	5	141949111	T	0.07143	0.5556	C	0.0009894	0.06154	3.0046281	
rs2531841	7	34686074	C	0.07143	0.5556	T	0.0009894	0.06154	3.0046281	AAA1, NPSR1
rs11179559	12	71811892	A	0.07143	0.5556	C	0.0009894	0.06154	3.0046281	
rs1982607	13	75440483	T	0.07143	0.5556	C	0.0009894	0.06154	3.0046281	
rs7338771	13	75444822	T	0.07143	0.5556	C	0.0009894	0.06154	3.0046281	
rs509497	18	6947193	C	0.9286	0.4519	T	0.0009899	15.77	3.0044087	LAMA1

Figure 2

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs6928719	6	166117879	C	0.1875	0.6711	A	5.292E-06	0.1131	5.2763802	
rs6928737	6	166118611	G	0.1875	0.6579	A	7.617E-06	0.12	5.118216	
rs12857230	13	42654650	G	0.7188	0.25	T	8.917E-06	7.667	5.0497812	
rs11713998	3	168613099	T	0.4375	0.06579	C	1.437E-05	11.04	4.8425432	
rs4762507	12	97659769	T	0	0.3553	C	0.0000171	0	4.7670039	ANKS1B
rs1838990	3	63142891	C	0.09375	0.5132	T	2.815E-05	0.09814	4.5505216	
rs13144587	4	67295867	C	0.4375	0.07895	A	3.895E-05	9.074	4.4094925	
rs12918939	16	64698060	G	0.4375	0.07895	A	3.895E-05	9.074	4.4094925	
rs6904237	6	166121014	C	0.1875	0.6316	T	4.141E-05	0.1346	4.3828948	
rs5999636	22	33661041	T	0	0.3289	C	4.165E-05	0	4.380385	
rs7288089	22	33671316	T	0	0.3289	C	4.165E-05	0	4.380385	
rs10953428	7	103814099	T	0.0625	0.4474	C	4.902E-05	0.08235	4.3096267	LHFPL3
rs1989823	7	103823052	C	0.0625	0.4474	T	4.902E-05	0.08235	4.3096267	LHFPL3
rs7335910	13	24220725	G	0.0625	0.4474	A	4.902E-05	0.08235	4.3096267	
rs4831616	8	14511299	T	0.4375	0.08108	C	4.997E-05	8.815	4.3012907	SGCZ
rs33053	3	161084457	T	0.03125	0.3947	C	4.998E-05	0.04946	4.3012037	SCHIP1
rs1439123	12	97600447	C	0.03125	0.3947	T	4.998E-05	0.04946	4.3012037	APAF1
rs11598274	10	130794532	T	0.4063	0.06579	G	5.073E-05	9.716	4.2947351	
rs11111712	12	102605853	T	0.4063	0.06579	C	5.073E-05	9.716	4.2947351	STAB2
rs9924119	16	69900898	C	0.4063	0.06579	T	5.073E-05	9.716	4.2947351	
rs4346287	18	60381151	A	0.4063	0.06579	G	5.073E-05	9.716	4.2947351	
rs11671104	19	22586526	C	0.2813	0.01316	A	5.672E-05	29.35	4.2462638	
rs12186252	4	6166295	T	0.5938	0.1842	C	5.976E-05	6.473	4.2235894	JAKMIP1
rs11695174	2	9705766	T	0.3125	0.02632	C	6.953E-05	16.82	4.1578278	
rs299728	18	44424510	T	0	0.3158	C	7.817E-05	0	4.1069599	KIAA0427
rs6791663	3	183452046	A	0.4375	0.09211	G	9.481E-05	7.667	4.0231459	
rs7779755	7	26538363	A	0.75	0.3289	G	0.000101	6.12	3.9956786	
rs740182	7	26543060	A	0.75	0.3289	G	0.000101	6.12	3.9956786	
rs1596860	13	24293067	G	0.03125	0.3816	A	0.000101	0.05228	3.9956786	RNF17
rs9507425	13	24338318	A	0.03125	0.3816	G	0.000101	0.05228	3.9956786	RNF17
rs2356417	16	69913636	C	0.4	0.06757	T	0.0001122	9.2	3.9500071	
rs2288726	12	97608518	T	0.03125	0.3684	G	0.0001184	0.0553	3.9266483	APAF1
rs6758414	2	121012955	A	0.2188	0	G	0.0001207		3.9182927	
rs9520550	13	107135055	A	0.2188	0	G	0.0001207		3.9182927	LOC728215
rs7320808	13	107138864	T	0.2188	0	C	0.0001207		3.9182927	LOC728215
rs4113420	13	107154330	T	0.2188	0	C	0.0001207		3.9182927	LOC728215
rs2117193	9	18751368	C	0.1875	0.5921	T	0.0001246	0.159	3.904482	
rs4690523	4	178598156	C	0.1563	0.5526	T	0.0001254	0.1499	3.9017025	AGA
rs995992	7	26543445	C	0.75	0.3421	T	0.0001271	5.769	3.8958544	
rs7901425	10	130778057	C	0.4063	0.07895	T	0.0001295	7.982	3.8877302	
rs9814318	3	63136521	T	0.09375	0.473	C	0.0001373	0.1153	3.8623295	
rs4688381	3	63202226	A	0.09375	0.4737	G	0.0001406	0.1149	3.8520147	
rs12193060	6	99797170	G	0	0.3026	A	0.0001604	0	3.7947956	
rs2767001	9	112623833	A	0.5625	0.1842	G	0.0001681	5.694	3.7744323	

rs1424140	16	69932963	T	0.5625	0.1842	C	0.0001681	5.694	3.7744323	
rs3802431	9	110932446	G	0.375	0.06579	A	0.0001689	8.52	3.7723704	
rs12774599	10	130795782	T	0.375	0.06579	G	0.0001689	8.52	3.7723704	
rs642407	5	32542605	A	0.09375	0.4605	G	0.0001706	0.1212	3.768021	
rs3748088	7	139864139	T	0.09375	0.4605	C	0.0001706	0.1212	3.768021	DENND 2A
rs10078211	5	57999775	T	0	0.2895	C	0.0001777	0	3.7503126	RAB3C
rs6568842	6	114907070	A	0	0.2895	G	0.0001777	0	3.7503126	
rs9298648	8	38918214	A	0.0625	0.4189	G	0.0001846	0.09247	3.7337683	PLEKHA 2
rs1549599	3	37506369	G	0.6563	0.2632	A	0.0001906	5.345	3.7198771	ITGA9
rs4854942	3	180871100	C	0.0625	0.4211	T	0.0001932	0.09167	3.7139929	USP13
rs586125	18	40693077	C	0.4688	0.1184	T	0.0002033	6.569	3.6918626	SETBP1
rs1554937	21	40500245	C	0.6875	0.2895	T	0.0002078	5.4	3.6823545	DSCAM
rs10275945	7	9323375	A	0.3438	0.05263	C	0.0002083	9.429	3.6813107	
rs9915945	17	6089542	A	0.3438	0.05263	G	0.0002083	9.429	3.6813107	
rs17020744	2	81845572	A	0.25	0.01316	G	0.0002115	25	3.6746896	
rs7326004	13	107155619	T	0.25	0.01316	C	0.0002115	25	3.6746896	LOC728 215
rs4326996	15	61567335	G	0.25	0.01316	T	0.0002115	25	3.6746896	
rs2162296	19	41792090	T	0.25	0.01316	C	0.0002115	25	3.6746896	ZNF382
rs1673082	19	41932981	A	0.25	0.01316	G	0.0002115	25	3.6746896	
rs2945861	8	8321077	T	0.0625	0.4079	C	0.0002144	0.09677	3.6687752	
rs680951	10	6267388	C	0.03125	0.3553	T	0.0002199	0.05854	3.6577748	
rs6864728	5	2680030	G	0.5313	0.1579	A	0.0002232	6.044	3.6513058	
rs7122962	11	123818932	A	0.5313	0.1579	G	0.0002232	6.044	3.6513058	
rs2938033	18	43510320	G	0.5313	0.1579	A	0.0002232	6.044	3.6513058	
rs6532729	4	99365459	C	0.5938	0.2105	T	0.0002244	5.481	3.6489771	
rs10416755	19	39975287	A	0.3125	0.03947	G	0.0002389	11.06	3.6217839	
rs2834772	21	35405029	T	0.3125	0.03947	C	0.0002389	11.06	3.6217839	
rs4659630	1	234359973	C	0.1875	0.5789	T	0.0002589	0.1678	3.5868679	
rs585224	12	51209139	A	0.5938	0.2162	G	0.0002626	5.298	3.5807053	
rs12696221	3	166354274	G	0.75	0.3553	A	0.0002667	5.444	3.573977	
rs721250	2	59630520	G	0.7188	0.3289	A	0.0002721	5.213	3.5652715	
rs6853651	4	157343816	A	0.7188	0.3289	C	0.0002721	5.213	3.5652715	
rs2340252	4	157348668	A	0.7188	0.3289	C	0.0002721	5.213	3.5652715	
rs7157453	14	54228954	C	0.7188	0.3289	T	0.0002721	5.213	3.5652715	SAMD4 A
rs13382133	19	17719936	C	0.7188	0.3289	T	0.0002721	5.213	3.5652715	
rs9884594	4	99578341	A	0.6875	0.3026	G	0.0002792	5.07	3.5540846	RAP1G DS1
rs694126	5	32551319	C	0.6875	0.3026	T	0.0002792	5.07	3.5540846	
rs7776	9	110822352	C	0.5313	0.1711	A	0.0002969	5.492	3.5273898	C9orf5
rs2141599	3	178325169	T	0.625	0.2368	C	0.0003044	5.37	3.5165554	TBL1XR 1
rs277973	5	70995578	T	0.625	0.2368	G	0.0003044	5.37	3.5165554	
rs12933802	16	87649419	A	0.3667	0.06579	G	0.0003062	8.221	3.5139948	
rs6933285	6	120383898	T	0.1875	0.5658	C	0.0003085	0.1771	3.5107448	
rs1569757	6	120389030	G	0.1875	0.5658	A	0.0003085	0.1771	3.5107448	
rs2110871	7	77918484	A	0.5938	0.2237	G	0.0003194	5.072	3.4956651	MAGI2
rs1274399	10	92347510	T	0.5938	0.2237	C	0.0003194	5.072	3.4956651	
rs669379	12	51213665	G	0.5938	0.2237	A	0.0003194	5.072	3.4956651	

rs12709230	16	8449241	C	0.5938	0.2237	T	0.0003194	5.072	3.4956651	
rs7755154	6	2558943	T	0.4688	0.1316	C	0.0003307	5.824	3.4805658	
rs4772778	13	105835851	A	0.4688	0.1316	G	0.0003307	5.824	3.4805658	
rs10077599	5	58022400	A	0	0.2763	G	0.0003311	0	3.4800408	RAB3C
rs10472069	5	58041554	C	0	0.2763	T	0.0003311	0	3.4800408	RAB3C
rs7350156	9	133715383	G	0.25	0.6316	A	0.0003338	0.1944	3.4765137	
rs6504487	17	62553814	A	0.75	0.3684	C	0.0003338	5.143	3.4765137	HELZ
rs7211695	17	62666433	G	0.75	0.3684	A	0.0003338	5.143	3.4765137	HELZ
rs6481260	10	58633464	C	0.6	0.2083	T	0.0003468	5.7	3.4599209	
rs5970533	23	150005809	T	0.08	0.4912	C	0.0003566	0.09006	3.4478187	
rs7837164	8	14510052	C	0.4375	0.1053	T	0.0003605	6.611	3.4430947	SGCZ
rs589623	11	102587800	C	0.4375	0.1053	T	0.0003605	6.611	3.4430947	DYNC2 H1
rs660994	11	102616867	G	0.4375	0.1053	T	0.0003605	6.611	3.4430947	DYNC2 H1
rs1891020	1	159961078	A	0.625	0.25	G	0.0003681	5	3.4340342	FCRLB
rs1417582	1	159962712	T	0.625	0.25	C	0.0003681	5	3.4340342	FCRLB
rs1572705	1	236374168	A	0.625	0.25	G	0.0003681	5	3.4340342	
rs11246756	12	130743401	G	0.625	0.25	T	0.0003681	5	3.4340342	
rs7771891	6	2570303	G	0.375	0.07895	A	0.0004052	7	3.3923306	C6orf19 5
rs7759042	6	2574150	C	0.375	0.07895	T	0.0004052	7	3.3923306	C6orf19 5
rs7715908	5	172176301	G	0.4688	0.1351	A	0.0004058	5.647	3.391688	
rs12489904	3	20359631	G	0.125	0.4868	A	0.0004131	0.1506	3.3839448	
rs11719694	3	20363109	T	0.125	0.4868	C	0.0004131	0.1506	3.3839448	
rs326832	20	55952451	A	0.125	0.4868	G	0.0004131	0.1506	3.3839448	
rs2028211	2	127618127	C	0.6563	0.2763	A	0.0004284	5	3.3681505	
rs7611110	3	183421131	C	0.6563	0.2763	A	0.0004284	5	3.3681505	
rs4444698	3	183422848	C	0.6563	0.2763	T	0.0004284	5	3.3681505	
rs320719	7	136674049	A	0.6563	0.2763	G	0.0004284	5	3.3681505	PTN
rs320682	7	136688632	C	0.6563	0.2763	T	0.0004284	5	3.3681505	
rs6092527	20	55746462	A	0.6563	0.2763	G	0.0004284	5	3.3681505	
rs2808067	10	32085938	A	0.5625	0.1974	G	0.0004322	5.229	3.3643152	
rs7073183	10	58640012	C	0.5625	0.1974	T	0.0004322	5.229	3.3643152	
rs4794558	17	50702952	A	0.5625	0.1974	G	0.0004322	5.229	3.3643152	HLF
rs6627850	23	150008593	C	0.08	0.4737	T	0.0004343	0.09662	3.3622102	
rs666595	10	6268232	T	0.03125	0.3421	C	0.0004413	0.06203	3.3552661	
rs1048878	20	49646660	C	0.03125	0.3421	T	0.0004413	0.06203	3.3552661	ATP9A
rs10910365	1	232346267	A	0.5313	0.1842	G	0.0004653	5.019	3.3322669	SLC35F 3
rs2373001	2	37451925	C	0.1875	0	T	0.0004736		3.3245883	QPCT
rs9553435	13	24235300	A	0.03125	0.3289	C	0.0004813	0.06581	3.3175841	RNF17
rs4883688	13	62434248	C	0.03125	0.3289	T	0.0004813	0.06581	3.3175841	
rs1878059	18	42488544	A	0.03125	0.3289	G	0.0004813	0.06581	3.3175841	LOC647 011
rs2423222	20	7297731	T	0.03125	0.3289	C	0.0004813	0.06581	3.3175841	
rs2315656	20	61888781	G	0.125	0.4737	A	0.0004872	0.1587	3.3122927	ZBTB46
rs12591365	15	23611690	G	0.1563	0.5263	A	0.0005032	0.1667	3.2982594	
rs8032023	15	59199434	C	0.1563	0.5263	T	0.0005032	0.1667	3.2982594	RORA
rs2680700	17	53795541	A	0.6563	0.2857	C	0.0005263	4.773	3.2787666	RNF43
rs6963754	7	9292495	C	0.5	0.1579	T	0.0005271	5.333	3.278107	

rs1322473	9	7969832	T	0.5	0.1579	C	0.0005271	5.333	3.278107	
rs2439422	15	64764858	G	0.5	0.1579	A	0.0005271	5.333	3.278107	
rs12957369	18	22190589	A	0.5	0.1579	G	0.0005271	5.333	3.278107	TAF4B
rs12962768	18	22220594	C	0.5	0.1579	T	0.0005271	5.333	3.278107	TAF4B
rs1028005	4	46635775	C	0.4375	0.1184	T	0.0005297	5.79	3.27597	GABRA 4
rs323391	17	69199193	A	0.4375	0.1184	C	0.0005297	5.79	3.27597	
rs3935319	7	9334882	T	0.3438	0.06579	C	0.0005303	7.438	3.2754784	
rs10099199	8	18422501	C	0.3438	0.06579	T	0.0005303	7.438	3.2754784	
rs7581	9	110819068	G	0.3438	0.06579	A	0.0005303	7.438	3.2754784	C9orf5
rs7200766	16	87658525	T	0.3438	0.06579	C	0.0005303	7.438	3.2754784	
rs4574540	5	124095527	G	0.6563	0.2895	A	0.0005399	4.686	3.2676867	ZNF608
rs7741833	6	121042746	A	0.6563	0.2895	G	0.0005399	4.686	3.2676867	
rs1431093	7	136666837	T	0.6563	0.2895	G	0.0005399	4.686	3.2676867	PTN
rs1536833	10	30739271	A	0.6563	0.2895	G	0.0005399	4.686	3.2676867	
rs303436	10	30771899	C	0.6563	0.2895	A	0.0005399	4.686	3.2676867	MAP3K8
rs12283389	11	86248925	T	0.6563	0.2895	C	0.0005399	4.686	3.2676867	
rs1548518	12	46439262	T	0.6563	0.2895	C	0.0005399	4.686	3.2676867	RAPGE F3
rs12904249	15	23622445	A	0.6563	0.2895	G	0.0005399	4.686	3.2676867	ATP10A
rs17777549	3	78417789	C	0	0.3182	T	0.0005487	0	3.260665	
rs2795492	9	99953197	A	0.1563	0.5132	G	0.0005522	0.1757	3.2579036	CORO2 A
rs7115014	11	102310143	A	0.1563	0.5132	G	0.0005522	0.1757	3.2579036	
rs9867568	3	23741555	C	0.6875	0.3158	T	0.0005592	4.767	3.2524328	
rs598672	10	30782394	C	0.6875	0.3158	T	0.0005592	4.767	3.2524328	MAP3K8
rs12336075	9	110422596	G	0.5625	0.2105	A	0.0005696	4.821	3.24443	
rs1275273	10	58676561	A	0.5625	0.2105	G	0.0005696	4.821	3.24443	
rs236736	23	150022841	T	0.6	0.193	C	0.0005805	6.273	3.2361978	
rs6550478	3	37501017	A	0.2813	0.6579	G	0.000583	0.2035	3.2343314	ITGA9
rs1607077	4	92648984	G	0.1875	0.5526	A	0.0005934	0.1868	3.2266525	
rs7677659	4	92650752	C	0.1875	0.5526	T	0.0005934	0.1868	3.2266525	
rs12705208	7	103808264	G	0.1875	0.5526	A	0.0005934	0.1868	3.2266525	LHFPL3
rs4766100	12	3305142	G	0.1875	0.5526	A	0.0005934	0.1868	3.2266525	
rs11795873	23	19588579	G	0.84	0.4211	A	0.0005945	7.219	3.2258481	SH3KBP 1
rs1934908	1	159947492	T	0.7813	0.4079	C	0.0006131	5.184	3.2124687	FCRLA
rs10215963	7	26550306	A	0.7813	0.4079	C	0.0006131	5.184	3.2124687	
rs10753789	1	160572831	G	0.09375	0.4342	A	0.000626	0.1348	3.2034257	NOS1A P
rs7899958	10	131493116	G	0.09375	0.4342	A	0.000626	0.1348	3.2034257	
rs1860394	12	3309312	A	0.09375	0.4342	C	0.000626	0.1348	3.2034257	
rs6550169	3	32888097	T	0.25	0.6184	C	0.0006494	0.2057	3.1874877	TRIM71
rs1173179	5	4856549	T	0.25	0.6184	G	0.0006494	0.2057	3.1874877	
rs7520519	1	159962263	G	0.3125	0.05263	T	0.000662	8.182	3.179142	FCRLB
rs17013522	4	129794377	C	0.3125	0.05263	T	0.000662	8.182	3.179142	
rs2433101	8	25605445	C	0.3125	0.05263	T	0.000662	8.182	3.179142	
rs2433105	8	25605996	G	0.3125	0.05263	T	0.000662	8.182	3.179142	
rs6755276	2	33795430	C	0	0.2632	T	0.000669	0	3.1745739	
rs11073678	15	85205147	A	0	0.2632	G	0.000669	0	3.1745739	
rs8036797	15	85236643	T	0	0.2632	G	0.000669	0	3.1745739	
rs1323723	1	110615530	T	0.2813	0.6447	C	0.0006899	0.2156	3.1612139	

rs12622579	2	41352004	C	0.7188	0.3553	T	0.0006899	4.638	3.1612139	
rs809845	13	49622056	T	0.2813	0.6447	C	0.0006899	0.2156	3.1612139	
rs10863402	1	216807938	G	0.09375	0.4211	A	0.0006907	0.1422	3.1607105	
rs10929527	2	8526851	C	0.09375	0.4211	T	0.0006907	0.1422	3.1607105	
rs236855	6	79398610	G	0.09375	0.4211	A	0.0006907	0.1422	3.1607105	
rs625061	11	102537638	G	0.09375	0.4211	T	0.0006907	0.1422	3.1607105	DYNC2H1
rs876026	12	75190027	T	0.09375	0.4211	C	0.0006907	0.1422	3.1607105	
rs2680698	17	53800383	C	0.09375	0.4211	T	0.0006907	0.1422	3.1607105	RNF43
rs4811738	20	54698950	C	0.09375	0.4211	T	0.0006907	0.1422	3.1607105	
rs2300769	3	180903360	A	0.7813	0.4211	C	0.0006973	4.911	3.1565803	USP13
rs197419	1	112116973	C	0.5938	0.2368	A	0.0007	4.709	3.154902	
rs1500422	3	20695142	T	0.5938	0.2368	C	0.0007	4.709	3.154902	
rs11953826	5	174410242	C	0.5938	0.2368	A	0.0007	4.709	3.154902	
rs1569091	7	94356064	A	0.5938	0.2368	G	0.0007	4.709	3.154902	
rs2035590	12	114510223	T	0.5938	0.2368	C	0.0007	4.709	3.154902	
rs9569891	13	58048371	T	0.5938	0.2368	C	0.0007	4.709	3.154902	
rs822711	3	166486499	C	0	0.25	T	0.0007093	0	3.14917	
rs13281010	8	17441995	C	0	0.25	T	0.0007093	0	3.14917	SLC7A2
rs11003258	10	54352401	T	0	0.25	C	0.0007093	0	3.14917	
rs1073051	20	17793755	A	0	0.25	G	0.0007093	0	3.14917	
rs1105355	16	82633064	C	0.1875	0.5395	A	0.00072	0.197	3.1426675	LOC146167
rs16953945	17	4319847	A	0.1875	0.5395	G	0.00072	0.197	3.1426675	SPNS3
rs2362255	1	244130482	C	0.2188	0.01316	T	0.0007565	21	3.1211911	SMYD3
rs12996382	2	166768141	C	0.2188	0.01316	T	0.0007565	21	3.1211911	SCN9A
rs13090386	3	103158639	A	0.2188	0.01316	C	0.0007565	21	3.1211911	
rs10517174	4	46677583	A	0.2188	0.01316	G	0.0007565	21	3.1211911	GABRA4
rs17030758	4	102245160	G	0.2188	0.01316	A	0.0007565	21	3.1211911	PPP3CA
rs6862847	5	108735450	G	0.2188	0.01316	A	0.0007565	21	3.1211911	PJA2
rs12654614	5	162918233	G	0.2188	0.01316	A	0.0007565	21	3.1211911	
rs1484248	10	106984746	G	0.2188	0.01316	A	0.0007565	21	3.1211911	SORCS3
rs10884125	10	107010780	G	0.2188	0.01316	A	0.0007565	21	3.1211911	SORCS3
rs4606589	13	62363177	C	0.2188	0.01316	A	0.0007565	21	3.1211911	
rs7493402	14	100882328	G	0.2188	0.01316	A	0.0007565	21	3.1211911	
rs12462101	19	51426846	C	0.2188	0.01316	T	0.0007565	21	3.1211911	
rs7556371	1	202723959	G	0.5	0.1711	A	0.0007714	4.846	3.1127204	PIK3C2B
rs449095	4	103332760	A	0.5	0.1711	G	0.0007714	4.846	3.1127204	
rs6875512	5	31367532	C	0.5	0.1711	A	0.0007714	4.846	3.1127204	
rs10816772	9	110925690	C	0.5	0.1711	T	0.0007714	4.846	3.1127204	
rs2417976	9	110930170	A	0.5	0.1711	C	0.0007714	4.846	3.1127204	
rs11641362	16	83893452	T	0.5	0.1711	G	0.0007714	4.846	3.1127204	
rs37389	5	35120937	T	0.2813	0.03947	C	0.0007766	9.522	3.1098026	PRLR
rs6887887	5	142516106	A	0.2813	0.03947	G	0.0007766	9.522	3.1098026	ARHGAP26
rs17120994	8	15035830	C	0.2813	0.03947	T	0.0007766	9.522	3.1098026	SGCZ
rs502357	11	91953156	T	0.2813	0.03947	C	0.0007766	9.522	3.1098026	FAT3
rs2075379	12	29707647	G	0.2813	0.03947	A	0.0007766	9.522	3.1098026	TMTC1
rs12585317	13	56458934	T	0.2813	0.03947	C	0.0007766	9.522	3.1098026	

rs9569579	13	56486602	A	0.2813	0.03947	G	0.0007766	9.522	3.1098026	
rs9563481	13	56690719	A	0.2813	0.03947	C	0.0007766	9.522	3.1098026	
rs9563483	13	56716744	C	0.2813	0.03947	T	0.0007766	9.522	3.1098026	
rs6076519	20	3379140	G	0.2813	0.03947	A	0.0007766	9.522	3.1098026	
rs4143737	9	72679274	T	0.0625	0.3784	C	0.000783	0.1095	3.1062382	TRPM3
rs533202	2	166691427	A	0.25	0.02632	C	0.0008309	12.33	3.0804512	
rs479250	2	166691902	G	0.25	0.02632	A	0.0008309	12.33	3.0804512	
rs10486067	7	13890487	G	0.25	0.02632	A	0.0008309	12.33	3.0804512	
rs3801091	7	13921849	T	0.25	0.02632	C	0.0008309	12.33	3.0804512	ETV1
rs7185008	16	78501239	A	0.25	0.02632	G	0.0008309	12.33	3.0804512	
rs17742683	17	39234600	C	0.25	0.02632	T	0.0008309	12.33	3.0804512	MPP3
rs17093560	20	29789374	A	0.25	0.02632	G	0.0008309	12.33	3.0804512	TPX2
rs285684	19	38963499	T	0.03125	0.3243	C	0.0008459	0.0672	3.072681	
rs10204812	2	236075518	A	0.0625	0.3684	G	0.0008572	0.1143	3.0669178	CENTG 2
rs35684	3	10301686	G	0.0625	0.3684	A	0.0008572	0.1143	3.0669178	C3orf42, GHRL
rs1453546	11	58979902	G	0.0625	0.3684	A	0.0008572	0.1143	3.0669178	OR4D6
rs4704050	5	70829327	G	0.625	0.2632	A	0.0008632	4.667	3.0638886	BDP1
rs1886714	16	19970009	C	0.625	0.2632	T	0.0008632	4.667	3.0638886	GPR139
rs4813023	20	10142246	T	0.625	0.2632	C	0.0008632	4.667	3.0638886	
rs2071931	1	9251876	A	0.4063	0.1053	G	0.0008636	5.816	3.0636874	H6PD
rs7523762	1	159946268	T	0.4063	0.1053	C	0.0008636	5.816	3.0636874	FCRLA
rs1891019	1	159958057	C	0.4063	0.1053	T	0.0008636	5.816	3.0636874	FCRLB
rs2099380	1	224720875	T	0.4063	0.1053	C	0.0008636	5.816	3.0636874	
rs17066769	8	3494133	G	0.4063	0.1053	A	0.0008636	5.816	3.0636874	CSMD1
rs1002665	9	103669957	A	0.4063	0.1053	G	0.0008636	5.816	3.0636874	
rs10764855	10	130809932	A	0.4063	0.1053	G	0.0008636	5.816	3.0636874	
rs188916	4	188023310	C	0.125	0.4605	T	0.000885	0.1673	3.0530567	
rs4409101	5	42891883	G	0.125	0.4605	A	0.000885	0.1673	3.0530567	
rs7460819	8	136804688	C	0.125	0.4605	T	0.000885	0.1673	3.0530567	
rs12964446	18	73061991	C	0.125	0.4605	A	0.000885	0.1673	3.0530567	
rs1405373	2	52577564	C	0.03125	0.3158	T	0.0008877	0.06989	3.0517338	
rs10519265	15	77715278	A	0.03125	0.3158	G	0.0008877	0.06989	3.0517338	
rs9823776	3	63414374	A	0.4375	0.1316	G	0.0009018	5.133	3.0448898	SYNPR
rs1009848	7	142265373	C	0.4375	0.1316	T	0.0009018	5.133	3.0448898	EPHB6
rs1530599	18	22085647	G	0.4375	0.1316	A	0.0009018	5.133	3.0448898	TAF4B
rs2893630	1	236480543	A	0.5938	0.25	C	0.0009328	4.385	3.0302115	
rs1492523	4	167571796	T	0.5938	0.25	C	0.0009328	4.385	3.0302115	
rs10857379	4	167619466	G	0.5938	0.25	A	0.0009328	4.385	3.0302115	
rs277921	5	71000819	G	0.5938	0.25	A	0.0009328	4.385	3.0302115	
rs10516126	5	174414039	G	0.5938	0.25	A	0.0009328	4.385	3.0302115	
rs1025547	9	8654838	G	0.5938	0.25	T	0.0009328	4.385	3.0302115	PTPRD
rs1649053	10	59991493	G	0.5938	0.25	A	0.0009328	4.385	3.0302115	BICC1
rs8073498	17	7510423	C	0.5938	0.25	A	0.0009328	4.385	3.0302115	
rs1979285	5	172176908	C	0.4688	0.1447	T	0.0009502	5.214	3.022185	
rs4946815	6	107567039	A	0.4688	0.1447	C	0.0009502	5.214	3.022185	
rs1416326	9	102608530	G	0.4688	0.1447	T	0.0009502	5.214	3.022185	
rs4551896	13	109880158	C	0.4688	0.1447	A	0.0009502	5.214	3.022185	
rs2051742	16	27881919	T	0.4688	0.1447	C	0.0009502	5.214	3.022185	

Figure 3

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs9915945	17	6089542	A	0.3636	0.05128	G	1.539E-05	10.57	4.8127614	
rs323391	17	69199193	A	0.4773	0.1154	C	1.732E-05	7	4.7614521	
rs7335910	13	24220725	G	0.09091	0.4615	A	1.775E-05	0.1167	4.7508016	
rs1549599	3	37506369	G	0.6818	0.2692	A	1.852E-05	5.816	4.732359	ITGA9
rs1554983	16	77425340	A	0.3182	0.7179	G	2.387E-05	0.1833	4.6221476	
rs11695174	2	9705766	T	0.2955	0.02564	C	2.682E-05	15.94	4.5715412	
rs1569091	7	94356064	A	0.6136	0.2308	G	3.676E-05	5.294	4.4346245	
rs4794558	17	50702952	A	0.5682	0.1923	G	4.192E-05	5.526	4.3775787	HLF
rs17020744	2	81845572	A	0.25	0.01282	G	4.771E-05	25.67	4.3213906	
rs4326996	15	61567335	G	0.25	0.01282	T	4.771E-05	25.67	4.3213906	
rs1439123	12	97600447	C	0.06818	0.3974	T	5.355E-05	0.1109	4.2712405	APAF1
rs4762507	12	97659769	T	0.04545	0.359	C	5.591E-05	0.08503	4.2525105	ANKS1B
rs17066769	8	3494133	G	0.4318	0.1026	A	6.178E-05	6.65	4.2091521	CSMD1
rs1002665	9	103669957	A	0.4318	0.1026	G	6.178E-05	6.65	4.2091521	
rs6719949	2	220404542	C	0.1364	0.5	T	7.055E-05	0.1579	4.151503	
rs1838990	3	63142891	C	0.1364	0.5	T	7.055E-05	0.1579	4.151503	
rs6481260	10	58633464	C	0.6	0.2162	T	7.238E-05	5.438	4.1403814	
rs11713998	3	168613099	T	0.3636	0.0641	C	7.475E-05	8.343	4.1263888	
rs3802431	9	110932446	G	0.3636	0.0641	A	7.475E-05	8.343	4.1263888	
rs11598274	10	130794532	T	0.3636	0.0641	G	7.475E-05	8.343	4.1263888	
rs4346287	18	60381151	A	0.3636	0.0641	G	7.475E-05	8.343	4.1263888	
rs10814297	9	35900945	A	0.09091	0.4231	G	8.433E-05	0.1364	4.0740179	LOC158376
rs7689639	4	25184635	A	0.02273	0.3026	G	9.583E-05	0.05359	4.0184985	
rs2017041	22	33670103	C	0.1591	0.5128	A	0.0001009	0.1797	3.9961088	
rs10490046	2	40484182	G	0.06818	0.3846	T	0.0001019	0.1171	3.9918258	SLC8A1
rs12857230	13	42654650	G	0.6364	0.2692	T	0.0001046	4.75	3.9804683	
rs7073183	10	58640012	C	0.5682	0.2051	T	0.0001115	5.099	3.9527251	
rs4075196	1	225608852	A	0.1818	0.5385	G	0.0001165	0.1905	3.9336741	
rs1522858	2	79151979	A	0.6818	0.3077	G	0.0001193	4.821	3.9233596	
rs9884594	4	99578341	A	0.6818	0.3077	G	0.0001193	4.821	3.9233596	RAP1GDS1
rs10497714	2	191875525	G	0	0.2436	A	0.000126	0	3.8996295	MYO1B
rs694126	5	32551319	C	0.6591	0.2949	T	0.0001265	4.623	3.8979095	
rs1548518	12	46439262	T	0.6591	0.2949	C	0.0001265	4.623	3.8979095	RAPGEF3
rs171406	3	10358517	G	0.25	0.6154	A	0.0001389	0.2083	3.8572978	ATP2B2
rs1275273	10	58676561	A	0.5682	0.2179	G	0.0001428	4.721	3.8452718	
rs11671104	19	22586526	C	0.2273	0.01282	A	0.0001434	22.65	3.8434508	
rs7813880	8	3499100	T	0.3636	0.07692	G	0.0001458	6.857	3.8362425	CSMD1
rs7901425	10	130778057	C	0.3636	0.07692	T	0.0001458	6.857	3.8362425	
rs1023825	2	79099616	T	0.5909	0.2308	G	0.0001497	4.815	3.8247782	
rs6532729	4	99365459	C	0.5909	0.2308	T	0.0001497	4.815	3.8247782	
rs277973	5	70995578	T	0.5909	0.2308	G	0.0001497	4.815	3.8247782	
rs9569891	13	58048371	T	0.5909	0.2308	C	0.0001497	4.815	3.8247782	
rs6550478	3	37501017	A	0.2955	0.6538	G	0.000163	0.222	3.7878124	ITGA9
rs7081958	10	58606559	A	0.5227	0.1795	G	0.0001652	5.007	3.78199	
rs12242643	10	58615726	C	0.5227	0.1795	T	0.0001652	5.007	3.78199	
rs3213858	5	146760179	T	0.3409	0.0641	C	0.0001773	7.552	3.7512913	DPYSL3
rs820082	6	35139419	A	0.3409	0.0641	G	0.0001773	7.552	3.7512913	ANKS1A
rs12774599	10	130795782	T	0.3409	0.0641	G	0.0001773	7.552	3.7512913	

rs2288726	12	97608518	T	0.06818	0.3718	G	0.0001983	0.1236	3.7026773	APAF1
rs7879330	23	14395566	A	0.4	0.0678	G	0.0002016	9.167	3.6955095	
rs2814734	9	87182609	A	0.02273	0.2821	C	0.0002097	0.0592	3.6784016	
rs10089613	8	122595227	C	0.4545	0.141	T	0.0002118	5.076	3.674074	
rs10520308	2	82003125	C	0.3864	0.08974	A	0.0002196	6.386	3.6583677	
rs1032719	5	7536911	G	0.04545	0.3333	A	0.000223	0.09524	3.6516951	ADCY2
rs16953945	17	4319847	A	0.1818	0.5256	G	0.0002246	0.2005	3.6485902	SPNS3
rs10953428	7	103814099	T	0.1136	0.4359	C	0.0002269	0.1659	3.6441655	LHFPL3
rs1989823	7	103823052	C	0.1136	0.4359	T	0.0002269	0.1659	3.6441655	LHFPL3
rs1865651	2	174015846	C	0.6364	0.2821	T	0.0002278	4.455	3.6424463	
rs6501658	17	69173224	C	0.5	0.1667	T	0.0002281	5	3.6418747	LOC728102
rs11890028	2	166651523	G	0.4773	0.1538	T	0.0002288	5.022	3.640544	
rs2938033	18	43510320	G	0.4773	0.1538	A	0.0002288	5.022	3.640544	
rs12186252	4	6166295	T	0.5227	0.1923	C	0.0002313	4.6	3.6358244	JAKMIP1
rs2808067	10	32085938	A	0.5227	0.1923	G	0.0002313	4.6	3.6358244	
rs3934812	16	87674956	C	0.5227	0.1923	T	0.0002313	4.6	3.6358244	
rs2204630	7	94409268	T	0.6136	0.2692	G	0.0002445	4.311	3.6117211	PPP1R9A
rs2056862	8	88643449	C	0.6136	0.2692	A	0.0002445	4.311	3.6117211	
rs1801783	1	225247481	G	0.04545	0.3205	A	0.0002458	0.101	3.6094181	CDC42BPA
rs1878059	18	42488544	A	0.04545	0.3205	G	0.0002458	0.101	3.6094181	LOC647011
rs5999636	22	33661041	T	0.04545	0.3205	C	0.0002458	0.101	3.6094181	
rs2033860	3	166372514	G	0.2045	0.5513	A	0.0002523	0.2093	3.5980827	
rs3792426	3	166392889	T	0.2045	0.5513	C	0.0002523	0.2093	3.5980827	SLITRK3
rs261861	1	239162199	A	0.6591	0.3077	G	0.0002631	4.35	3.5798792	RGS7
rs17503919	6	89622456	G	0	0.2308	A	0.000264	0	3.5783961	RNGTT
rs940522	3	181194826	T	0	0.2179	G	0.0002812	0	3.5509847	PEX5L
rs10013819	4	25186282	A	0	0.2179	G	0.0002812	0	3.5509847	
rs1535678	9	8499378	C	0.2727	0.03846	A	0.0002874	9.375	3.5415132	PTPRD
rs233557	16	64918319	T	0.2727	0.03846	C	0.0002874	9.375	3.5415132	
rs7974562	12	114502535	T	0.2727	0.6282	C	0.0002907	0.2219	3.536555	
rs10198974	2	41350234	C	0.6818	0.3333	T	0.0002929	4.286	3.5332806	
rs6085283	20	580959	T	0.6818	0.3333	C	0.0002929	4.286	3.5332806	SRXN1
rs2066593	13	49619118	C	0.6364	0.2949	T	0.0002971	4.185	3.5270973	
rs12904249	15	23622445	A	0.6364	0.2949	G	0.0002971	4.185	3.5270973	ATP10A
rs4688381	3	63202226	A	0.1364	0.4615	G	0.0002986	0.1842	3.5249102	
rs2894401	6	35516937	A	0.1364	0.4615	G	0.0002986	0.1842	3.5249102	
rs13274046	8	116082698	T	0.1364	0.4615	C	0.0002986	0.1842	3.5249102	
rs33053	3	161084457	T	0.09091	0.3974	C	0.0003098	0.1516	3.5089186	SCHIP1
rs1596860	13	24293067	G	0.09091	0.3974	A	0.0003098	0.1516	3.5089186	RNF17
rs9507425	13	24338318	A	0.09091	0.3974	G	0.0003098	0.1516	3.5089186	RNF17
rs12622579	2	41352004	C	0.7045	0.359	T	0.0003155	4.258	3.5010006	
rs10506125	12	37406554	T	0.2955	0.641	C	0.0003155	0.2348	3.5010006	CPNE8
rs11672145	19	12361149	G	0.5682	0.2308	T	0.0003199	4.386	3.4949858	ZNF799
rs6747268	2	209355227	G	0.7727	0.4359	T	0.0003268	4.4	3.485718	
rs11770288	7	94355331	T	0.5455	0.2179	C	0.0003284	4.306	3.4835969	
rs10839595	11	6676762	A	0.7273	0.3846	G	0.0003292	4.267	3.4825402	
rs6632863	23	16592583	C	0.6286	0.2373	T	0.0003563	5.44	3.4481842	CTPS2
rs6875512	5	31367532	C	0.5	0.1795	A	0.0003566	4.571	3.4478187	
rs3098360	10	58495356	C	0.5	0.1795	T	0.0003566	4.571	3.4478187	
rs12918939	16	64698060	G	0.3409	0.07692	A	0.0003627	6.207	3.4404524	
rs4746004	10	71228236	G	0.02273	0.2692	A	0.0004014	0.06312	3.3964226	

rs1275828	14	69271895	G	0.02273	0.2692	A	0.0004014	0.06312	3.3964226	
rs4704050	5	70829327	G	0.5909	0.2564	A	0.0004061	4.189	3.391367	BDP1
rs11246756	12	130743401	G	0.5909	0.2564	T	0.0004061	4.189	3.391367	
rs4813023	20	10142246	T	0.5909	0.2564	C	0.0004061	4.189	3.391367	
rs7920439	10	13332410	T	0.2045	0.01282	G	0.0004192	19.8	3.3775787	
rs12418369	11	4621018	A	0.2045	0.01282	G	0.0004192	19.8	3.3775787	
rs7326004	13	107155619	T	0.2045	0.01282	C	0.0004192	19.8	3.3775787	LOC728215
rs2034127	3	59343114	A	0.3182	0.0641	G	0.0004221	6.813	3.3745846	
rs7628370	3	59345640	C	0.3182	0.0641	A	0.0004221	6.813	3.3745846	
rs7581	9	110819068	G	0.3182	0.0641	A	0.0004221	6.813	3.3745846	C9orf5
rs627432	13	28430501	T	0.3182	0.0641	C	0.0004221	6.813	3.3745846	
rs799467	14	34571253	C	0.3182	0.0641	T	0.0004221	6.813	3.3745846	
rs9924119	16	69900898	C	0.3182	0.0641	T	0.0004221	6.813	3.3745846	
rs11653735	17	77802222	T	0.3182	0.0641	C	0.0004221	6.813	3.3745846	CSNK1D
rs13269936	8	25994155	G	0.06818	0.3462	T	0.0004266	0.1382	3.3699791	
rs9553435	13	24235300	A	0.06818	0.3462	C	0.0004266	0.1382	3.3699791	RNF17
rs642407	5	32542605	A	0.1591	0.4744	G	0.000437	0.2096	3.3595186	
rs495487	11	78709319	G	0.1591	0.4744	A	0.000437	0.2096	3.3595186	
rs625061	11	102537638	G	0.1136	0.4231	T	0.0004391	0.1748	3.3574366	DYNC2H1
rs4600965	4	157364111	G	0.1818	0.5128	A	0.00044	0.2111	3.3565473	
rs2795492	9	99953197	A	0.1818	0.5128	G	0.00044	0.2111	3.3565473	CORO2A
rs2680700	17	53795541	A	0.6136	0.2778	C	0.0004546	4.129	3.3423706	RNF43
rs7823558	8	101948774	G	0.4091	0.1154	A	0.0004597	5.308	3.3375255	
rs6481254	10	58586765	A	0.4091	0.1154	C	0.0004597	5.308	3.3375255	
rs7089692	10	58603555	C	0.4091	0.1154	T	0.0004597	5.308	3.3375255	
rs5980319	23	16611686	G	0.6286	0.2542	A	0.0004612	4.964	3.3361107	CTPS2
rs1432180	2	81933368	A	0.3636	0.08974	G	0.0004786	5.796	3.3200273	
rs13144587	4	67295867	C	0.3636	0.08974	A	0.0004786	5.796	3.3200273	
rs4945442	11	80244906	A	0.5455	0.2143	G	0.000486	4.4	3.3133637	
rs4920935	5	116134125	G	0.4091	0.1184	A	0.0004872	5.154	3.3122927	
rs391224	3	37498640	T	0.6136	0.2821	C	0.0004924	4.043	3.307682	ITGA9
rs191649	18	31332044	G	0.6136	0.2821	A	0.0004924	4.043	3.307682	C18orf37
rs10082587	11	132762982	A	0.1136	0.4103	G	0.0004987	0.1843	3.3021606	OPCML
rs2760912	13	49630676	A	0.1136	0.4103	G	0.0004987	0.1843	3.3021606	
rs4949509	1	30124116	C	0.4545	0.1538	T	0.0005011	4.583	3.3000756	
rs172823	3	25331332	T	0.4545	0.1538	C	0.0005011	4.583	3.3000756	
rs10499030	6	100851002	T	0.4545	0.1538	C	0.0005011	4.583	3.3000756	
rs7122962	11	123818932	A	0.4545	0.1538	G	0.0005011	4.583	3.3000756	
rs876144	14	34536335	C	0.4545	0.1538	A	0.0005011	4.583	3.3000756	SRP54
rs4765821	12	1482107	T	0.2045	0.5385	G	0.0005023	0.2204	3.2990368	
rs2066910	22	41859461	C	0.2045	0.5385	T	0.0005023	0.2204	3.2990368	MCAT
rs4140754	2	41372882	A	0.1818	0.5	G	0.0005027	0.2222	3.2986911	
rs2927633	5	73816540	A	0.1818	0.5	G	0.0005027	0.2222	3.2986911	
rs10764851	10	130807814	C	0.1818	0.5	T	0.0005027	0.2222	3.2986911	
rs1173179	5	4856549	T	0.2857	0.6282	G	0.0005065	0.2367	3.2954206	
rs2893721	10	58623966	G	0.5227	0.2051	A	0.000509	4.244	3.2932822	
rs4713842	6	35302610	G	0	0.2051	A	0.0005225	0	3.2819137	SCUBE3
rs4713843	6	35311723	T	0	0.2051	C	0.0005225	0	3.2819137	SCUBE3
rs707969	6	35397424	A	0	0.2051	G	0.0005225	0	3.2819137	DEF6
rs16913276	11	13838859	A	0	0.2051	G	0.0005225	0	3.2819137	LOC729147
rs4303985	4	99618771	T	0.6591	0.3205	G	0.0005545	4.099	3.2560984	TSPAN5

rs10506126	12	37409511	A	0.6591	0.3205	G	0.0005545	4.099	3.2560984	CPNE8
rs2073835	9	135522004	T	0.2045	0.5256	C	0.0005567	0.2321	3.2543788	SARDH
rs16943741	15	84079483	G	0.2045	0.5256	A	0.0005567	0.2321	3.2543788	AKAP13
rs8091335	18	31282121	C	0.6667	0.3333	A	0.0005589	4	3.2526659	
rs2373001	2	37451925	C	0.1591	0	T	0.0005721		3.2425281	QPCT
rs6758414	2	121012955	A	0.1591	0	G	0.0005721		3.2425281	
rs2361323	12	51201099	A	0.1591	0	G	0.0005721		3.2425281	
rs9520550	13	107135055	A	0.1591	0	G	0.0005721		3.2425281	LOC728215
rs7320808	13	107138864	T	0.1591	0	C	0.0005721		3.2425281	LOC728215
rs4113420	13	107154330	T	0.1591	0	C	0.0005721		3.2425281	LOC728215
rs10520223	2	79081765	A	0.6364	0.3077	G	0.0005747	3.938	3.2405588	
rs12614588	2	79082779	C	0.6364	0.3077	T	0.0005747	3.938	3.2405588	
rs12510203	4	129696979	C	0.6364	0.3077	T	0.0005747	3.938	3.2405588	
rs1405842	7	94356931	G	0.3636	0.6923	A	0.0005747	0.254	3.2405588	
rs1527676	7	94403058	A	0.6364	0.3077	G	0.0005747	3.938	3.2405588	PPP1R9A
rs870431	12	37239340	G	0.6364	0.3077	A	0.0005747	3.938	3.2405588	
rs11376	14	50274746	G	0.2273	0.5526	A	0.0005778	0.2381	3.2382225	NIN
rs1021813	3	59388100	C	0.1364	0.4487	T	0.0005799	0.194	3.2366469	
rs6536157	4	157340270	T	0.1364	0.4487	C	0.0005799	0.194	3.2366469	
rs6469563	8	116079356	T	0.1364	0.4487	C	0.0005799	0.194	3.2366469	
rs547043	23	150087901	A	0.6571	0.2881	G	0.0005936	4.735	3.2265061	
rs10495026	1	214767553	C	0.6818	0.3462	T	0.0005941	4.048	3.2261404	ESRRG
rs12696221	3	166354274	G	0.6818	0.3462	A	0.0005941	4.048	3.2261404	
rs809845	13	49622056	T	0.3182	0.6538	C	0.0005941	0.2471	3.2261404	
rs738118	2	41376902	G	0.2273	0.5513	A	0.0005965	0.2394	3.2243896	
rs2858	5	173889562	G	0.2273	0.5513	T	0.0005965	0.2394	3.2243896	
rs4346964	8	99421813	G	0.09091	0.3846	A	0.0006092	0.16	3.2152401	
rs1865874	8	116106295	G	0.09091	0.3846	A	0.0006092	0.16	3.2152401	
rs2511887	11	86275132	A	0.2955	0.6282	G	0.0006191	0.2482	3.2082392	
rs712306	14	34465568	G	0.7045	0.3718	T	0.0006191	4.029	3.2082392	
rs672856	18	210658	G	0.25	0.5769	A	0.0006206	0.2444	3.2071882	THOC1
rs16864725	3	190890138	A	0.2273	0.02564	G	0.0006218	11.18	3.2063493	TP63
rs883073	7	22150784	A	0.2273	0.02564	G	0.0006218	11.18	3.2063493	RAPGEF5
rs4500599	13	57753504	C	0.2273	0.02564	A	0.0006218	11.18	3.2063493	
rs6451438	5	39673322	C	0.2727	0.6026	T	0.0006282	0.2473	3.2019021	
rs7281481	21	45621434	G	0.2727	0.6026	A	0.0006282	0.2473	3.2019021	
rs2466066	8	32557958	T	0.4773	0.1711	C	0.0006304	4.425	3.2003838	NRG1
rs10972619	9	35898488	G	0.1364	0.4359	A	0.0006383	0.2043	3.1949752	LOC158376
rs9309717	2	3474085	G	0.09091	0.3718	A	0.0006437	0.169	3.1913165	
rs721250	2	59630520	G	0.6591	0.3333	A	0.0006486	3.867	3.1880231	
rs6853651	4	157343816	A	0.6591	0.3333	C	0.0006486	3.867	3.1880231	
rs2340252	4	157348668	A	0.6591	0.3333	C	0.0006486	3.867	3.1880231	
rs5944265	23	25937892	A	0.2	0	C	0.000657		3.1824346	
rs563002	1	112118658	C	0.4091	0.1282	T	0.0006579	4.708	3.1818401	KCND3
rs13639	2	41957833	T	0.4091	0.1282	G	0.0006579	4.708	3.1818401	
rs2141599	3	178325169	T	0.5455	0.2308	C	0.0006797	4	3.1676827	TBL1XR1
rs11953826	5	174410242	C	0.5455	0.2308	A	0.0006797	4	3.1676827	
rs1441234	2	41341895	G	0.6818	0.359	A	0.0007103	3.827	3.1485582	
rs6472054	8	49881005	C	0.6818	0.359	T	0.0007103	3.827	3.1485582	
rs2094394	9	36692096	C	0.6818	0.359	T	0.0007103	3.827	3.1485582	
rs197419	1	112116973	C	0.5682	0.2436	A	0.0007253	4.086	3.1394823	

rs777354	2	166260054	A	0.5682	0.2436	G	0.0007253	4.086	3.1394823	TTC21B
rs11067819	12	114810647	G	0.5682	0.2436	A	0.0007253	4.086	3.1394823	
rs2075379	12	29707647	G	0.25	0.03846	A	0.0007612	8.333	3.1185012	TMTC1
rs12957214	18	35189538	C	0.25	0.03846	A	0.0007612	8.333	3.1185012	
rs5752585	22	26266871	A	0.25	0.03846	C	0.0007612	8.333	3.1185012	
rs4949503	1	30102287	C	0.4773	0.1795	T	0.0007642	4.174	3.116793	
rs4949507	1	30110659	A	0.4773	0.1795	C	0.0007642	4.174	3.116793	
rs4504262	4	96428827	T	0.4773	0.1795	G	0.0007642	4.174	3.116793	UNC5C
rs2767001	9	112623833	A	0.4773	0.1795	G	0.0007642	4.174	3.116793	
rs5970533	23	150005809	T	0.1429	0.4915	C	0.0007679	0.1724	3.1146953	
rs7711344	5	117758026	A	0.06818	0.3333	C	0.0007714	0.1463	3.1127204	
rs10454357	8	26008080	G	0.06818	0.3333	A	0.0007714	0.1463	3.1127204	
rs16932803	9	35951087	T	0.06818	0.3333	G	0.0007714	0.1463	3.1127204	
rs1430475	14	81710262	A	0.02273	0.25	G	0.0007722	0.06977	3.1122702	
rs7316843	12	69736078	C	0.1591	0.4615	T	0.0007743	0.2207	3.1110907	
rs9814318	3	63136521	T	0.1591	0.4605	C	0.0007813	0.2216	3.1071822	
rs17528049	1	225258279	C	0.02273	0.2564	A	0.0007876	0.06744	3.1036943	CDC42BPA
rs13132933	4	123230037	C	0.02273	0.2564	T	0.0007876	0.06744	3.1036943	
rs1490819	5	67135554	T	0.02273	0.2564	C	0.0007876	0.06744	3.1036943	
rs1388122	5	67136012	G	0.02273	0.2564	A	0.0007876	0.06744	3.1036943	
rs1490822	5	67137077	G	0.02273	0.2564	A	0.0007876	0.06744	3.1036943	
rs991264	15	52063843	T	0.1905	0.5128	C	0.0007898	0.2235	3.1024829	
rs1864551	2	79620045	A	0.3636	0.1026	G	0.0007983	5	3.0978339	CTNNA2
rs12186253	4	6166347	T	0.3636	0.1026	C	0.0007983	5	3.0978339	JAKMIP1
rs10764855	10	130809932	A	0.3636	0.1026	G	0.0007983	5	3.0978339	
rs2068099	3	46524308	T	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	
rs10078211	5	57999775	T	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	RAB3C
rs17435904	8	71017763	T	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	
rs10742158	11	26714051	A	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	
rs11656239	17	9891392	T	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	GAS7
rs1997810	20	11972709	T	0.04545	0.2949	C	0.0008386	0.1139	3.0764451	
rs2356417	16	69913636	C	0.3095	0.06579	T	0.0008571	6.366	3.0669685	
rs449095	4	103332760	A	0.5	0.1923	G	0.0008596	4.2	3.0657036	
rs823922	9	103697095	A	0.5	0.1923	C	0.0008596	4.2	3.0657036	
rs3761966	5	70836231	T	0.5682	0.2564	C	0.0008616	3.816	3.0646943	BDP1
rs3808899	9	124032645	T	0.5682	0.2564	C	0.0008616	3.816	3.0646943	
rs1946977	4	187686129	G	0.04762	0.3077	T	0.0008631	0.1125	3.0639389	
rs1323690	11	34457263	T	0.5909	0.2692	C	0.0008685	3.921	3.0612302	ELF5
rs1886714	16	19970009	C	0.5909	0.2692	T	0.0008685	3.921	3.0612302	GPR139
rs6092527	20	55746462	A	0.5909	0.2692	G	0.0008685	3.921	3.0612302	
rs1538389	1	112128667	A	0.3182	0.07692	G	0.0008767	5.6	3.057149	KCND3
rs4839168	1	112144032	T	0.3182	0.07692	C	0.0008767	5.6	3.057149	KCND3
rs631037	1	112145890	A	0.3182	0.07692	G	0.0008767	5.6	3.057149	KCND3
rs10979638	9	110784592	C	0.3182	0.07692	A	0.0008767	5.6	3.057149	CTNNAL1
rs2039372	10	130790379	C	0.3182	0.07692	T	0.0008767	5.6	3.057149	
rs12778834	10	130792327	A	0.3182	0.07692	C	0.0008767	5.6	3.057149	
rs726207	20	15962926	T	0.3182	0.07692	G	0.0008767	5.6	3.057149	MACROD2
rs9570815	13	62759990	C	0.1136	0.3974	A	0.0008844	0.1944	3.0533513	
rs1886779	14	32728645	C	0.1136	0.3974	T	0.0008844	0.1944	3.0533513	NPAS3
rs7049850	23	16607104	C	0.6286	0.2586	T	0.0008857	4.851	3.0527134	CTPS2
rs10112994	8	116016470	C	0.1818	0.4872	T	0.0009002	0.2339	3.045661	

rs10846577	12	122966214	C	0.1818	0.4872	T	0.0009002	0.2339	3.045661	
rs2423413	20	9606534	C	0.1818	0.4872	T	0.0009002	0.2339	3.045661	PAK7
rs12451131	17	3365426	T	0.619	0.2973	C	0.0009006	3.841	3.0454681	TRPV3
rs5936422	23	147619197	A	0.4286	0.1186	G	0.0009536	5.571	3.0206338	AFF2
rs930516	13	70225002	T	0.3864	0.1154	C	0.0009565	4.827	3.019315	
rs6063739	20	50065209	C	0.3864	0.1154	A	0.0009565	4.827	3.019315	
rs12776148	10	130803689	C	0.3095	0.06757	T	0.0009808	6.186	3.0084195	
rs4957661	5	105922009	T	0.2045	0.5132	C	0.0009842	0.244	3.0069166	
rs1980977	21	45640447	A	0.2045	0.5132	G	0.0009842	0.244	3.0069166	
rs12540943	7	151141463	A	0.2955	0.0641	G	0.0009958	6.123	3.0018279	PRKAG2
rs12155715	8	19270615	C	0.2955	0.0641	T	0.0009958	6.123	3.0018279	SH2D4A
rs725076	10	105571255	C	0.2955	0.0641	A	0.0009958	6.123	3.0018279	SH3PXD2A
rs11111712	12	102605853	T	0.2955	0.0641	C	0.0009958	6.123	3.0018279	STAB2
rs906363	1	210925420	G	0	0.1923	A	0.0009968	0	3.001392	SNFT
rs4692399	4	25760155	A	0	0.1923	G	0.0009968	0	3.001392	
rs16871870	5	73778817	C	0	0.1923	A	0.0009968	0	3.001392	
rs6581016	12	53744697	A	0	0.1923	C	0.0009968	0	3.001392	
rs7146578	14	69237392	G	0	0.1923	A	0.0009968	0	3.001392	KIAA0247
rs3784556	15	72119241	T	0	0.1923	G	0.0009968	0	3.001392	PML

Figure 4.
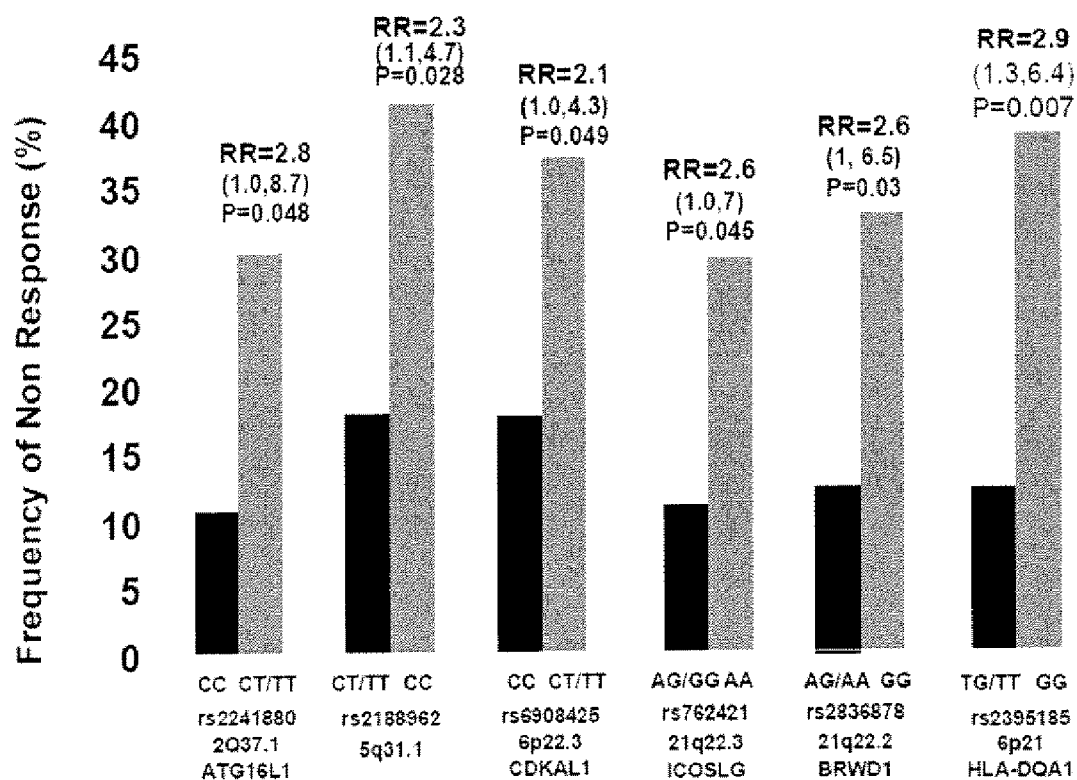
Figure 5.
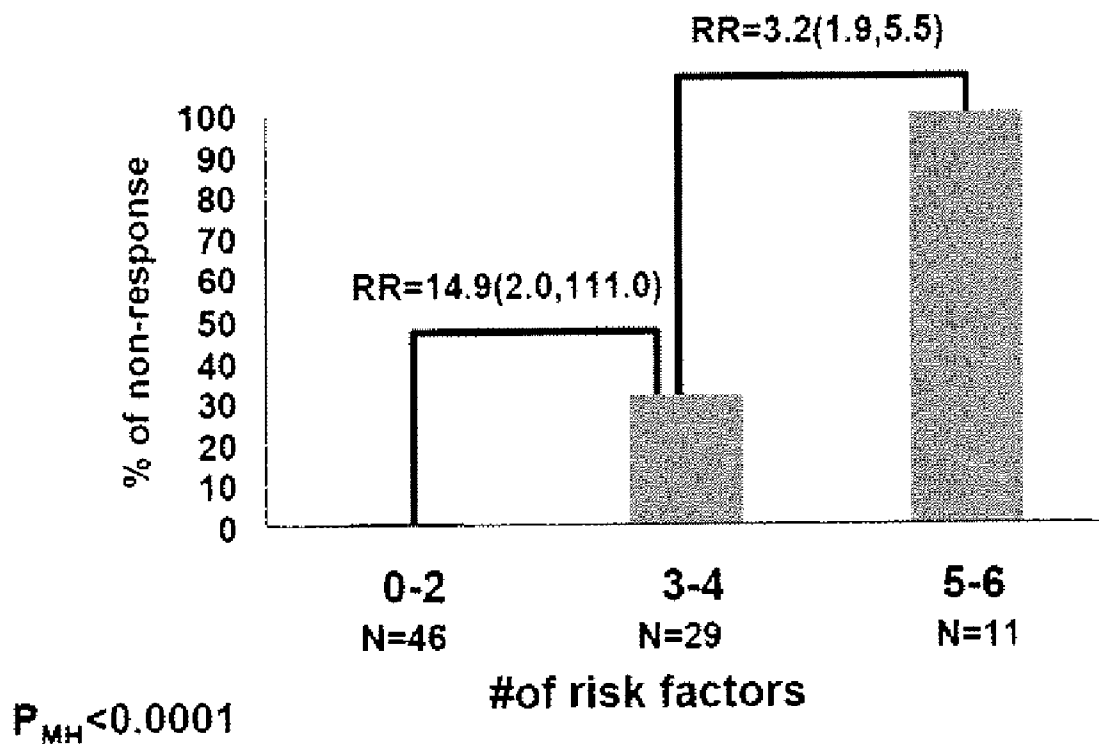
METHODS OF DETERMINING RESPONSIVENESS TO ANTI-TNF ALPHA THERAPY IN INFLAMMATORY BOWEL DISEASE

GOVERNMENT RIGHTS

[0001] This invention was made with government support under Contract Nos. P01 DK046763, M01 RR00425 and DK063491 awarded by the National Institutes of Health. The government has certain rights in the invention.

FIELD OF THE INVENTION

[0002] The invention relates generally to the field of inflammatory bowel disease and, more specifically, to genetic methods for diagnosing, prognosing, and treating inflammatory bowel disease.

BACKGROUND

[0003] All publications herein are incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference. The following description includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

[0004] Natural history observations in both early and later onset inflammatory bowel disease (IBD) have prompted the increasing use of anti-TNFα therapy for IBD patients. Various past studies have demonstrated that infliximab has the potential to be effective for the induction and maintenance response and remission in some CD patients. However, the clinical trial data for all anti-TNFα therapies among adult CD patients report that 40% of patients do not respond to the induction phase (primary non-responder) and that approximately 40% of those patients who do enter the maintenance phase of the trial lose response over time. The pediatric REACH trial, for example, reported that close to 90% of children responded to induction, suggesting a more robust acute response to anti-TNFα therapy in children as compared to adults with CD. This primary response outcome did not, however, require children to have weaned corticosteroids to meet response criteria. This would be a more clinically robust outcome definition given that the importance of steroid sparing in the induction and maintenance phase of these therapies. Moreover, approximately 40% of children, like their adult counterparts, who entered the maintenance phase lost response and were no longer in remission and off steroids at 12 months. More studies are needed to assess the true incidence of primary non-response in children in a non clinical trial setting. The adult UC trials (ACT 1 and ACT 2) reported similar response rates among adult UC patients receiving infliximab as the CD trials. Infliximab is being used off label in children with UC and the official clinical trial for indication is currently underway. There are many differences in the patient population and outcome measures making a comparison across trials difficult and hard to interpret.

[0005] Inter-individual variability in therapeutic response may be best explained by genetic variability as it relates to disease pathogenesis and mechanism of action of this class of therapies. Other than NOD2 and IBD5, IBD susceptibility genes identified via genome wide linkage approach or Genome Wide Association Studies (GWAS) have not been evaluated as predictors of response to anti-TNFα therapies. NOD2 was not found to be associated with therapeutic response to infliximab in these limited studies. It is conceivable that disease susceptibility genes do not influence the ultimate response to therapeutic targets given the multifactorial influences on disease and the relatively unknown functionality of these susceptibility genes. However, the GWAS approach, which identifies portions of the genome that contain genetic variants associated with specific phenotypes, can also identity novel variants that contribute to therapeutic outcome i.e. discovery of genetic loci that are responsible for the mechanism of altered drug response, such as to anti-TNFα. There may also be important non genetic factors that influence or modify primary response to anti-TNFα. Among the serologic immune responses, pANCA has been shown to be negatively associated with primary response in both CD and UC patients. PANCA is present in both CD and UC and defines a specific colitis phenotype suggesting a degree of overlap in the underlying pathway biology of these two disease subtypes. Other than duration of disease at initiation of therapy, there are likely important clinical and demographic variables that also influence therapeutic outcomes. To date, however, it remains unknown whether these are independent of genetic variability. Thus, there is a need in the art to study associations of known IBD susceptibility loci as well as novel loci identified by pharmacogenetic GWAS with anti-TNFα response in pediatric IBD patients, and to develop predictive models of anti-TNFα primary non-response using clinical phenotype, serologic and genetic variables.

BRIEF DESCRIPTION OF THE FIGURES

[0006] Exemplary embodiments are illustrated in referenced figures. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0007] FIG. 1 depicts, in accordance with embodiments herein, associations of genetic variants with primary non-response to anti-TNFα therapy as the outcome in patients with IBD. Results of SNPs with significance $>10^{-3}$

[0008] FIG. 2 depicts, in accordance with embodiments herein, associations of genetic variants with secondary loss of response to anti-TNFα therapy as the outcome in patients with IBD.

[0009] FIG. 3 depicts, in accordance with embodiments herein, associations of genetic variants with failure for any reason to anti-TNFα therapy as the outcome in patients with IBD.

[0010] FIG. 4 depicts, in accordance with embodiments herein, genotype associations of known IBD susceptibility loci with primary non-response. The dominant rare allele model (i.e. presence of the rare allele) was assumed for the statistical analyses). The relative risk (RR) and frequency of non-response are shown for the genotypes for each locus that met p value significance in univariate analysis.

[0011] FIG. 5 depicts, in accordance with embodiments herein, relative risk (RR) of non-response based on number of risk factors derived from Model V (the most general model). Risk of non response was compared between patients with 2 or less risk factors as compared to 3-4 markers and then as compared to at least 5 of the 6 risk factors for non-response.

SUMMARY OF THE INVENTION

[0012] Various embodiments include a method of determining a high risk relative to a normal subject of non-respon-

siveness to treatment with an anti tumor necrosis actor alpha (TNFα) therapy in an individual, comprising obtaining a sample from the individual, assaying the sample for the presence or absence of one or more genetic and/or serological risk factors, and determining the high risk relative to a normal subject of non-responsiveness to the anti TNFα therapy based on the presence of one or more risk factors carried by the individual. In another embodiment, the presence of each genetic and/or serological risk factor has an additive effect on increasing the risk of non-responsiveness in the individual. In another embodiment, the individual is diagnosed with inflammatory bowel disease (IBD). In another embodiment, the individual is diagnosed with ulcerative colitis (UC). In another embodiment, the individual is a child. In another embodiment, the one or more genetic risk factors comprise genetic variants at the loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1). In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 1, SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID NO.: 4, SEQ. ID. NO 5 and/or SEQ. ID. NO.: 6. In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 7, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, SEQ. ID. NO.: 10, SEQ. ID. NO.: 11, SEQ. ID. NO.: 12, SEQ. ID. NO.: 13, SEQ. ID. NO.: 14, SEQ. ID. NO.: 15, and/or SEQ. ID. NO.: 16. In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 17, SEQ. ID. NO.: 8, SEQ. ID. NO.: 19, and/or SEQ. ID. NO.: 6. In another embodiment, the one or more genetic risk factors comprise genetic variants at the loci of ATG16, Orf13, inducible T-cell co-stimulator ligand (ICOSLG) and/or major histocompatibility complex class II DQ alpha 1 (HLADQA1). In another embodiment, one of the one or more serological risk factors comprise perinuclear anti-neutrophil cytoplasmic antibody (pANCA). In another embodiment, the anti TNFα therapy comprises infliximab. In another embodiment, the anti TNFα therapy comprises cyclosporin.

[0013] Other embodiments include a method of determining a significant likelihood of responsiveness to treatment with anti tumor necrosis factor alpha (TNF-α) therapy in an individual, comprising obtaining a sample from the individual assaying the sample for the presence of one or more serological markers associated with responsiveness to anti TNFα therapy, and determining a significant likelihood of responsiveness based on the presence of one or more serological markers associated with responsiveness to anti TNFα therapy. In another embodiment, the individual is diagnosed with inflammatory bowel disease (IBD). In another embodiment, the individual is diagnosed with ulcerative colitis (UC). In another embodiment, the individual is a child. In another embodiment, one of the one or more serological markers comprises anti-*saccharomyces cerevisiae* antibodies (ASCA).

[0014] Other embodiments include a method of predicting a high risk relative to a normal subject of non-responsiveness to anti tumor necrosis factor alpha (TNF-α) therapy in an individual with inflammatory bowel disease (IBD), comprising determining the presence or absence of one or more nonresponsive genetic risk variants, determining the presence or absence of positive expression of perinuclear anti-neutrophil cytoplasmic antibody (pANCA), determining the presence or absence of an ulcerative colitis phenotype, and predicting a high risk relative to a normal subject of non

responsiveness to anti TNF-α therapy based on the presence of one or more responsive risk variants, the presence of positive expression of pANCA, and/or the presence of the ulcerative colitis phenotype. In another embodiment, one of the one or more nonresponsive genetic risk variants comprise variants at the genetic loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1). In another embodiment, the high risk relative to a normal subject of non-responsiveness comprises a range of 7 to 10 fold increase in risk of non-responsiveness to treatment with anti TNFα therapy.

[0015] Various embodiments include a method of diagnosing an inflammatory bowel disease (IBD) subtype in an individual, comprising obtaining a sample from the individual, assaying the sample for the presence or absence of one or more genetic and/or serological risk factors of nonresponsiveness to anti TNFα therapy, and diagnosing the IBD subtype based upon the presence of one or more genetic and/or serological risk factors of nonresponsiveness to anti TNFα therapy. In another embodiment, the individual is a child. In another embodiment, the one or more genetic risk factors comprise genetic variants at the loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1). In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 1, SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID NO.: 4, SEQ. ID. NO.: 5 and/or SEQ. ID. NO.: 6. In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 7, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, SEQ. ID. NO.: 10, SEQ. ID. NO.: 11, SEQ. ID. NO.: 12, SEQ. ID, NO.: 13, SEQ. ID. NO.: 14, SEQ. ID. NO.: 15, and/or SEQ. ID. NO.: 16. In another embodiment, the one or more genetic risk factors comprise SEQ. ID. NO.: 17, SEQ. ID. NO.: 8, SEQ. ID. NO.: 19, and/or SEQ. ID. NO.: 6. In another embodiment, one of the one or more serological risk factors comprise perinuclear anti-neutrophil cytoplasmic antibody (pANCA).

[0016] Other embodiments include a method of treating an individual, comprising diagnosing the individual as susceptible to non-responsiveness to anti tumor necrosis factor alpha (TNF-α) therapy, and treating the individual. In another embodiment, treating the individual comprises administering a therapeutically effective dosage of natalizumab. In another embodiment, the individual has inflammatory bowel disease (IBD),

[0017] Other features and advantages of the invention will become apparent from the following detailed description, taken in conjunction with the accompanying drawings, which illustrate, by way of example, various embodiments of the invention.

DESCRIPTION OF INVENTION

[0018] All references cited herein are incorporated by reference in their entirety as though fully set forth. Unless defined otherwise, technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Singleton et al., *Dictionary of Microbiology and Molecular Biology* 2nd ed., J. Wiley & Sons (New York, N.Y. 1994); March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure* 4th ed., J. Wiley & Sons (New York, N.Y.

1992); and Sambrook and Russel, *Molecular Cloning: A Laboratory Manual* 3rd ed., Cold Spring Harbor Laboratory Press (Cold Spring Harbor, N.Y. 2001), provide one skilled in the art with a general guide to many of the terms used in the present application.

[0019] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described.

[0020] One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. Indeed, the present invention is in no way limited to the methods and materials described.

[0021] "IBD" as used herein is an abbreviation of inflammatory bowel disease.

[0022] "CD" as used herein is an abbreviation of Crohn's Disease.

[0023] "UC" as used herein is an abbreviation of ulcerative colitis.

[0024] "GWA" as used herein is an abbreviation of genome wide associations.

[0025] "IFX" as used herein is an abbreviation of infliximab.

[0026] "TNFα" as used herein is an abbreviation of tumor necrosis factor alpha.

[0027] "SNP" as used herein is an abbreviation of single-nucleotide polymorphism

[0028] "ATI" as used herein is an abbreviation of anti infliximab antibodies.

[0029] "CDAI" as used herein is an abbreviation of Crohn's Disease activity index.

[0030] "PCDAI" as used herein is an abbreviation of pediatric Crohn's Disease activity index.

[0031] "pANCA" as used herein is an abbreviation of peri-nuclear anti-neutrophil cytoplasmic antibodies.

[0032] "RSCA" as used herein is an abbreviation of Anti-*Saccharomyces cerevisiae* antibodies.

[0033] As used herein, the term "biological sample" means any biological material from which nucleic acid molecules can be prepared. As non-limiting examples, the term material encompasses whole blood, plasma, saliva, cheek swab, or other bodily fluid or tissue that contains nucleic acid.

[0034] As used herein, the term "normal subject" means an individual who has an average likelihood of successful treatment.

[0035] As used herein, the term "positive likelihood ratio of non-response" means the value that when multiplied by the odds of non-responsiveness in a normal subject yields the total odds of non-responsiveness in an individual.

[0036] As readily apparent to one of skill in the art, any number of examples may be used for various genetic loci and variants described herein and the invention is in no way limited to specific examples of sequences used and described herein. For example, SNPs rs2241880, rs2188962, rs3764147, rs762421, rs9271568, rs2836878, described herein as SEQ. ID. NO.: 1, SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID NO.: 4, SEQ. ID. NO.: 5, and SEQ. ID. NO.: 6, respectively, are not limited to the specific sequences described and various additional genetic sequences may also be used while still containing the relevant allele. Similarly, as apparent to one of skill in the art, various examples of sequences may be used to represent SNPs rs13079040,

rs4855535, rs17048128, rs17048129, rs17039556, rs12640159, rs880330, rs2057917, rs2983478, rs4776127, rs975664, rs6100556, and rs2836878, and thus the aforementioned genetic variants are not specifically limited to the sequences described herein as SEQ. ID. NO.: 7, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, SEQ. ID. NO.: 10, SEQ. ID. NO.: 11, SEQ. ID. NO.: 12, SEQ. ID. NO.: 13, SEQ. ID. NO.: 14, SEQ. ID. NO.: 15, and SEQ. ID. NO.: 16, SEQ. ID. NO.: 17, and SEQ. ID. NO.: 19, respectively.

[0037] As further described herein, inter-individual variation in response to anti-TNFα therapy may be explained by genetic variability in disease pathogenesis or mechanism of action. Recent genome wide association studies (GWAS) in IBD have increased understanding of the genetic susceptibility to IBD.

[0038] As described herein, the inventors have developed various predictive models, including a predicted model of primary response by testing associations of known IBD susceptibility loci and novel "pharmacogenetic" GWAS identified loci with primary non-response to anti-TNFα in pediatric IBD patients. Primary non response was defined using the HBI for CD and partial Mayo score for UC. Genotyping was performed using the lumina Infinium platform. Chi square analysis tested associations of phenotype and genotype with primary non-response. Genetic associations were identified by testing known IBD susceptibility loci and by performing a GWAS for primary non-response. Step-wise multiple logistic regression was performed to build predictive models.

[0039] As further described herein, non-response occurred in 22 of 94 subjects. Six known susceptibility loci were associated with primary non-response (p<0.05). The 21q22.2/BRWDI loci remained significant in the predictive model. The most predictive model included 3 novel "pharmacogenetic" GWAS loci, previously identified BRWD1, pANCA and a UC diagnosis (R^2=0.82 and AUC=0.98%). The relative risk of non-response increased 15 fold when number of risk factors increased from 0-2 to ≧3.

[0040] As further disclosed herein, the inventors have described the combination of phenotype and genotype as most predictive of primary non response to anti-TNFα in pediatric IBD. Defining predictors of response to anti-TNFα allows the identification of patients who will not benefit from this class of therapy.

[0041] In one embodiment, the present invention provides a method of evaluating the prognosis of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the presence or absence of a non-response genetic variant and/or non-response serological marker, where the presence of the non-response genetic variant and/or non-response serological marker is indicative of inflammatory bowel disease that is non-responsive to anti-TNFα therapy. In another embodiment, the non-response genetic variant and/or non response serological marker is described in Tables 1, 2 and/or 3(A)-(D). In another embodiment, the non-response genetic variant is at the genetic loci of ATG16, Orfl3, ICOSLG, HLADQA1 and/or BRWD1. In another embodiment, the non-response serological marker is pANCA. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0042] In one embodiment, the present invention provides a method of evaluating the prognosis of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the presence or absence of a non-re-

sponse genetic variant and/or a response serological marker, where the absence of the non-response genetic variant and/or the presence of the response serological marker is indicative of inflammatory bowel disease responsive to anti-TNFα therapy. In another embodiment, the non-response genetic variant and/or response serological marker is described in Tables 1, 2 and/or 3(A)-(D). In another embodiment, the non-response genetic variant is at the genetic loci of ATG16, Orf13, ICOSLG, HLADQA1 and/or BRWD1. In another embodiment, the response serological marker is ASCA. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0043] In one embodiment, the present invention provides a method of diagnosing an inflammatory bowel subtype in an individual by determining the presence or absence of a non-response genetic variant and/or non-response serological marker, where the presence of the non-response genetic variant and/or non-response serological marker is indicative of the inflammatory bowel disease subtype in the individual. In another embodiment, the individual is a child.

[0044] In one embodiment, the present invention provides a method of treating inflammatory bowel disease in an individual by determining the presence of a non-response genetic variant and/or non-response serological marker, and treating the individual. In another embodiment, the individual is a child. In another embodiment, the treatment includes the use of anti-TNFα therapy.

[0045] As disclosed herein, the inventors conducted association studies of anti-TNFα responsiveness against the whole genome. Three (3) outcomes were evaluated (primary non-response, loss of response, and failure for any reason), with the analysis of such outcomes described in Table 4 and FIGS. 1-3 herein, including novel findings in the FAM19 genetic locus.

[0046] In one embodiment, the present invention provides a method of evaluating the prognosis of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the presence or absence of a non-response genetic variant, where the presence of the non-response genetic variant is indicative of inflammatory bowel disease that is non-responsive to anti-TNFα therapy. In another embodiment, the non-response genetic variant is described in Table 4 and/or FIGS. 1-3 herein. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0047] In one embodiment, the present invention provides a method of evaluating the prognosis of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the absence of a non-response genetic variant, where the absence of the non-response genetic variant is indicative of inflammatory bowel disease responsive to anti-TNFα therapy. In another embodiment, the non-response genetic variant is described in Table 4 and/or FIGS. 1-3. In another embodiment, the response genetic variant is at the FAM19A4 genetic locus. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0048] As disclosed herein, the inventors tested associations of genetic loci with anti-TNFα response in pediatric IBD patients by pursing a variety of strategies. The result was the development of various predictive models of anti-TNFα response using phenotype, serologic and genetic variables.

[0049] In one embodiment, the present invention provides a method of evaluating the prognosis and/or predicting responsiveness of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the presence or absence of a non-response genetic variant, where the presence of the non-response genetic variant is indicative of inflammatory bowel disease that is non-responsive to anti-TNFα therapy. In another embodiment, the non-response genetic variant is a known IBD susceptibility locus. In another embodiment, the non-response genetic variant is described in Tables 6-10 herein. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0050] In another embodiment, the present invention provides a method of evaluating the prognosis and/or predicting responsiveness of anti-TNFα therapy in an individual undergoing inflammatory bowel disease treatment by determining the presence or absence of one or more risk factors, where the presence of each risk factor has an additive effect for an increased risk of nonresponsiveness to anti-TNFα therapy. In another embodiment, one of the risk factors is a non-response genetic variant. In another embodiment, the non-response genetic variant is described in Tables 6-10 herein. In another embodiment, one of the risk factors is positive expression of a serological marker. In another embodiment, the serological marker is pANCA. In another embodiment, one of the risk factors is the diagnosis of the individual, where a diagnosis of ulcerative colitis predicts non-responsiveness to anti-TNFα therapy. In another embodiment, the anti-TNFα therapy includes the use of Infliximab. In another embodiment, the individual is a child.

[0051] In one embodiment, the present invention provides a method of treating inflammatory bowel disease in an individual by determining the presence of one or more risk factors and treating the individual. In another embodiment, one of the risk factors is a non-response genetic variant. In another embodiment, the non-response genetic variant is described in Tables 6-10 herein. In another embodiment, one of the risk factors is positive expression of a serological marker. In another embodiment, the serological marker is pANCA. In another embodiment, one of the risk factors is the diagnosis of the individual, where a diagnosis of ulcerative colitis predicts non-responsiveness to anti-TNFα therapy. In another embodiment, the individual is a child. In another embodiment, the treatment includes the administration of a therapeutically effective amount of anti-TNFα therapy to the individual.

[0052] In one embodiment, the present invention provides a method of diagnosing an inflammatory bowel subtype in an individual by determining the presence or absence of one or more risk factors, where the presence of one or more risk factors is indicative of the inflammatory bowel disease subtype in the individual. In another embodiment, one of the risk factors is a non-response genetic variant. In another embodiment, the non-response genetic variant is described in Tables 6-10 herein. In another embodiment, one of the risk factors is positive expression of a serological marker. In another embodiment, the serological marker is pANCA. In another embodiment, one of the risk factors is the diagnosis of the individual, where a diagnosis of ulcerative colitis predicts non-responsiveness to anti-TNFα therapy. In another embodiment, the individual is a child.

[0053] A variety of methods can be used to determine the presence or absence of a variant allele or haplotype. As an

5

example, enzymatic amplification of nucleic acid from an individual may be used to obtain nucleic acid for subsequent analysis. The presence or absence of a variant allele or haplotype may also be determined directly from the individual's nucleic acid without enzymatic amplification.

[0054] Analysis of the nucleic acid from an individual, whether amplified or not, may be performed using any of various techniques. Useful techniques include, without limitation, polymerase chain reaction based analysis, sequence analysis and electrophoretic analysis. As used herein, the term "nucleic acid" means a polynucleotide such as a single or double-stranded DNA or RNA molecule including, for example, genomic DNA, cDNA and mRNA. The term nucleic acid encompasses nucleic acid molecules of both natural and synthetic origin as well as molecules of linear, circular or branched configuration representing either the sense or antisense strand, or both, of a native nucleic acid molecule.

[0055] The presence or absence of a variant allele or haplotype may involve amplification of an individual's nucleic acid by the polymerase chain reaction. Use of the polymerase chain reaction for the amplification of nucleic acids is well known in the art (see, for example, Mullis et al. (Eds.), The Polymerase Chain Reaction, Birkhauser, Boston, (1994)).

[0056] A TagmanB allelic discrimination assay available from Applied Biosystems may be useful for determining the presence or absence of a variant allele. In a TagmanB TO allelic discrimination assay, a specific, fluorescent, dye-labeled probe for each allele is constructed. The probes contain different fluorescent reporter dyes such as FAM and VICTM to differentiate the amplification of each allele. In addition, each probe has a quencher dye at one end which quenches fluorescence by fluorescence resonant energy transfer (FRET). During PCR, each probe anneals specifically to complementary sequences in the nucleic acid from the individual. The 5' nuclease activity of Taq polymerase is used to cleave only probe that hybridize to the allele. Cleavage separates the reporter dye from the quencher dye, resulting in increased fluorescence by the reporter dye. Thus, the fluorescence signal generated by PCR amplification indicates which alleles are present in the sample. Mismatches between a probe and allele reduce the efficiency of both probe hybridization and cleavage by Taq polymerase, resulting in little to no fluorescent signal. Improved specificity in allelic discrimination assays can be achieved by conjugating a DNA minor grove binder (MGB) group to a DNA probe as described, for example, in Kutyavin et al., "3'-minor groove binder-DNA probes increase sequence specificity at PCR extension temperature, "Nucleic Acids Research 28:655-661 (2000)). Minor grove binders include, but are not limited to, compounds such as dihydrocyclopyrroloindole tripeptide (DPI,).

[0057] Sequence analysis also may also be useful for determining the presence or absence of a variant allele or haplotype.

[0058] Restriction fragment length polymorphism (RFLP) analysis may also be useful for determining the presence or absence of a particular allele (Jarcho et al. in Dracopoli et al., Current Protocols in Human Genetics pages 2.7.1-2.7.5, John Wiley & Sons, New York; Innis et al., (Ed.), PCR Protocols, San Diego: Academic Press, Inc. (1990)). As used herein, restriction fragment length polymorphism analysis is any method for distinguishing genetic polymorphisms using a restriction enzyme, which is an endonuclease that catalyzes the degradation of nucleic acid and recognizes a specific base

sequence, generally a palindrome or inverted repeat. One skilled in the art understands that the use of RFLP analysis depends upon an enzyme that can differentiate two alleles at a polymorphic site.

[0059] Allele-specific oligonucleotide hybridization may also be used to detect a disease-predisposing allele. Allele-specific oligonucleotide hybridization is based on the use of a labeled oligonucleotide probe having a sequence perfectly complementary, for example, to the sequence encompassing a disease-predisposing allele. Under appropriate conditions, the allele-specific probe hybridizes to a nucleic acid containing the disease-predisposing allele but does not hybridize to the one or more other alleles, which have one or more nucleotide mismatches as compared to the probe. If desired, a second allele-specific oligonucleotide probe that matches an alternate allele also can be used. Similarly, the technique of allele-specific oligonucleotide amplification can be used to selectively amplify, for example, a disease-predisposing allele by using an allele-specific oligonucleotide primer that is perfectly complementary to the nucleotide sequence of the disease-predisposing allele but which has one or more mismatches as compared to other alleles (Mullis et al., supra, (1994)). One skilled in the art understands that the one or more nucleotide mismatches that distinguish between the disease-predisposing allele and one or more other alleles are preferably located in the center of an allele-specific oligonucleotide primer to be used in allele-specific oligonucleotide hybridization. In contrast, an allele-specific oligonucleotide primer to be used in PCR amplification preferably contains the one or more nucleotide mismatches that distinguish between the disease-associated and other alleles at the 3' end of the primer.

[0060] A heteroduplex mobility assay (HMA) is another well known assay that may be used to detect a SNP or a haplotype. HMA is useful for detecting the presence of a polymorphic sequence since a DNA duplex carrying a mismatch has reduced mobility in a polyacrylamide gel compared to the mobility of a perfectly base-paired duplex (Delwart et al., Science 262:1257-1261 (1993); White et al., Genomics 12:301-306 (1992)).

[0061] The technique of single strand conformational, polymorphism (SSCP) also may be used to detect the presence or absence of a SNP and/or a haplotype (see Hayashi, K., Methods Applic. 1:34-38 (1991)). This technique can be used to detect mutations based on differences in the secondary structure of single-strand DNA that produce an altered electrophoretic mobility upon non-denaturing gel electrophoresis. Polymorphic fragments are detected by comparison of the electrophoretic pattern of the test fragment to corresponding standard fragments containing known alleles.

[0062] Denaturing gradient gel electrophoresis (DGGE) also may be used to detect a SNP and/or a haplotype. In DGGE, double-stranded DNA is electrophoresed in a gel containing an increasing concentration of denaturant; double-stranded fragments made up of mismatched alleles have segments that melt more rapidly, causing such fragments to migrate differently as compared to perfectly complementary sequences (Sheffield et al., "Identifying DNA Polymorphisms by Denaturing Gradient Gel Electrophoresis" in Innis et al., supra, 1990).

[0063] Other molecular methods useful for determining the presence or absence of a SNP and/or a haplotype are known in the art and useful in the methods of the invention. Other well-known approaches for determining the presence or

absence of a SNP and/or a haplotype include automated sequencing and RNAase mismatch techniques (Winter et al., Proc. Natl. Acad. Sci. 82:7575-7579 (1985)). Furthermore, one skilled in the art understands that, where the presence or absence of multiple alleles or haplotype(s) is to be determined, individual alleles can be detected by any combination of molecular methods. See, in general, Birren et al. (Eds.) Genome Analysis: A Laboratory Manual Volume 1 (Analyzing DNA) New York, Cold Spring Harbor Laboratory Press (1997). In addition, one skilled in the art understands that multiple alleles can be detected in individual reactions or in a single reaction (a "multiplex" assay). In view of the above, one skilled in the art realizes that the methods of the present invention for diagnosing or predicting susceptibility to or protection against CD in an individual may be practiced using one or any combination of the well known assays described above or another art-recognized genetic assay.

[0064] Similarly, there are many techniques readily available in the field for detecting the presence or absence of serotypes, antibodies, polypeptides or other biomarkers, including protein microarrays. For example, some of the detection paradigms that can be employed to this end include optical methods, electrochemical methods (voltametry and amperometry techniques), atomic force microscopy, and radio frequency methods, e.g., multipolar resonance spectroscopy. Illustrative of optical methods, in addition to microscopy, both confocal and non-confocal, are detection of fluorescence, luminescence, chemiluminescence, absorbance, reflectance, transmittance, and birefringence or refractive index (e.g., surface plasmon resonance, ellipsometry, a resonant mirror method, a grating coupler waveguide method or interferometry).

[0065] Similarly, there are any number of techniques that may be employed to isolate and/or fractionate biomarkers. For example, a biomarker may be captured using biospecific capture reagents, such as antibodies, aptamers or antibodies that recognize the biomarker and modified forms of it. This method could also result in the capture of protein interactors that are bound to the proteins or that are otherwise recognized by antibodies and that, themselves, can be biomarkers. The biospecific capture reagents may also be bound to a solid phase. Then, the captured proteins can be detected by SELDI mass spectrometry or by eluting the proteins from the capture reagent and detecting the eluted proteins by traditional MALDI or by SEMI. One example of SELDI is called "affinity capture mass spectrometry," or "Surface-Enhanced Affinity Capture" or "SEAC," which involves the use of probes that have a material on the probe surface that captures analytes through a non-covalent affinity interaction (adsorption) between the material and the analyte. Some examples of mass spectrometers are time-of-flight, magnetic sector, quadrupole filter, ion trap, ion cyclotron resonance, electrostatic sector analyzer and hybrids of these.

[0066] Alternatively, for example, the presence of biomarkers such as polypeptides maybe detected using traditional immunoassay techniques. Immunoassay requires biospecific capture reagents, such as antibodies, to capture the analytes. The assay may also be designed to specifically distinguish protein and modified forms of protein, which can be done by employing a sandwich assay in which one antibody captures

more than one form and second, distinctly labeled antibodies, specifically bind, and provide distinct detection of, the various forms. Antibodies can be produced by immunizing animals with the biomolecules. Traditional immunoassays may also include sandwich immunoassays including ELISA or fluorescence-based immunoassays, as well as other enzyme immunoassays.

[0067] Prior to detection, biomarkers may also be fractionated to isolate them from other components in a solution or of blood that may interfere with detection. Fractionation may include platelet isolation from other blood components, subcellular fractionation of platelet components and/or fractionation of the desired biomarkers from other biomolecules found in platelets using techniques such as chromatography, affinity purification, 1D and 2D mapping, and other methodologies for purification known to those of skill in the art. In one embodiment, a sample is analyzed by means of a biochip. Biochips generally comprise solid substrates and have a generally planar surface, to which a capture reagent (also called an adsorbent or affinity reagent) is attached. Frequently, the surface of a biochip comprises a plurality of addressable locations, each of which has the capture reagent bound there.

EXAMPLES

[0068] The following examples are provided to better illustrate the claimed invention and are not to be interpreted as limiting the scope of the invention. To the extent that specific materials are mentioned, it is merely for purposes of illustration and is not intended to limit the invention. One skilled in the art may develop equivalent means or reactants without the exercise of inventive capacity and without departing from the scope of the invention.

Example 1

Generally

[0069] Genetics, immune responses and environmental factors for disease susceptibility and development, as well as their interactions, are important determinants of inflammatory bowel disease phenotype and disease progression. These factors may also interact in such a way that influences the outcome of therapies used to treat these heterogeneous phenotypes. Recent genomic discoveries from Genome Wide Association (GWA) studies in both Crohn's disease (CD) and ulcerative colitis (UC) have increased understanding of the genetic susceptibility to IBD. This novel genetic information provides important insight regarding the various mechanisms of inflammation involved in disease pathogenesis. Targeting these various pathways with effective therapies is the key to the successful management of the IBD patient. When introduced, the monoclonal antibodies targeting tumor necrosis factor alpha (TNFα) represented the largest advance in decades made in the realm of IBD therapeutics. However there is clear inter-individual variability in both efficacy and safety outcomes to this class of therapy which has yet to be explained. The inventors have demonstrated that therapeutic outcomes to anti-TNFα in children and young adults with IBD are associated with inter-individual genetic variability, and determined that genetic loci identified by Genome Wide

Association (GWA) studies alone or in combination with clinical and/or immune markers are associated with and predictive of therapeutic responsiveness to anti-TNFα therapy in pediatric IBD patients.

Example 2

Significance of Defining Predictors of Response to Anti-TNFα

[0070] Defining predictors of response to anti-TNFα will allow clinicians to choose the appropriate therapy for the appropriate IBD patient with the goal of maximizing efficacy and minimizing toxicity. Research described herein will allow the individualization of therapy based on who will or perhaps more importantly will not respond to different classes of therapeutic interventions currently available to IBD patients. The development of lymphoma, particularly a rare almost uniformly fatal sub-type of hepatosplenic T cell lymphoma in individuals receiving infliximab along with immunomodulators have resulted in clinicians wanting to carefully

select those patients who are appropriate candidates for these therapies. The novel pharmacogenetic information described herein can not only improve the management of patients in the clinic with an existing anti-TNFα agent but also ultimately change the way large scale clinical trials are conducted, such that only patients with a higher probability of response to specific therapies will be enrolled to negate exposure to ineffective therapies and protect patients from treatment related serious and potentially fatal adverse events. The data described herein will aid in the translation of significant genetic findings into the clinical setting for IBD patients and for other patients receiving anti-TNFα for other immune mediated disorders.

Example 3

Pharmacogenetic GWAS and Primary Non-Response

[0071] The inventors tested the association of the most significant CD susceptibility loci previously identified with infliximab responsiveness in pediatric IBD patients receiving infliximab from which there was complete clinical follow up. For these preliminary analyses, two (2) outcomes were evaluated:

[0072] 1) primary non-response: patient did not respond to the induction regimen as defined by patient did not receive a clinical benefit from the first 3 infusions of infliximab and did not receive any further treatment doses. All significant associations are shown in Table 1 below. Remainder of analyses are detailed in Table 3.

[0073] 2) secondary loss of response: patient responded to the induction regimen and despite dose escalation and/or frequency intensification of infliximab the drug was discontinued as of last follow up. Time to loss of response was also analyzed and data are shown in Table 3.

Example 4

Table 1—Significant Associations Between GWAS Loci and Primary Non-Response

[0074]

TABLE 1 (A)

SNP	Chromosome	Primary Non Response (YES = 1, NO = 0)	Genotype 12/22	Genotype 11	P value	OR*	Gene of interest
rs2241880	2q37	0	30(58.8%)	21(41.2%)	0.04		ATG16
		1	7(100.0%)			10.6	
rs2188962	5q23	0	45(83.3%)	9(16.7%)	0.03	6.7	unknown
		1	3(42.9%)	4(57.1%)			
rs3764147	13q14	0	31(57.4%)	23(42.6%)	0.004	20.1	Orf13
		1		7100.0%)			
rs762421	21q22	0	34(63.0%)	20(37.0%)	0.03	10.2	ICOSLG
		1	1(14.3%)	6(85.7%)			
rs9271568	6p21.32	0	31(58.5%)	22(41.5%)	0.004	21.0	HLADQA1
		1		7(100.0%)			
rs2836878	21q22.2	0	29(53.7%)	25(46.3%)	0.01	17.4	BRWD1
		1		7(100.0%)			

*If there is any zero cell, 0.5 is added to each cell count to calculate OR.

[0075] As described in Table 1(A), there were 6 SNPs that were found to be significantly associated with primary non-response. Interestingly there was no overlap with any SNP found to be associated with secondary loss of response and time to loss of response. This shows that there may be different genetic predictors and biological explanations for the 2 therapeutic response outcomes.

[0076] In conjunction with the various genotypes and SNPs listed in Table 1(A) above, the alleles are listed in Table 1(B) below:

TABLE 1(B)

SNP	Alleles Corresponding to Genotype
rs2241880	11 = CC, 12 = CT, 22 = TT
rs2188962	11 = CC, 12 = CT, 22 = TT
rs3764147	11 = AA, 12 = AG, 22 = GG
rs762421	11 = AA, 12 = AG, 22 = GG
rs9271568	11 = GG, 12 = GA, 22 = AA
rs2836878	11 = GG, 12 = GA, 22 = AA

Example 5

Serological Immune Responses and Therapeutic Response

[0077] The associations between ASCA, pANCA, OmpC, I2 and CBIr-1 antibodies and therapeutic outcome was analyzed. Only significant associations with primary non-response are illustrated in Table 2. pANCA positivity was associated with primary non-response and ASCA positivity was protective against primary non-response. There was no association found anti-OmpC, anti-I2 and anti-CBir-1 for primary non-response and none of the serologies were associated with loss of response.

Example 6

Table 2—Significant Associations Between Serological Immune Responses and Therapeutic Outcome

[0078]

TABLE 2

Immune Responses	Positive = 1, Negative = 0	Primary non response yes	no	P	OR*	95% CI
pANCA	0	3(30.0%)	44(69.8%)			
	1	6(85.7%)	12(25.5%)	0.002	17.5	1.9-160.6
ASCA IgA and/or IgG	0	1(14.3%)	35(74.5%)			
	1		30(47.6%)	0.004	0.05	

*If there is any zero cell, 0.5 is added to each cell count to calculate OR.

Example 7

Table 3 (A)-(D)—Details of SNPs Analyzed and Includes Outcomes: Primary Non-Response, Secondary Loss of Response, and Time to Loss of Response

[0079]

TABLE 3(A)

Table 3(A) depicts top IBD risk loci from GWA studies and primary non-response.

SNP	Primary non response Yes = 1 No = 0	Genotype 12/22	Genotype 11	P value
rs2476601	0	7(12.96)	47(87.04)	0.311
	1		7(100.00)	
rs2274910	0	23(42.59)	31(57.41)	0.150
	1	5(71.43)	2(28.57)	
rs9286879	0	28(51.85)	26(48.15)	0.654
	1	3(42.86)	4(57.14)	
rs2241880	0	30(56.82)	21(41.18)	0.04
	1	7(100.00)		
rs3197999	0	34(62.96)	20(37.04)	0.082
	1	2(28.57)	5(71.43)	
rs4613763	0	4(7.41)	50(92.59)	0.533
	1	1(14.29)	6(85.71)	
rs10044354	0	38(70.37)	16(29.63)	0.477
	1	4(57.14)	3(42.86)	
rs2188962	0	45(63.33)	9(16.67)	0.03
	1	3(42.86)	4(57.14)	
rs10045431	0	22(40.74)	32(59.26)	0.535
	1	2(28.57)	5(71.43)	
rs6908425	0	13(24.07)	41(75.93)	0.066
	1	4(57.14)	3(42.86)	

TABLE 3(A)-continued

Table 3(A) depicts top IBD risk loci from GWA studies and primary non-response.

SNP	Primary non response Yes = 1 No = 0	Genotype 12/22	Genotype 11	P value
rs2844480	0	22(40.74)	32(59.26)	0.535
	1	2(28.57)	5(71.43)	
rs2301436	0	36(66.67)	18(33.33)	0.618
	1	4(57.14)	3(42.86)	
rs1456893	0	29(53.70)	25(46.30)	0.211
	1	2(28.57)	5(71.43)	
rs1551398	0	32(59.26)	22(40.74)	0.535
	1	5(71.43)	2(28.57)	
rs2456449	0	31(57.41)	23(42.59)	0.466
	1	3(42.86)	4(57.14)	
rs10758669	0	43(79.63)	11(20.37)	0.618
	1	5(71.43)	2(28.57)	
rs4574921	0	21(38.89)	33(61.11)	0.202
	1	1(14.29)	6(85.71)	

TABLE 3(A)-continued

Table 3(A) depicts top IBD risk loci from GWA studies and primary non-response.

SNP	Primary non response Yes = 1 No = 0	Genotype 12/22	Genotype 11	P value
rs10995239	0	35(64.81)	19(35.19)	0.259
	1	3(42.86)	4(57.14)	
rs11190140	0	39(72.22)	15(27.78)	0.445
	1	6(85.71)	1(14.29)	
rs3764147	0	31(57.41)	23(42.59)	0.004
	1		7(100.00)	
rs1968752	0	26(51.65)	26(48.15)	0.654
	1	3(42.86)	4(57.14)	
rs8049439	0	25(46.30)	29(53.70)	0.864
	1	3(42.86)	4(57.14)	
rs2076756	0	32(59.26)	22(40.74)	0.409
	1	3(42.86)	4(57.14)	
rs2872507	0	41(75.93)	13(24.07)	0.143
	1	7(100.00)		
rs744166	0	27(50.00)	27(50.00)	0.285
	1	5(71.43)	2(28.57)	
rs762421	0	34(62.96)	20(37.04)	0.03
	1	1(14.29)	6(85.71)	
rs10489630	0	36(66.67)	18(33.33)	0.050
	1	2(28.57)	5(71.43)	
rs917997	0	26(46.15)	28(51.85)	0.792
	1	3(42.86)	4(57.14)	
rs9271568	0	31(58.49)	22(41.51)	0.004
	1		7(100.00)	
rs11174631	0	9(16.67)	45(83.33)	0.242
	1		7(100.00)	
rs991804	0	24(44.44)	30(55.56)	0.424
	1	2(28.57)	5(71.43)	

TABLE 3(A)-continued

Table 3(A) depicts top IBD risk loci from GWA studies and primary non-response.

SNP	Primary non response Yes = 1 No = 0	Genotype 12/22	Genotype 11	P value
rs2836878	0	29(53.70)	25(46.30)	0.01
	1		7(100.00)	
rs3749946	0	36(66.67)	18(33.33)	0.050
	1	2(28.57)	5(71.43)	
rs7228236	0	26(48.15)	28(51.85)	0.792
	1	3(42.86)	4(57.14)	

TABLE 3(B)

Table 3(B) depicts top IBD loci from GWA studies and secondary loss of response.

SNP	Secondary Loss of response YES = 1, NO = 0	genotype 12/22	genotype 11	P value
rs2476601	0	7(18.42)	31(81.58)	0.066
	1		16(100.00)	
rs2274910	0	16(42.11)	22(57.89)	0.911
	1	7(43.75)	9(56.25)	
rs9266879	0	19(50.00)	19(50.00)	0.675
	1	9(56.25)	7(43.75)	
rs2241880	0	22(57.89)	16(42.11)	0.818
	1	8(61.54)	5(38.46)	
rs3197999	0	23(60.53)	15(39.47)	0.568
	1	11(68.75)	5(31.25)	
rs4613763	0	4(10.53)	34(89.47)	0.177
	1		16(100.00)	
rs10044354	0	30(78.95)	8(21.05)	0.033
	1	8(50.00)	8(50.00)	
rs2188962	0	31(81.58)	7(18.42)	0.594
	1	14(87.50)	2(12.50)	
rs10045431	0	16(42.11)	22(57.89)	0.753
	1	6(37.50)	10(62.50)	
rs6908425	0	6(15.79)	32(84.21)	0.028
	1	7(43.75)	9(56.25)	
rs2844480	0	15(39.47)	23(60.53)	0.770
	1	7(43.75)	9(56.25)	
rs2301436	0	26(68.42)	12(31.58)	0.673
	1	10(62.50)	6(37.50)	
rs1456893	0	20(52.63)	18(47.37)	0.808
	1	9(56.25)	7(43.75)	
rs1551398	0	23(60.53)	15(39.47)	0.770
	1	9(56.25)	7(43.75)	
rs2456449	0	18(47.37)	20(52.63)	0.021
	1	13(81.25)	3(18.75)	
rs10758669	0	31(61.58)	7(18.42)	0.584
	1	12(75.00)	4(25.00)	
rs4674921	0	16(42.11)	22(57.89)	0.455
	1	5(31.25)	11(68.75)	
rs10995239	0	27(71.05)	11(28.95)	0.139
	1	8(50.00)	8(50.00)	
rs11190140	0	26(68.42)	12(31.58)	0.337
	1	13(81.25)	3(18.75)	
rs3764147	0	22(57.89)	16(42.11)	0.911
	1	9(56.25)	7(43.75)	
rs1968752	0	19(50.00)	19(50.00)	0.675
	1	9(56.25)	7(43.75)	
rs8049439	0	14(36.84)	24(63.16)	0.032
	1	11(68.75)	5(31.25)	
rs2076756	0	23(60.53)	15(39.47)	0.770
	1	9(56.25)	7(43.75)	
rs2872507	0	30(78.95)	8(21.05)	0.424
	1	11(68.75)	5(31.25)	
rs744166	0	19(50.00)	19(50.00)	1.000
	1	8(50.00)	8(50.00)	
rs762421	0	24(63.16)	14(36.84)	0.964
	1	10(62.50)	6(37.50)	

TABLE 3(B)-continued

Table 3(B) depicts top IBD loci from GWA studies and secondary loss of response.

SNP	Secondary Loss of response YES = 1, NO = 0	genotype 12/22	genotype 11	P value
rs10489630	0	24(63.16)	14(36.84)	0.399
	1	12(75.00)	4(25.00)	
rs917997	0	19(50.00)	19(50.00)	0.675
	1	7(43.75)	9(56.25)	
rs9271568	0	22(59.46)	15(40.54)	0.828
	1	9(56.25)	7(43.75)	
rs11174631	0	9(23.68)	29(76.32)	0.033
	1		16(100.00)	
rs991804	0	15(39.47)	23(60.53)	0.257
	1	9(86.25)	7(43.75)	
rs2836878	0	19(50.00)	19(50.00)	0.400
	1	10(62.50)	6(37.50)	
rs3749946	0	24(63.16)	14(36.84)	0.399
	1	12(75.00)	4(25.00)	
rs7228236	0	19(50.00)	19(50.00)	0.675
	1	7(43.75)	9(56.25)	

TABLE 3(C)

Table 3(C) depicts time of loss of response: Kaplan Meier Survival Analysis (time to loss of response).

SNP	genotype	number	mean duration	P	% censored	P
rs2476601	11	47	26.234	0.893	67%	0.12
	12/22	7	25.000		100%	
rs2274910	11	31	24.613	0.582	71%	0.94
	12/22	23	28.043		69.60%	
rs9286879	11	26	23.808	0.478	73.10%	0.94
	12/22	26	28.179		67.90%	
rs2241880	11	21	33.238	0.098	76.20%	0.48
	12/22	30	22.567		73.30%	
rs3197999	11	20	28.550	0.537	75%	0.62
	12/22	34	24.618		67.70%	
rs4613763	11	50	25.840	0.788	68%	0.21
	12/22	4	29.000		100%	
rs10044354	11	16	20.938	0.277	50%	0.02
	12/22	38	28.237		78.90%	
rs2188962	11	9	21.556	0.511	77.80%	0.67
	12/22	45	26.978		68.90%	
rs10045431	11	32	25.031	0.683	68.80%	0.68
	12/22	22	27.591		72.70%	
rs6908425	11	41	27.122	0.545	78.10%	0.04
	12/22	13	22.769		46.20%	
rs2844480	11	32	23.625	0.336	71.90%	0.95
	12/22	22	23.636		68.20%	
rs2301436	11	18	24.222	0.671	66.70%	0.62
	12/22	36	27.000		72.20%	
rs1456893	11	25	27.200	0.734	72%	0.94
	12/22	29	25.103		69%	
rs1551398	11	22	28.818	0.459	68.20%	0.99
	12/22	32	24.188		71.90%	
rs2456449	11	23	26.913	0.815	87%	0.03
	12/22	31	25.452		58.10%	
rs10758669	11	11	20.455	0.355	64.60%	0.28
	12/22	43	27.512		72.10%	
rs4574921	11	33	25.061	0.680	66.70%	0.49
	12/22	21	27.667		76.20%	
rs10995239	11	19	24.105	0.638	57.90%	0.16
	12/22	35	27.143		77.10%	
rs11190140	11	15	31.267	0.294	80%	0.25
	12/22	39	24.077		66.70%	
rs3764147	11	23	26.522	0.900	69.60%	0.93
	12/22	31	25.742		71%	

TABLE 3(C)-continued

Table 3(C) depicts time of loss of response: Kaplan
Meier Survival Analysis (time to loss of response).

SNP	genotype	number	mean duration	P	% censored	P
rs1968752	11	26	19.231	0.029	73.10%	0.86
	12/22	28	32.429		67.90%	
rs8049439	11	29	27.000	0.746	82.80%	0.07
	12/22	25	25.000		56%	
rs2076756	11	22	26.909	0.822	68.20%	0.89
	12/22	32	25.500		71.90%	
rs2872507	11	13	31.462	0.323	61.50%	0.63
	12/22	41	24.366		73.20%	
rs744166	11	27	21.519	0.135	70.40%	0.68
	12/22	27	30.630		70.40%	
rs762421	11	20	22.900	0.428	70%	0.89
	12/22	34	27.941		70.60%	
rs10489630	11	18	31.556	0.205	77.90%	0.42
	12/22	36	23.333		66.70%	
rs917997	11	28	27.571	0.614	67.90%	0.57
	12/22	26	24.462		73.10%	
rs9271568	11	22	30.045	0.340	68.20%	0.99
	12/22	31	24.065		71%	
rs11174631	11	45	22.622	0.010	64.40%	0.03
	12/22	9	43.333		100%	
rs991804	11	30	27.500	0.605	76.70%	0.24
	12/22	24	24.292		62.50%	
rs2836878	11	25	29.000	0.376	76%	0.42
	12/22	29	23.552		65.50%	
rs3749946	11	18	31.556	0.205	77.80%	0.42
	12/22	36	23.333		66.70%	
rs7228236	11	28	27.571	0.614	67.90%	0.57
	12/22	26	24.462		73.10%	

TABLE 3(D)

Table 3(D) depicts serological immune markers and
anti-TNFα responsiveness (n = 63).

Immune Response	Positive = 1 Negative = 0	Primary non response		P	OR	95% CI
		yes	no			
pANCA	1	6(85.71)	12(25.53)	0.002	17.5	1.91-160.5
	0	1(14.29)	35(74.47)			
ASCA IgA and/or IgG	1		30(47.62)	0.004	0.05	
	0	10(100.00)	33(52.38)			
OmpC	1	1(10.00)	16(25.40)	0.29	0.33	0.04-2.78
	0	9(90.00)	47(74.60)			
I2	1	3(30.00)	19(30.65)	0.97	0.97	0.23-4.16
	0	7(70.00)	43(69.35)			
CBir1	1	5(50.00)	28(45.16)	0.78	1.20	0.32-4.62
	0	5(50.00)	34(54.84)			

		Secondary Loss of response				
		Yes	no			
pANCA	1	4(36.36)	8(22.22)	0.35	2.000	0.47-8.60
	0	7(63.64)	28(77.78)			
ASCA IgA and/or IgG	1	6(33.33)	24(53.33)	0.15	0.438	0.14-1.37
	0	12(66.67)	21(46.67)			
OmpC	1	6(33.33)	10(22.22)	0.36	1.750	0.52-5.85
	0	12(66.67)	35(77.78)			
I2	1	8(44.44)	11(25.00)	0.13	2.400	0.76-7.60
	0	10(55.56)	33(75.00)			
CBir1	1	7(38.89)	21(47.73)	0.53	0.697	0.23-2.13
	0	11(61.11)	23(52.27)			

Example 8

Enrollment Criteria

Inclusion Criteria:

[0080] 1. IBD patients <21 years of age
2. Active CD or UC patients initiating infliximab therapy as prescribed by the treating physician.
3. No predetermined minimum Crohn's Disease Activity Index (CDAI) or Pediatric Crohn's Disease Activity Index (PCDAI) or Partial Mayo score will be necessary for inclusion (see justification below)
4. Willingness to participate
5. Able to give consent by patient or legal guardian
6. Willing to provide blood

Exclusion Criteria:

[0081] 1. IBD Patients not receiving infliximab
2. Patients in remission at time of initiating infliximab
3. IBD patients who are on low dose prednisone for adrenal insufficiency and unable to wean in designated time frame.
4. CD patients with exclusive perianal fistulizing disease (see justification below)

Example 9

Association of Anti-TNF Responsiveness Against the Whole Genome

[0082] Three (3) outcomes were evaluated:

[0083] 1) primary non-response: patient did not respond to the induction regimen as defined by patient did not receive a

clinical benefit from the first 3 infusions of infliximab and did not receive any further treatment doses.

[0084]   2) secondary loss of response: patient responded to the induction regimen and despite dose escalation and/or frequency intensification of infliximab the drug was discontinued as of last follow up.

[0085]   3) failure for any reason.

[0086]   The results and analysis of the three outcomes are further described in Tables 1(A-C) and 2 (A-C) below.

Example 10

Table 4(A-C)—Results of Top Ten (10) Most Significant Associations

[0087]

Example 11

Methods—Patient Population

[0088]   94 pediatric CD and UC patients (age <21 years), followed at CSMC. Each received at least 2 doses (week 0 and 2) of infliximab. Clinical data was collected and stored in a secure database at CSMC. Serological immune responses (ELISA EU/ml) collected and analyzed at CSMC. Specifically, ASCA (IgG and IgA), anti-Cbir1 (IgG), pANCA (IgG) I2 (IgA), OmpC (IgA). Genotype data was also obtained.

Example 12

Methods—Primary Outcome Definitions

[0089]   Primary non-response was evaluated for patients. For Crohn's Disease, primary non response was defined by no

TABLE 4(A)

Analysis of top ten (10) most significant associations for primary non-response as an outcome.

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs13079040	3	68988334	C	0.7143	0.1574	T	0.00003361	13.38	4.47353149	FAM19A
rs4855535	3	69017124	G	0.5714	0.05556	T	6.987E–06	22.67	5.15570926	FAM19A
rs17048128	3	69028502	A	0.5714	0.05556	G	6.987E–06	22.67	5.15570926	FAM19A
rs17048129	3	69031452	A	0.5714	0.05556	G	6.987E–06	22.67	5.15570926	FAM19A
rs17039556	4	161545059	A	0.7143	0.1296	G	8.744E–06	16.79	5.05828985	
rs12640159	4	161586073	A	0.7857	0.1944	G	0.00001882	15.19	4.72538038	
rs880330	7	67842575	T	0.7857	0.213	C	0.00003927	13.55	4.4059391	
rs2057917	7	67867804	C	0.8571	0.2778	T	0.00004331	15.6	4.36341182	
rs2983478	14	94433843	C	1	0.4167	T	0.00001555		4.80826961	
rs4776127	15	51373815	G	0.7857	0.213	A	0.00003927	13.55	4.4059391	

TABLE 4(B)

Analysis of top ten (10) most significant associations for secondary loss of response as an outcome.

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs1838990	3	63142891	C	0.09375	0.5132	T	0.00002815	0.09814	4.5505216	
rs11713998	3	168613099	T	0.4375	0.06579	C	0.00001437	11.04	4.84254323	
rs13144587	4	67295867	C	0.4375	0.07895	A	0.00003895	9.074	4.40949254	
rs6928719	6	166117879	C	0.1875	0.6711	A	5.292E–06	0.1131	5.27638016	
rs6928737	6	166118611	G	0.1875	0.6579	A	7.617E–06	0.12	5.11821604	
rs6904237	6	166121014	C	0.1875	0.6316	T	0.00004141	0.1346	4.38289477	
rs4762507	12	97659769	T	0	0.3553	C	0.0000171	0	4.76700389	ANKS1B
rs12857230	13	42654650	G	0.7188	0.25	T	8.917E–06	7.667	5.04978123	
rs12918939	16	64698060	G	0.4375	0.07895	A	0.00003895	9.074	4.40949254	
rs5999636	22	33661041	T	0	0.3289	C	0.00004165	0	4.38038499	

TABLE 4(C)

Analysis of top ten (10) most significant associations for failure for any reason as an outcome.

snp	CHR	BP	A1	F_A	F_U	A2	fisher_p	OR	l_p	loci
rs11695174	2	9705766	T	0.2955	0.02564	C	0.00002682	15.94	4.57154123	
rs17020744	2	81845572	A	0.25	0.01282	G	0.00004771	25.67	4.32139058	
rs1549599	3	37506369	G	0.6818	0.2692	A	0.00001852	5.816	4.73235902	ITGA9
rs1569091	7	94356064	A	0.6136	0.2308	G	0.00003676	5.294	4.4346245	
rs7335910	13	24220725	G	0.09091	0.4615	A	0.00001775	0.1167	4.75080164	
rs4326996	15	61567335	G	0.25	0.01282	T	0.00004771	25.67	4.32139058	
rs1554983	16	77425340	A	0.3182	0.7179	G	0.00002387	0.1833	4.62214758	
rs9915945	17	6089542	A	0.3636	0.05128	G	0.00001539	10.57	4.81276138	
rs4794558	17	50702952	A	0.5682	0.1923	G	0.00004192	5.526	4.37757873	HLF
rs323391	17	69199193	A	0.4773	0.1154	C	0.00001732	7	4.76145211	

change or increase in HBI from baseline at week 10 or earlier if drug discontinued before week 6 infusion. For ulcerative colitis, primary non response was defined by no change or increase from baseline in the sum of stool frequency and rectal bleeding subscores of the partial Mayo score and no improvement in the physician's global assessment subscore.

Example 13

Methods—Association Variables

[0090] SNP selection of known IBD susceptibility SNPs (GWA significance) were taken from previous adult CD meta GWAS (32 loci), adult UC GWAS (5 loci), and pediatric IBD GWAS (2 loci). SNP selection was also taken of top 10 significant SNPs from pharmacogenetic GWAS, using chi square test. Serology status, of positive or negative, was determined with chi square test. Finally, demographic and phenotype data was taken with t-test for continuous variables and chi-square test for categorical variables.

Example 14

Methods—Predictive Models

[0091] Predictive models of non-response were created using Strategy A, B and C. Strategy A utilizes known susceptibility IBD SNPs, using logistic multiple regression, and stepwise selection of phenotype, serologic and genetic variables with univariate association p<0.1. Strategy B utilizes the top 10 SNPs from pharmacogenetics GWAS (p<2*10^{-5}), using logistic multiple regression, and stepwise selection of phenotype, serologic and genetic variables with univariate association p<0.1. Strategy C is the combination of Strategy A and B (also known as Final Model).

[0092] With regard to clinical utility, the sensitivity, specificity, accuracy, ROC, positive likelihood ratio calculated for the models.

Example 15

Table 5—Results of Demographic and Phenotype Associations with Primary Non Response

[0093] From 94 patients meeting inclusion criteria, 22 exhibited primary non response, and 72 exhibited primary response.

TABLE 5

CLINICAL VARIABLE	NON RESPONSE	RESPONSE	P Value
UC vs. CD	14:8	6:66	<0.0001
Mean age at diagnosis (years)	10.1	10.5	0.71
Gender M:F	8:14	40:32	0.12
Disease duration at start of IFX (months)	26	25	0.96
IMM use at start of IFX (%)	79%	92.8%	0.1
Duration of IMM at start of IFX (months)	12.7	15.3	0.57
pANCA+	76.2%	29%	0.0001
ASCA+	0%	46.9%	0.0003

Example 16

Table 6—Results of Strategy A: Models of Primary Non-Response with Known Susceptibility Loci

[0094]

TABLE 6

Model	Variable	Description	P value	OR (95% CI)	R-square
I	Diagnosis	UC vs. CD	0.0001	15.0 (4.1, 55.8)	0.48
	pANCA	Pos vs. Neg	0.01	5.4 (1.5, 19.9)	
II (known IBD susceptibility SNPs only)	rs2188962 5q31.1	CC vs. CT/TT	0.04	3.3 (1.03, 10.9)	0.30
	rs6908425 6p22.3 CDKA1	CT/TT vs. CC	0.04	3.2 (1.01, 10.4)	
	rs2836878 21q22.2/ BRWD1	GG vs AG/AA	0.05	3.3 (0.98, 11.2)	
	rs2395185 6p21/HLA-DQA1	GG vs. TG/TT	0.01	4.6 (1.4, 14.9)	

Example 17

Table 7—Results of Strategy A: Models of Primary Non-Response with Known Susceptibility Loci

[0095]

TABLE 7

Model	Variable	Description	P value	OR (95% CI)	R-square
III: I & II (Combined)	Diagnosis	UC vs. CD	0.0008	14.7 (3.1, 70.4)	0.59

TABLE 7-continued

Model	Variable	Description	P value	OR (95% CI)	R-square
	pANCA	Pos vs. Neg	0.004	15.3 (2.4, 96.2)	
	rs6908425 6p22.3 CDKA1	CT/TT vs. CC	0.05	4.6 (1.0, 21.0)	
	rs2836878 21q22.2/ BRWD1	GG vs. AG/AA	0.02	9.8 (1.5, 64.0)	
	rs2395185 6p21/HLA-DQA1	GG vs. TG/TT	0.047	5.4 (1.0, 28.6)	

Example 18

Table 8—Results of Strategy B: Model of Primary Non-Response with Pharmacogenetic GWAS Loci

[0096]

TABLE 8

Model	Variable	Description	P Value	R square
IV (pharmacogenetic GWAS genes only)	rs975664 2p12 TACR1	TT vs. CT/CC	0.0006	0.67
	rs4855535 3p14 FAM19A4	GG/GT vs. TT	0.006	
	Rs4796606 17q21 KRT35, 32, 36, 13 Keratin gene cluster	CC/CT vs. TT	0.01	
	Rs765132 Xq26	TT/TC vs. CC	0.03	

Example 19

Results—Strategy C: Final Model of Primary Non-Response with Pharmacogenetic GWA and Known Susceptibility SNPs and Clinical Phenotype and Serology Status

[0097]

TABLE 9

Model	Variable	Description	P value	R-square
V: III & IV	Dx	UC vs. CD	0.008	0.82
	pANCA	Pos vs. Neg	0.03	
	rs975664 2p12/TACR1	TT vs. CT/CC	0.01	
	rs4855535 3p14/FAM19A4	GG/GT vs. TT	0.02	
	rs6100556 20q13/PHACTR3	TG/TT vs. GG	0.02	
	rs2836878 21q22/BRWD1	GG vs. AG/AA	0.07	

Example 20

Table 10—Results Demonstrating Diagnostic Utility of Final Model for Non-Response to Anti-TNFα

[0098]

TABLE 10

Model	Variable	Description	ROC	SN	SP	ACC	Positive Likelihood Ratio of NR
V: III & IV	Dx	UC vs. CD	0.98	0.95 (cut-off: ≧3 risk factors	0.88	0.92	8
	pANCA	Pos vs. Neg					
	rs975664 2p12/TACR1	TT vs CT/CC					
	rs4855535 3p14/FAM19A4	GG/GT vs TT					
	rs6100556 20q13/PHACTR3	TG/TT vs GG					
	rs2836878 21q22/BRWD1	GG vs AG/AA					

SN = sensitivity; SP = specificity; ACC = accuracy.

Example 21

Conclusions

[0099] 4 known IBD susceptibility genes were associated with non-response to infliximab.

[0100] UC—independent predictor of non-response to infliximab and may be the most important predictor.

[0101] pANCA positive independently predicts non-response to infliximab.

[0102] Pharmacogenetic GWAS top loci improved prediction of non-response compared to known susceptibility loci.

[0103] The combination of genotype, phenotype and serotype was best predictor of non-response to anti-TNFα.

[0104] Defining predictors of response to anti-TNFα aid clinicians in choosing the right therapy for the right patient.

[0105] Trial design may be enhanced using genetic markers.

Example 22

Genotyping

[0106] Genotyping may be performed at Cedars-Sinai Medical Center in the GCRC phenotyping/genotyping Core Facility. Genotyping for single nucleotide polymorphisms (SNPs) is performed using ABI TaqMan MGB chemistry with an ABI 7900 instrument in 384 well format. A robotic workstation (Tecan Genesis) is used to set up the PCR plates and the current throughput is 6×384 assays per day. TaqMan chemistry results in the release of dye as the 5'-nuclease activity of Taq polymerase degrades a probe/quencher bound to a particular allele. The use of two dyes, one for each allele, allows the SNP genotyping in a single PCR reaction. The "MGB" system has several advantages over earlier version of this chemistry for SNP genotyping and is therefore a "second generation" technology that includes: 1) a more sensitive VIC dye rather than TET, 2) an improved optical system in the ABI7900 instrument eliminates missed reads due to scratches in the caps, 3) primer and probe design software that considerably lowers the amount of trouble-shooting 4) 384-well format for high throughput, and 5) use of a minor groove binder (MGB) shortens the length of the probe and thus increases discrimination between the two alleles of the SNP. This technology has been used extensively in the CSMC genotyping core.

Example 23

Definitions of Therapeutic Responsiveness

[0107] Response criteria described below have been employed in phase 3 clinical trials in both pediatric and adult IBD patients receiving infliximab. It is important to determine whether a patient is responding to their induction regimen. This will negate any non responders from continuing to receive ineffective therapy. The primary goal of using anti-TNFα is to induce and maintain a steroid free remission. The side effect profile and the potential growth stunting effects of corticosteroids make this steroid sparing agent very important in IBD patients, especially children. Having a strict corticosteroid specification for response makes for a more robust end point and potentially more clinically meaningful.

[0108] Primary Non-Response:

[0109] CD: Inability to achieve a drop in PCDAI of >15 points from baseline or CDAI drop of >70 points and >75% reduction in corticosteroid dose at week 10 if on steroids at initiation of infliximab.

[0110] UC: Inability to achieve an improvement of at least 2 points in the sum of stool frequency and rectal bleeding subscores of the partial Mayo score, and no worsening in the physician's global assessment subscore OR the sum of the subject's stool frequency and rectal bleeding subscores is less than or equal to 1, and no worsening in the physician's global assessment subscore and >75% reduction in corticosteroid dose at week 10 if on corticosteroids at initiation of infliximab.

[0111] Response:

[0112] CD: Drop in PCDAI of >15 points from baseline or CDAI drop of >70 points from baseline for CD and >75% reduction in corticosteroid dose at week 10 if on corticosteroids at initiation of infliximab. For example a patient started on 40 mg/day will need to be weaned to <10 mg/day.

[0113] UC: An improvement of at least 2 points in the sum of stool frequency and rectal bleeding subscores of the partial Mayo score, and no worsening in the physician's global assessment subscore OR the sum of the subject's stool frequency and rectal bleeding subscores is less than or equal to 1, and no worsening in the physician's global assessment subscore and >75% reduction in corticosteroid dose at week 10 if on corticosteroids at initiation of infliximab.

[0114] Forced Corticosteroid Taper: (Standard Corticosteroid Wean Based on Clinical Trials and Routine Clinical Care):

[0115] Subjects on oral prednisone or equivalent will keep their enrollment dose stable for 2 weeks as anti-TNFα may take 10-14 days to have a clinical effect. Starting at week 2, corticosteroids will be tapered at the following rate:

[0116] Prednisone or equivalent: >20 mg/day 5 mg/q 5 days

[0117] >10-<20 mg/day 5 mg/week

[0118] <10 mg/day 2.5 mg/week

[0119] Sustained Remission:

[0120] CD: PCDAI <10 or CDAI <150 for CD and off corticosteroids at week 10 and week 54 without rescue therapy with steroids or infliximab dose increase or frequency escalation in between.

[0121] UC: partial mayo score ≦2 points, with no individual subscore >1 and off corticosteroids at week 10 and week 54 without rescue therapy with steroids or infliximab dose increase or frequency escalation in between.

[0122] Loss of Response:

[0123] Recurrence of symptoms as determined by the treating physician necessitating rescue therapy with corticosteroids or an increase dose of infliximab from 5 mg/kg to 10 mg/kg or the patient requires infliximab more frequent then every 8 weeks. Physician Global Assessment Score will be used to document the condition of the patient at time of the visit determining loss of response and change in clinical condition from week 10 assessment. The physician global assessment of change is a 5-point scale used to assess the change from baseline (week 10) in the subject's disease activity from the perspective of the physician.

[0124] Immunogenicity and Infliximab Trough Drug Levels:

[0125] Immunogenicity may be determined based on the development of antibodies to infliximab. Antibody levels will be measured as detectable vs. non detectable. Levels >8 ug/dl

have been shown to be associated with loss of response and will be chosen as cut point for detectable vs. non detectable.

[0126] Trough drug levels: levels of infliximab in the blood at the time of the infliximab infusion. Levels <12 ug/ml have been shown to be associated with loss of response and will be chosen as threshold for detectable vs. non detectable.

[0127] mRNA Expression:

[0128] Subject's mRNA expression may be classified as respondents or non-respondents. Respondents will be determined by a more than 2-fold increase in mRNA expression after induction.

[0129] Clinical Phenotype:

[0130] The baseline clinical features to be analyzed include: age at diagnosis, gender, disease location (upper tract, small bowel, large bowel, perianal), disease behavior (fistulizing and or stricturing disease), duration of disease at baseline, disease activity at baseline, smoking (active or passive) history and use of concomitant immunomodulators.

Example 24

Serological Immune Response Processing

[0131] ASCA/ANCA ELISA:

[0132] ASCA: the samples will be analyzed by ELISA with phosphopeptidomannan extracted from *Saccharomyces cerevisiae* serving as the antigen. Briefly, plasma diluted 1:80 (for IgA detection) or 1:800 (for IgG detection) will be added to plates previously coated with mannan at 100 ug/ml. After incubation and washing, alkaline phosphatase labeled goat anti-human IgA and IgG are added to their respective plates. Finally, after another incubation and wash, substrate (p-nitrophenyl phosphate) is added and color change is detected at 405 nm. All samples are compared to standard positive control samples and expressed as ELISA units (EU).

[0133] ANCA/pANCA: the samples will be quantitatively analyzed by ELISA and ELISA positive samples will be further characterized qualitatively by immunofluorescence binding pattern including DNase treatment of samples with pANCA binding. For ELISA analysis, microtiter plates are coated with a monolayer of neutrophils (25,000/well) and air-dried, fixed with 100% methanol, dried again and stored at −20° C. For use, the plates are blocked for non specific binding by 0.5% bovine serum albumin in phosphate buffered saline (BSA/PBS), the blocking material is discarded and samples at a 1:100 dilution in BSA/PBS are added. After incubation and washing, alkaline phosphatase labeled goat anti-human IgG (gamma chain specific) is added. Finally, after another incubation and wash, substrate (p-nitrophenyl phosphate) is added and color change is detected at 405 nm. All samples are compared to standard positive control samples and expressed as ELISA units (EU). For indirect immunofluorescence analysis of ANCA, slides are prepared by cytocentrifugation of 100,000 neutrophils. The slides are air-dried and fixed in 100% methanol, then air-dried and stored at −20° C. For use, the slides are rehydrated in PBS and samples diluted 1:20 in BSA/PBS are added. After washing, fluoroscein labeled goat F (ab)$_2$ anti human IgG (gamma chain specific) is added. The slides are washed again and evaluated by fluorescence microscopy. For evaluation of DNase sensitivity of pANCA patterns, slides are pretreated with 100 U/ml of RNase free DNase for 30 minutes. Slides are stained as above with a pair of DNase-treated and untreated slides used for each sample.

[0134] CBir1 ELISA:

[0135] ELISA analysis of anti-CBir1 was performed as previously described 21 but using NH2-terminal fragment of CBir1 (147aa) without knowledge of diagnosis or other serology results. Briefly, ELISA plates were coated overnight with 100 ng/well of CBir1, then blocked with 1% BSA in PBS for 2 hours. Plates were washed and serum was added at a 1:200 dilution in 1% BSA-PBS for a 30 minute incubation. After washing, horseradish peroxidase conjugated anti-human IgG at a 1:10,000 dilution was added and incubated for 30 minutes. After another wash, the plates were incubated with tetramethylbenzidine substrate for 15 minutes. The reaction was stopped with 1 N sulfuric acid and read at 450 nm. Positive was defined as the mean+2 SD of the healthy controls. For Cohort 2 and the longitudinal cohorts and phenotype cohorts, this assay was modified to be more similar to the ANCA, OmpC and I2 protocols: alkaline phosphatase was substituted as the secondary conjugate and incubated for 1 hour followed by paranitrophenyl phosphate as substrate for 30 minutes.

[0136] OmpC/I2 Purification

[0137] Trimeric OmpC is biochemically purified from an OmpF−/−/OmpA−/− disruptive insertion mutant *E. coli* K12 (provided by R. Misra). Mutant *E. coli* glycerol stocks are inoculated into 10-20 ml of Luria Bertani broth supplemented with 100 ug/ml Streptomycin (LB-Strep), and culture vigorously at 37° C. for ~8 hours to log phase followed by expansion to 1 liter in LB-Strep over 15 hours at 25° C. Cells are harvested by centrifugation, washed twice with 100 ml of ice cold 20 mM Tris-Cl pH 7.5, and resuspend in cold spheroplast forming buffer (20 mM Tris-Cl pH 7.5, 20% Sucrose, 0.1M EDTA pH 8.0, 1 mg/ml Lysozyme). Spheroplasts are allowed to form for 1 hour on ice with occasional mixing, and then lysed by 14 fold dilution into ice cold 10 mM Tris-Cl pH 7.5, 1 mg/ml DNase-1, and vigorous vortexing followed by pulse sonication (4×30 seconds, On time=1 second at high power). Cell debris is by low speed centrifugation, and membrane preparation collected by ultra centrifugation at 100,000 g in a swing bucket rotor. Membrane pellet is resuspended by homogenizing into 20 mM Tris-Cl pH 7.5, and extracted for 1 hour in 20 mM Tris-Cl pH 7.5+1% SDS by rotating at 37° C. Pre-extracted membrane preparation is then pelleted by ultracentrifugation and resuspended by homogenizing into 20 mM Tris-Cl pH 7.5 as above, and OmpC is extracted for 1 hour rotating at 37° C. with 20 mM Tris-Cl pH 7.5, 3% SDS, and 0.5M NaCl. Membrane is then pelleted by ultracentrifugation and the supernatant containing trimeric OmpC is collected. SDS is removed from OmpC preparations by detergent exchange dialysis against >10,000 volumes of 0.2% triton ×100 followed by dialysis against >10,000 volumes Tris-Cl pH 7.5. Purified OmpC is quantified using the Bradford reagent (Biorad, Hercules, Calif.) and purity of >95% is validated by SDS-PAGE and Silver staining (Biorad). Purified protein is aliquoted and stored at −20° C. until used.

[0138] The 100 amino acid open reading frame (ORF) of I2 is subcloned into pGEX-KG and expressed in *E. coli* XL-1 blue (Stratagene, La Jolla, Calif.). I2-GST fusion protein is present as an inclusion body, and purified according to manufacturer's instructions by differential solubilization in 0.1% sodium dodecyl sulfate (SOS). The glutathione-S-transferase (GST) control is produced with unmodified pGEX-KG and XL-1 blue cells, and is present about 50% in the soluble and inclusion body fractions. The latter is purified exactly as I2-GST, and the former is purified by G-Sepharose affinity

chromatography. All protein preparations are >90% pure by SDS polyacrylamide gel electrophoresis (PAGE) and Coomassie blue protein staining.

[0139] Determination and Characterization of the OmpC/I2 Response:

[0140] Human IgA antibodies that bind I2 or OmpC will be detected by direct ELISA assays. Plates (Greiner, USA Scientific, Ocala, Fla.) will be coated overnight at 4 C with 100 μl/well of GST alone and I2-GST (5 μg/ml) or OmpC (0.25 μg/ml) in borate buffered saline, pH 8.5. After three washes in 0.05% Tween 20 in phosphate buffered saline (PBS), the plates will be blocked with 150 μl/well of 0.5% bovine serum albumin in PBS, pH 7.4 (BSA-PBS) for 30 minutes at room temperature (RT). The blocking solution will then be discarded and 100 μl/well of sera diluted 1:100 will be added and incubated for 2 hours at RT. The plates will be washed as before and alkaline phosphatase conjugated goat anti-human IgA L-chain specific, Jackson ImmunoResearch, West Grove, Pa.) at a dilution of 1:1000 in BSA-PBS will be added for 2 hours at RT. The plates will be washed three times with 0.05% Tween 20 in phosphate buffered saline followed by another three washes with Tris buffered normal saline, pH7.5. Substrate solution (1.5 mg/ml disodium P-nitrophenol phosphate (Amresco, Solon, Ohio), 2.5 mM MgCl2, 0.01 M Tris, pH 8.6) will be added at 100 _l/well and color will be allowed to develop for one hour at which time the plates will be read at 405 nm. Nonspecific binding of sera to GST alone (typically <0.1) will be subtracted from raw values of I2-GST binding to obtain I2 specific absorbances. Levels will be determined relative to a standard consisting of serum obtained from a well-characterized CD patient. Results will be expressed as ELISA units (EU/ml). Sera with antibody levels exceeding the normal reference range value will be termed positive.

Example 25

Blood Stimulation

[0141] Anti-TCR antibody (IgG1) or controls (control IgG1 BioLegend, San Diego, Calif.) may be stored at −20° C. in 6-well strip microtubes until use. Sixty microliters of whole blood will be added into 6 wells of microwell strip (3 wells for control IgG and 3 wells for anti-TCR antibody) and incubated at 37° C. for 4 hours with the cap closed. Following each treatment, blood samples were stored frozen at _80° C.

Example 26

Final Predictive Model—Overall

[0142] Inter-individual variation in response to anti-TNFα therapy may be explained by genetic variability in disease pathogenesis or mechanism of action. Recent genome wide association studies (GWAS) in IBD have increased understanding of the genetic susceptibility to IBD.

[0143] As disclosed herein, the inventors tested associations of known IBD susceptibility loci and novel "pharmacogenetic" GWAS identified loci with primary non-response to anti-TNFα in pediatric IBD patients and developed a predictive model of primary non-response. Primary non response was defined using the HBI for CD and partial Mayo score for UC. Genotyping was performed using the Illumina Infinium platform. Chi square analysis tested associations of phenotype and genotype with primary non-response. Genetic associations were identified by testing known IBD susceptibility

loci and by performing a GWAS for primary non-response. Step-wise multiple logistic regression was performed to build predictive models.

[0144] As further disclosed herein, non-response occurred in 22 of 94 subjects. Six known susceptibility loci were associated with primary non-response (p<0.05). The 21q22.2/BRWDI loci remained significant in the predictive model. The most predictive model included 3 novel "pharmacogenetic" GWAS loci, the previously identified BRWDI, pANCA and a UC diagnosis (R^2=0.82 and AUC=0.98%). The relative risk of non-response increased 15 fold when number of risk factors increased from 0-2 to ≧3. The combination of phenotype and genotype is most predictive of primary non response to anti-TNFα in pediatric IBD. Defining predictors of response to anti-TNFα will allow the identification of patients who will not benefit from this class of therapy.

Example 27

Final Predictive Model Patient Population

[0145] A total of 94 pediatric CD and UC patients (age at diagnosis <21 years) followed at Cedars-Sinai Medical Center (CSMC) by one clinician (MD) were enrolled in this study. All subjects must have received at least 2 doses of (weeks 0 and 2) of infliximab to be eligible. Infliximab was chosen as the first line anti-TNFα used in both CD and UC for children. This study was approved by the institutional IRB.

Example 28

Final Predictive Model Phenotyping

[0146] All data was collected by chart review and stored in a secured database. For the purpose of this study phenotype was defined as all variables that were not genetic.

[0147] Clinical Phenotype: These included demographic and clinical variables: age, gender, IBD subtype (CD vs. UC), disease duration, age at diagnosis, age at initiation of infliximab, immunomodulator history, steroid history, Harvey Bradshaw Index (HBI) activity scores, Partial Mayo scores and reason for infliximab discontinuation.

[0148] Immune Phenotype: Serum was collected on all patients and analyzed at CSMC. Serum immune responses: anti-*saccharomyces cereviciae* antibodies (ASCA IgG and IgA), perinuclear anti-nuclear cytoplasmic antibody (pANCA), anti-flagellin (antiCBir1), anti-outer membrane porin C (anti-OmpC) and anti-*Pseudomonas fluorescens*-associated sequence I2 (anti-I2) were analyzed blinded to therapeutic responsiveness by ELISA as previously described.

Example 29

Final Predictive Model—Genotype

[0149] Genotyping was performed at Children's Hospital of Philadelphia (CHOP) using the Illumina Human550 platform (n=70) and the Medical Genetics Institute at CSMC using the Illumina Human610 platform for CD samples (n=17) and HumanCNV370 platform for UC samples (n=11) (23). First, genotype data were tested for association between previously reported IBD susceptibility SNPs and anti-TNFα response. Table 11 illustrates the 28 SNPs included in this part of the analysis and references the GWAS that first reported these associations with disease. Twenty-one SNPs from a previous CD meta-analysis GWAS, 5 SNPS from various UC GWAS and 2 SNPs from a pediatric IBD GWAS were ana-

lyzed. Second, the genome wide data were tested for association with anti-TNFα response ("pharmacogenetic" GWAS, see below).

TABLE 11

Known Genetic Susceptibility Loci	
Chromosome/ Loci of interest	GWAS Reference 1 = Adult CD (14) 2 = Adult UC (15-17) 3 = Pediatric IBD (18)
1p13/PTPN22	1
1p36	2
1q23/ITLN1	1
1q24	1
1q21.2/ECM1	2
1q32.1/IL10	2
1p31/IL23R	1
2q37/ATG16L1	1
3p21/MST1	1
5p13/PTGER4	1
5q31/IBD5	1
5q33/IL12b	1
6p21/HLA-DQA1/TNFα, TNFβ	2
6p22/CDKAL1	1
6q27/CCR6	1
8q24.13/TRIB1	1
9p24/JAK2	1
9q32/TNFSF15	1
10q21/ZNF365	1
10q24/NKX2-3	1
12q15	2
13q14/C13orf31	1
16q12/NOD2	1
17q12/CCL2	1
17q21/ORMDL3/STAT3	1
20q13/TNFRSR6B	3
21q22/COSLG	1
21q22.2/BRWD1	3

Example 30

Final Predictive Model Outcomes and Definitions

[0150] The primary outcome of this study was to identify genetic loci associated with primary non-response defined as:

[0151] CD: Failure to decrease HBI $\geqq$3 points (24) or increase from baseline at week 10 or 4 weeks after their last infusion if they did not receive the 3rd induction dose

[0152] UC: Failure to decrease $\geqq$2 points or increase from baseline in the sum of stool frequency and rectal bleeding subscores of the partial Mayo score (7) and no improvement in the physician's global assessment subscore at week 10 or 4 weeks after their last infusion if they did not receive the 3rd induction dose

Example 31

Final Predictive Model—Univariate Analysis

[0153] Association between clinical and demographic variables and primary non-response: The Chi-square test was used to check the association of primary non-response with the following categorical variables: CD vs. UC, male vs. female, serum immune response positivity, percentage of immunomodulator use at the start of infliximab and primary non-response. The Student t test was used for associations of continuous variables; age of diagnosis, disease duration and duration of immunomodulator use at the start of infliximab.

[0154] Association between known IBD susceptibility loci and primary non-response: The Chi-square test was applied to test the association between each SNP (Table 11) and primary non-response. A dominant model based on the presence of the rare allele was assumed. Relative risk was calculated by comparing the risk of non-response in the patients with a specific genotype versus those without the genotype.

[0155] Pharmacogenetic Genome Wide Association Study (GWAS):

a. Principal components (PC) analysis (using Eigenstrat) was conducted to examine population stratification (25). All the subjects formed one cluster with no significant outliers. There was no need to correct for population stratification during the association analysis, as the first ten PC evaluated were not significantly associated with primary non-response.

b. For the purpose of quality control, SNPs with a minor allele frequency (MAF)<0.01, genotype failure rate >0.10, HWE P value <0.001 were excluded from the analysis. Allelic association between an individual SNP and primary non-response was carried out by chi-square test in PLINK (26). The first 10 SNPs with the most significant results were then retained for modeling. Following quality control, 301,742 SNPs were available in all data sets for analysis.

Example 32

Final Predictive Model—Multivariate Analysis

[0156] Predictive models of primary non-response: Models to predict non-response were built using step-wise multiple logistic regression, combining a) IBD susceptibility SNPs, b) the top 10 hits from the pharmacogenetic GWAS analysis, c) serology status and d) IBD subtypes. Since rs5975493 and rs7059861 are in high linkage disequilibrium, only rs7059861 was kept in the model. Exact logistic regression was used if the estimate from a regular regression model was not available. The significance level for a variable to enter and stay in the model was 10%. The likelihood based pseudo-R squared from the logistic regression model was used to measure the strength of association as well as the proportion of variance of the outcome accounted by the model's independent variables.

[0157] Models were built at five different levels:

[0158] I. demographic variables, serology status and IBD subtype only

[0159] II. known IBD susceptibility SNPs only

[0160] III. model I and II combined

[0161] IV. pharmacogenetic GWAS SNPs (dominant model assumed) only

[0162] V. model III and IV combined (final model). (known IBD susceptibility SNPs, pharmacogenetic GWAS top hits, serologic status and clinical variables)

[0163] Clinical Utility Measures: The area under the Receiver Operating Characteristic (ROC) curve (AUC) was used as a measure of the predictive performance of the final model. The risk score was calculated based on the final model by assigning each risk phenotype or genotype as 1 point. Sensitivity [# true positives/(#of true positives+#of false negatives)], specificity [#of true negatives/(#of true negatives+#of false positives)], accuracy [(sensitivity+specificity)/2] and positive likelihood ratio test (sensitivity/(1−specificity)) for primary non response were also calculated for the

final model (28). All statistical analysis was conducted by SAS software v9.1 (SAS Institute; Cary, N.C.).

Example 33

Final Predictive Model—Results of Patient Population and Phenotype Associations

[0164] Of the 94 patients evaluated, 22 patients (23%) met the criteria of primary non-response. Table 12 illustrates the key demographic data for both responders and non responders. A diagnosis of UC (p<0.0001) and pANCA positivity (p=0.0001) were associated with primary non-response. Gender, mean age at diagnosis, disease duration at initiation of infliximab, percentage of immunomodulator use and duration of use at start of infliximab did not differ between the two groups.

TABLE 12

Phenotype Associations with Therapeutic
Outcomes to Anti-TNFα

CLINICAL VARIABLE	NON-RESPONSE	RESPONSE	P Value
UC vs. CD	14:8	6:66	<0.0001
Mean age at diagnosis (years)	10.1	10.5	0.71
Gender M:F	8:14	40:32	0.12
Disease duration at start of IFX (months)	26	25	0.96
IMM use at start of IFX (%)	79%	92.8%	0.1
Duration of IMM at start of IFX (months)	12.7	15.3	0.57
pANCA+	76.2%	29%	0.0001
ASCA+	0%	46.9%	0.0003

Example 34

Final Predictive Model Results of Genetic Associations: Univariate Analysis

[0165] Known IBD Susceptibility Loci: Of the 28 previously identified genetic loci (Table 11), 6 were found to be significantly associated with primary non-response. FIG. **4**

herein illustrates the frequency of primary non-response for the different genotypes of these 6 SNPs. Four of the 6 SNPs are from the CD meta-analysis, 1 from the UC GWAS and 1 from pediatric IBD GWAS. For this analysis, the dominant model of the rare allele was assumed. The common allelic variant was associated with non-response in 4 of the 6 SNPs. Table 13 compares the reported IBD risk allele with the allele found to be associated with non-response in this study for all 6 SNPs. In only 2 of the SNPs was the disease risk allele the same as that found to be associated with non response to anti-TNFα.

TABLE 13

Allelic Variants

SNP and Gene/Locus	GWAS Reference 1 = Adult CD (14) 2 = Adult UC (15-17) 3 = Pediatric IBD (18	IBD Risk Allele	Non-Response Allele
rs2241880 2q37/ATG16L1	1	C	T
rs2188962 5q31	1	T	C
rs6908425 6p22/CDKAL1	1	C	T
rs762421 21q22/ICOSLG	1	G	A
rs2395185 6p21/HLA-DAQ1	2	G	G
rs2836878 21q22/BRWD1	3	G	G

[0166] Pharmacogenetic GWAS: Table 14 lists the results of the chi square analyses for the pharmacogenetic GWAS. Only those SNPs with a p value $<10^{-4}$ are listed.

TABLE 14

Pharmacogenetic GWAS: p < 0.0001

Chromosome	SNP	Position*	Gene db129*,	Other loci**,	OR	P
13	rs1155848	78786477		RBM26	35.73	5.35E−07
5	rs1592749	159904599			5.949	1.09E−06
X	rs765132	133150270		347475 |402425 |644403	35	1.09E−06
6	rs4707930	72463040			6.603	5.55E−06
10	rs7905482	81853944		PLAC9 |389988 642506 |642521 |642538 |727879	4.875	1.08E−05
20	rs6100556	57701043	PHACTR3	PHACTR3	4.951	1.23E−05
X	rs7059861	133191565		347475 |402425	8.333	1.62E−05
X	rs5975453	133212999		347475 402425	8.333	1.62E−05

TABLE 14-continued

			Gene	Other		
Chromosome	SNP	Position*	db129*,	loci**,	OR	P
				Pharmacogenetic GWAS: p < 0.0001		
10	rs4077511	5568172		CALML3 CALML5 100132159	8.214	1.74E−05
2	rs975664	75222305	TACR1	TACR1	0.1667	1.75E−05
3	rs4855535	69017124	FAM19A4	FAM19A4	5.619	1.77E−05
17	rs4796606	36917613		KRT13 |KRT15 |KRT32 |KRT35 |KRT38 |KRT37 |KRT36	11.73	1.98E−05
8	rs2943177	88121513	CNBD1	CNBD1	6.412	2.06E−05
8	rs11991611	139676572	COL22A1	FAM135B COL22A1	15.29	2.12E−05
10	rs3740543	129140065	DOCK1	DOCK1	NPS	4.932	2.18E−05
21	rs2825673	19888587		100128057	6.438	2.28E−05
1	rs7521532	70351206	LRRC7	SFRS11 |LRRC7	7.143	2.54E−05
3	rs4605505	141323576	CLSTN2	CLSTN2	7.143	2.54E−05
8	rs7003556	5213929			7.143	2.54E−05
14	rs1243519	94370110		GSC	6	3.06E−05
5	rs2044111	22897160		CDH12	4.444	3.54E−05
6	rs2103867	47374655	TNFRSF21	TNFRSF21	12.07	3.6E−05
7	rs17168564	14977349			8.286	3.68E−05
6	rs10485363	13245751	PHACTR1	PHACTR1	5.182	3.87E−05
5	rs7726515	129736249			5.187	4E−05
11	rs835780	44816947		TSPAN18	5.187	4E−05
11	rs835791	44823513		TSPAN18	5.187	4E−05
1	rs3795727	154856074	HAPLN2	GPATCH4 |HAPLN2 BCAN IQGAP3 646129	4.5	4.1E−05
6	rs6906890	13069206	PHACTR1	PHACTR1	5.899	4.31E−05
11	rs7124825	44812803		TSPAN18	0.1263	4.31E−05
19	rs302827	61102034	NLRP13	NLRP13 NLRP8 NLRP1	4.545	4.45E−05
12	rs2723829	11819364	ETV6	ETV6	4.333	4.47E−05
2	rs1372256	141070866	LRP1B	LRP1B	4.626	4.65E−05
4	rs13138970	155494510	DCHS2	DCHS2	5.297	4.75E−05
20	rs1205434	36302930	KIAA1755	BPI	TGM2 KIAA1755	0.1526	4.75E−05
13	rs9556658	96476252		OXGR1	6.111	4.92E−05
2	rs7588326	75202554	TACR1	TACR1	0.1826	5.07E−05
2	rs3771823	75205456	TACR1	TACR1	0.1826	5.07E−05
20	rs1555901	20762132			0.1826	5.07E−05
X	rs4465121	133249071		PHF6	7	5.26E−05
6	rs12527937	16652564	ATXN1	ATXN1	5.5	5.74E−05
7	rs10269232	10442565		100128638	6.368	6.33E−05
6	rs3757105	73950398	KCNQ5	KCNQ5	24.2	6.51E−05
18	rs1667216	27383929		DSG2	TTR	4.952	6.75E−05
12	rs278917	39666755	CNTN1	CNTN1	4.172	6.93E−05
6	rs9404502	104605814		100129694	5.409	7.01E−05
X	rs5977968	133151511		347475 402425 644403	7.333	7.03E−05
1	rs12567958	154861280	HAPLN2	GPATCH4 HAPLN2 BCAN IQGAP3 646129	4.167	7.03E−05
8	rs1880473	88079222	CNBD1	CNBD1	5.085	7.09E−05
4	rs7689941	182246739	hCG__2025798	728081	4.244	7.3E−05
17	rs12937472	15194290		PMP22 TEKT3	8.509	7.5E−05
5	rs4301261	159902033			5.433	7.59E−05
X	rs1264379	132893432	GPC3	GPC3	6.092	7.59E−05
X	rs6529954	4194349			0.1781	7.69E−05

TABLE 14-continued

			Gene	Other		
Chromosome	SNP	Position*	db129*,	loci**,	OR	P
22	rs3088103	25250048	TPST2	CRYBA4	4.308	7.77E–05
				ITPST2		
				TFIP11		
				HPS4		
				644380		
				653715		
				729905		
				100128401		
				HMGB1L10		
6	rs4711716	42375201	TRERF1	TRERF1	8.727	7.82E–05
				387535		
				653802		
7	rs10464448	141433796	MGAM	MGAM	0.134	8.32E–05
X	rs12559781	4225952			7.973	8.49E–05
7	rs2540678	36227249	EEPD1	EEPD1	4.6	8.54E–05
4	rs7659755	182246126	hCG__2025798	728081	4.461	8.62E–05
13	rs770389	50043157	LOC730194	730194	5.1	8.96E–05
21	rs2825699	19934102			5.1	8.96E–05
12	rs7309734	39564210	CNTN1	CNTN1	4.171	9.7E–05
2	rs11903032	3840992			5.469	9.78E–05
8	rs10808755	68679235	CPA6	CPA6	0.08701	9.87E–05

*Defined using dbSNP Build 129

**Loci include genes that overlap each SNP within 100 kb of 5' end and 10 kb of 3' end of each gene. Numbers refer to dbGene (NCBI).

Example 36

Final Predictive Model Results of Multivariate Analysis

[0167] Predictive models of non-response: Logistic multiple regression was employed to develop models of primary non-response. Five different models were developed. Model 1 examined the significance of pANCA and IBD subtype (UC vs. CD). Both pANCA (OR 5.4; p=0.01) and the diagnosis of UC(OR15.0; p=0.0001) remained significant in model I, with an R squared (R^2) of 0.48. Model II (R^2=0.30) examined the 6 SNPs from the univariate analysis. Four (4) of the 6 IBD susceptibility SNPs remained significant; rs2188962 (5q31) (OR 3.3; p=0.04), rs6908425 (6p22/CDKAL1) (OR12; p=0.04), rs2836878 (21q22/BRWD1) (OR 3.3; p=0.05) and rs2395185 (6p21/HLA-DAQ1) (OR 4.6; p=0.01). Table 15 shows the results of Model III which included serology, IBD subtype and susceptibility SNPs (combining the variables of models 1 and II). 3 SNPs survived the model when combined with these other independent variables. Model IV analyzed the top 10 SNPs from the pharmacogenetic GWAS and only 4 SNPs remained significant; rs975664 (TACR1) (OR17.6, p=0.0006), rs4855535 (FAM19A4) (OR 8.8, p=0.006), rs4796606 (KRT32 KRT35 KRT36 KRT13) (OR13.4, p=0.01) and rs765132 (OR 30.1, p=0.03). The R squared for this particular model was 0.67. The results of the final model (V) are shown in Table 16. Model V (R^2=0.82, including all variables) examined the associations of pANCA, diagnosis of UC, the 6 known susceptibility SNPs and the top 10 SNPs from the pharmacogenetic GWAS. UC, pANCA, 3 SNPs from the pharmacogenetic GWAS, and rs2836878 (21q22/BRWD1), a susceptibility SNP remained significant.

TABLE 15

Model III: susceptibility SNPs and phenotype				
Model	Variable	P value	OR	R squared
III:	UC vs. CD	0.0008	14.7	0.59
	pANCA pos	0.004	15.3	
	rs6908425	0.05	4.6	
	6p22.3			
	CDKA1			
	rs2836878	0.02	9.8	
	21q22.2 BRWD1			
	rs2395185	0.047	5.4	
	6p21			
	HLA-DQA1			

TABLE 16

Model V: Final Model				
Model	Variable	P value	OR	R squared
V:	Diagnosis: UC vs. CD	0.008	28.9	0.82
	pANCA pos vs neg	0.03	15.4	
	rs975664	0.01	26.5	
	2p12/TACR1			
	rs4855535	0.02	10.8	
	3p14/FAM19A4			
	rs6100556	0.02	13.8	
	20q13/PHACTR3			
	rs2836878	0.07	8.0	
	21q22/BRWD1			

Example 37

Final Predictive Model—Results of Clinical Utility Measures

[0168] The potential clinical utility of the final model (V) was calculated. Table 17 lists the AUC, sensitivity, specificity,

accuracy and positive likelihood ratio of non response in a patient who had at least 3 of the 6 risk factors of non response based on model V. In addition, the negative likelihood ratio, i.e. the likelihood that a patient will not be a non-responder if at least 3 risk factors are absent, was calculated at 0.06.

TABLE 17

| | | | | | Positive |
| | | | Sensi- | Speci- | Accu- | Likelihood |
Model	Variable	AUC	tivity	ficity	racy	Ratio
V:	Diagnosis	0.98	0.95	0.88	0.92	8
	pANCA					
	rs975664 2p12					
	TACR1					
	rs4855535					
	3p14					
	FAM19A4					
	rs6100556					
	20q13					
	PHACTR3					
	rs2836878					
	21q22 BRWD1					

The relative risk of non-response was calculated based on the number of risk factors (model V) carried by an individual patient. Both the frequency of non-response and the relative risk increase with increasing number of risk factors (p<0.0001) (FIG. 5).

Example 38

Final Predictive Model

[0169]

TABLE 18

MODEL	MODEL DESCRIPTOR	R SQUARED	AUC
1	Diagnosis and pANCA	0.48	0.9
II	Known Susceptibility SNPs only	0.3	0.8
III	Diagnosis, pANCA and known susceptibility SNPs	0.59	0.93
IV	Pharmacogenetic GWAS SNPS only	0.67	0.94
V	Diagnosis, pANCA, known susceptibility SNPs AND pharmacogenetic GWAS SNPs	0.82	0.98

[0170] Anti-TNFα is an important and effective class of therapies for the management of both adult and pediatric IBD patients. Clinical experience suggests inter-individual variation in efficacy, both induction and maintenance, and in the occurrence of side effects. There are likely multiple host factors that influence these variations such as disease and immune phenotype as well as genetic background. The ability to predict which patient would have a lower likelihood of response before treatment is initiated in order to minimize exposure to potentially ineffective therapies may be an important consideration in IBD patients. In the current era of risk/benefit balance, this concept may be very timely.

[0171] As described herein, the inventors tested the associations of known and novel genetic loci with primary response outcome and developed a predictive model of primary non response using clinical phenotype, serologic and genetic variables. Six of the 28 known susceptibility loci tested were found to be associated with primary non response

in the univariate analysis. The relative risk of primary non response ranged from 2.1-2.9. When tested in the multivariate analysis, 4 of these loci remained significant. However when combined with the novel pharmacogenetic GWAS loci, only 1 loci remained significant. This one locus was initially reported in the pediatric IBD GWAS reported by Kugathasan et al. The functional significance of this locus remains unknown. Of the 10 novel pharmacogenetic GWAS loci tested in the predictive model, 3 remained significant in the final model. TACR1 is a receptor for substance P a known pro-inflammatory molecule. PHACTR3 (phosphatase and actin regulator 3) is associated with the nuclear scaffold in proliferating cells. While there is little known about FAM19A4 it is thought to be structurally related to MIP1α and function as a chemokine. The pharmacogenetic GWAS identified top loci did substantially improve the strength of the prediction of non-response compared to known susceptibility loci. In addition, a diagnosis of UC and pANCA positivity was independently associated with primary non-response. Table 18 compares the r-squared and AUC values for all 5 models. The combination of genotype, phenotype and serotype was the best predictive model of non response to anti-TNFα with an r-squared of 0.82 and an AUC of 0.98, and substantially better than the models that included only known IBD SNPs. (models II or III).

[0172] The findings suggest that the majority of the known IBD susceptibility loci do not appear to greatly modify or influence primary response outcomes to anti-TNFα in pediatric IBD patients. This raises the possibility that the majority of genes that are associated with risk of disease may not influence the immune pathways that should be targeted to control or modify disease activity. The results of previously reported candidate gene association studies with anti-TNFα response have not been translated into the clinic and the functional significance of the genes tested remain unknown (8-13). The functionality of the cytokines and/or receptor renders them of interest as it relates to therapeutic outcome. With the GWAS approach, however, no a priori assumptions need to be set, as there is not a prior focus on a particular protein or target or enzyme as it relates to drug response. This hypothesis generating approach allows the identification of genetic variants that are associated with response and non-response and thus potentially identify pathways that are responsible and may well be apparent from a functional and mechanistic perspective. In this study the inventors have analyzed the associations with primary non-response only, as believed this was of the greatest clinical relevance.

[0173] As described herein, the inventors have included all pediatric IBD subjects receiving anti-TNFα therapy. Currently clinicians treat both CD and UC with anti-TNF therapy and the clinical trial data suggest similar primary non response and steroid free remission outcomes for both disease subtypes. Moreover there is genetic and serologic evidence that there is pathway biology overlap within the spectrum of CD and UC phenotype. The inventors analyzed UC, CD and shared susceptibility loci and the pharmacogenetic GWAS would identify loci that are independent of disease phenotype.

[0174] Defining predictors of response to anti-TNFα will assist clinicians in choosing the appropriate therapy for the appropriate IBD patient, with the goal of maximizing efficacy and minimizing toxicity. As research progresses in defining the characteristics of patients who require biologics, of equal importance will be the research as proposed herein to indi-

vidualize therapy based on who will or will not respond to different classes of IBD therapeutic interventions. The development of adverse events to anti-TNF therapies such as lymphoma, and sepsis naturally induce caution in clinicians who would like the ability to appropriately select patients who are most likely to respond to these therapies.

[0175] As readily apparent to one of skill in the art, after a diagnosis of nonresponsiveness to anti TNFα in an individual, the invention also includes the administration of any number of treatments that may act as an alternative to anti TNFα therapy, such as natalizumab for example. Similarly, after a diagnosis of responsiveness to anti TNFα therapy, any number of examples of anti TNFα therapy may be used, such as infliximab or cyclosporin. Additionally, as apparent to one of skill in the art, the various embodiments described herein may be used in conjunction with any number of additional inflammatory bowel disease treatments, therapies and methods of diagnosis and prognosis. Finally, as apparent to one of skill in the art, the invention may be applied to any number of conditions and diseases related to or potentially affected by anti TNFα therapy and the invention is not limited to inflammatory bowel disease. While the description above refers to particular embodiments of the present invention, it should be readily apparent to people of ordinary skill in the art that a number of modifications may be made without departing from the spirit thereof. The presently disclosed embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

[0176] Various embodiments of the invention are described above in the Detailed Description. While these descriptions directly describe the above embodiments, it is understood that those skilled in the art may conceive modifications and/or variations to the specific embodiments shown and described herein. Any such modifications or variations that fall within the purview of this description are intended to be included therein as well. Unless specifically noted, it is the intention of the inventor that the words and phrases in the specification and claims be given the ordinary and accustomed meanings to those of ordinary skill in the applicable art(s).

[0177] The foregoing description of various embodiments of the invention known to the applicant at this time of filing the application has been presented and is intended for the purposes of illustration and description. The present description is not intended to be exhaustive nor limit the invention to the precise form disclosed and many modifications and variations are possible in the light of the above teachings. The embodiments described serve to explain the principles of the invention and its practical application and to enable others skilled in the art to utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. Therefore, it is intended that the invention not be limited to the particular embodiments disclosed for carrying out the invention.

[0178] While particular embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that, based upon the teachings herein, changes and modifications may be made without departing from this invention and its broader aspects and, therefore, the appended claims are to encompass within their scope all such changes and modifications as are within the true spirit and scope of this invention. Furthermore, it is to be understood that the invention is solely defined by the appended claims. It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims

(e.g., bodies of the appended claims) are generally intended as "open" terms (e.g., the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims may contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to inventions containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (e.g., "a" and/or "an" should typically be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should typically be interpreted to mean at least the recited number (e.g., the bare recitation of "two recitations," without other modifiers, typically means at least two recitations, or two or more recitations).

[0179] Accordingly, the invention is not limited except as by the appended claims.

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SEQUENCE LISTING

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<160> NUMBER OF SEQ ID NOS: 18

<210> SEQ ID NO 1
<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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gtggaaaggc ttgatataag taaaacaatg gaatgcttag ctgcaggcct agaaaggacc     180

ctttaattgc caggctctgt caccatatca agcgtggtag ggttcggggc tgaagcatac     240

ttacgaagac acacaaggca gtagctggta ccctcacttc tttaccagaa ccaggatgag     300

yatccacatt gtcctggggg actgggaagg aagagacaga gcgtctccta agaaataaca     360

taaagacaaa tattagacag gattgcagag gtttactgct catcaaattg ttagaaagga     420

ctccaagacg accttgctta agcagactgc ctctgttgat agcctgtcct tctagattct     480

tcaaactaca gaacaattca caaaaaaatc aaaagcaccc tcactcaaat gagaaagaga     540

gccagcacat gccttactct cctgcacact aacctgtgga ctccaaaacc caacaatgaa     600

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 2

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agtacggaga gaaaagacag ctttcagact gcagtccaga tctaactctg ggacgcaaga     120

gagggaagga taattctgtt gaaagagcat cagactgtga tgcggctgta agagtgtctc     180
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aacgagccca gtggggagtt ccagccaaag attgcccagg agaagagtcg cactttgggc     240

agaaatggac aggcccgagc aaccctgcca tgttctgtca ttggctgggg gccacccagg     300

aggcaacatg gtctgacttg aatggtgtgg atccgaggct gcagcctgtc agctgtctgc     360

actccatgca acaggtcctt tgaatggcat gtgttcgtgg ctgccataaa ctgcagcctg     420

ccttttagcc ttacctcctt tgctcttgct ctctgacccy gtgttctggc aacactggcc     480

tgactacacg ccgtatcaca tacaaccaac tgcccatacc aaccccaacc ctgacctttg     540

ctcactcagt tctttctgcc tggaatgcca ctccttccca gttatcccca gcaaaatcct     600

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<213> ORGANISM: Homo sapiens

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taaattttgt gttttcccat atataaaagt gatatattta atgaatgcta gtaatcttaa     180

actggttata taattttata ctacaatgag taccttcgag aaagcttatg gtataagaaa     240

tactatttcc aaaacatttt tgttgcacat ttttggtatt agactcatca ttccaatgac     300

rtctggatta tgggaagaaa ggagcctgac tcttatgatg gaataaccac aaatcagaga     360

ggagtcacaa tagcagctct tggtgcagac tgtataccga tagttttttgc agatccagtc     420

aaaaaagcat gtggggttgc tcacgctggt aagtatactt aattaaacat ttagaatttt     480

actcatttttg ttgtgcagga aaaattgtaa tttctttctg atggacatgg caaacagtta     540

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c                                                                       601
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ctctgtcaag aaggagccac gagttggctt tcatggaatg ggtgctcttg gtggccaaat     180

agaaataaaa cctggctgtc tggtcctgat ccactcacag aagtggcgta aacacccttat     240

ttatgatctg ggacattcaa caccatctta taaaagattc atagaataca cattcacaca     300

cccacaaaaa tcaaragagc agattttcca aaaataggtg caagaaagat ccaacttcca     360

ggataaaatt ttagaaccaa catttccatt agcaaaagcg gtcttgtcta aaactctacc     420

gaccgcgcta aaatcccatt caaaacagag ctctggttac gtagatcgtg atcaataatg     480

agaaactgtg aggcgtcccc gtgggatctg acacttccta ggggagcttc tctccactgg     540

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<211> LENGTH: 801
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<213> ORGANISM: Homo sapiens

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gcatttgcca ccctggctca aaatatcagc catcacattt agtaaattct aacatacaaa     180

gcaaattagc actgatttat cagatttacc attgggtggg gtgaggagga ggaggatgct     240

ggctgactta gcccagtccc ttaagagctc tgttccagag aatatacttg tgctcttcct     300

ccatggccca gcatatgcac agggctccag tcatttgcct ccagcagggg gctcttccac     360

actcattcac agtcagctgg attccaatct ctgctcaagt rtgagcaatg tagatccagc     420

cccctggtta atgtattcat cactgttcaa gcccagtctc tttcagatgt tgagacagtg     480

gccctaactc tgtgtggctg cccagagct gtgcacctac cctcactttc ataccacatt      540

aatttcagat ccttattgtc atgggtttcc caactacttt tttttcttca ggggaaacct     600

ccacaatgta gtttctaata tgttgaattc atactccaga aagtgtcctg tagaataatg     660

tcttactgaa aacggccatc acagccagga gtccttaact atgttctttg atacccttag     720

ttacagtttg ttgtcatgtt cttcacatct tgtgtgaaga ttgttcaagt attggccaaa     780

ggatatgtca ctatctaaaa t                                                801


<210> SEQ ID NO 6
<211> LENGTH: 401
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

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attagaggtc agtgaaaagg aagatgcagt ttgttcccgt ccaggcacaa ggactcttga     180

atttgtccat agttaagaac rgctcatcca ggagcagagc gagaggccgg gctgcgcgtc     240

ctcatctcct ctcccagcct tcgcatcctc ctggctgcct cgcgtttcct ccacgggcct     300

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tgtaaaacag tcactatggg atgacggtga ctggacagtg g                         401


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<211> LENGTH: 601
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

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gaggaagatt gagaggtcta aggcaacttt atctactttc caaaatgttt taaaataaga     120

atgctttatt atttgtgtca tttttaaatt aataaagtag gcatgccatt ctgaaattcc     180

acgtctaaat ggcacaaaag tgtaagatag gcaccacagt tgcttataca acattactct     240

ccaaagatta tattcccaaa cgctttacct attccctctt agaaaagact tccagagtct     300
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ytcagtcttc atcttggcct gtatttttaa cccattaggc atcctcttgg ggtaacttca        360

gcaggctcca taggtacaac aaccttcacg tgatctttaa attagctcca taatagtgat        420

aatgaggcag gaaccttgag ataaaaagca gatattacag gttccacttt cgcttctagc        480

actaatgatt acatggaaag tcgctcaacc caagttatag cttccacatt catatggaag        540

gaataacaac aagaattata cctcactcct actcagggac atgcaggtag gaaccacaac        600

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

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gtcaaacaca cttattccag gatatatttc agagtgactc caaattccca tctgttgcta        180

gaaccaatca tttctgccgt kccaaaaaat tatcgtagct cagaagacct atgttaaaaa        240

ggccaaaaaa aaaaaaggaa tcaattagca ttttaatgtt aaaatgaaac taatttccag        300

tagcaaaata atggtttta accatgacac ctgcagtttc aggcaagtgg cagacagcca        360

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<210> SEQ ID NO 9
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

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gaaaaagtgg caaaacacct tattgactgc ttgttcgcag rctaaggttg tgacgagaag        120

tacaagagaa tgaatttggc cagctatctg gagagtaggg tacctgtgaa gcccaggcct        180

ctaaatgggg tcctctcaca t                                                  201


<210> SEQ ID NO 10
<211> LENGTH: 401
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

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gcagcagttc acatttataa cgcattacaa ccagaacttg aggcctaaga aatttctatg        180

tcgagtccac agtttcaaac rcaaattcac tcatcaaggc tttgttcagg catcagggaa        240

acatcctggc agcaagtata cctatataag gaaatattag gtcacgatcc cataactcca        300

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

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tataaacaaa tcattcaaaa aggaggaaat taaagcttca gagaagcatg taaaggtaat     120

atccaactcc actaacaaga agggaaaaat tgaaatgaaa attaaaactg taatacagca     180

gtattcttat gagaaagaac rtagaatttc tgtgatacac tgtgctttca aaggcatata     240

gacaaagtac tcatgcattg ttagaagaag ggtaatttaa caatatctat caatgttaaa     300

aattgcttac atcttttgat gcagcaaatt gatgtatata tgtttcccta taaacatata     360

tacaaaggta ttcttcccat cattgtttgg aatagcccca a                         401


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<211> LENGTH: 1001
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

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aagaaaatca acacattatt ttgcacctga aatgcagttc ttgacgcggt gaattccccc     120

tccacccatc ccccgcatac ctggtaatga acatcatcag aagaagttga ttttaagcta     180

ggtagtcaag tacacatctt cattgtttaa ttgcagaact ctatcaaatc tccaactcaa     240

actatcctat gtgggctttc cacaaatgac agcatcattc tggctcattc gattcatcaa     300

caatttgctg atcagaccaa ctcaaaggta aatagcaatt attttagaaa ttgtaataag     360

ggacacgttg cagagagcag gaaataaatc tcaccaaaaa gtgagggcct gctaccttgg     420

tgaagtttct acatatggtt tggaagatat cctggtccca tctgaagttg ctagttgcgt     480

tgccacagct ccatgcagga rtgcctatga tggacaaaag tgaagaaaaa tcttcccggt     540

gggcagagtt ttgagcagag caccaagtaa ttcatttttt aatggaggta gaaattgatc     600

aatacataga tctatgttga ctgatgagca gtaacaaatt ggctgcataa tgggtaactt     660

ggaaaggata tagctaagag attttaggta agaaattttg ctgaataaat ctaaggataa     720

acttctttca gttggcacag aatgtgaaga tatatgtgcc caacataaat gttaacctag     780

gaaaaaccta ttagtaatta ggcggataag atactctgtt ctctagacat aattcccct      840

tttccccaac cactctgtcc ttgcaaatgt ggttcatgag caacatggct atgacagcag     900

agattaagtt atgcatggac tcactaaata atacctattg ctgagtgcct aacttgccaa     960

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<210> SEQ ID NO 13
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

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tctaattcgc cactaatatg cagatgccaa gctagttggt gcttgctttc acytgttttg     180

gctaattgtt ttcggtgtga tttagaaact ccataccttа tgatgcagtt gtacctgatg     240
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caacaactca ccagtgctgg actgtgggag gtcacatcat ttagactgca aattcagaag      300

tgactttcga ggaaatttgg tcccgttccc aagcaataaa gccgtcgcat cataatcagc      360

ttagaacaat ttgccaatga tagttttctg tgttgcgcca tcagagattc tgattcagca      420

agtcctcgtt ggatctcata catctcaatt aaaaatcaac aatagatcgg gcgtggtggc      480

tcacgcctgt ctgtcatccc agcactttga gaggccaagc caggtggatc aggagttcca      540

gaccagcctg gccaacatgg tgaaacccca tctctgctaa aagtacaaaa attagccagg      600

cgtggtggtg catgcctgta gtcccagcta ctggggaggc tgaggcagga gaataacttg      660

agtccgggag gcggaggttg caatgagcca agatcgtgca actgtactcc agccctgggt      720

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aggttgagaa ctataaaaca atctgttgat ttatgcattt aaaacctcaa gactttttt       180

ttttttttt tctggagatg gagtttcgct cttgttgccc aggctggagt gcaatggtgt       240

gatctcggct cactgtaacc tccaccttcc gggttcaagc cattcttttg cctcagcctc       300

cccagtagct ggaattataa gtaagcacca ccatgcccgg ctaattttt atatttttag       360

tagagacgag gttttttccat gttagtcagg ctggtctcga actcccgacc tcaggtggtc      420

ctcccacctc agcctcccaa agtgctggaa ttacaggcat gagccaccac gcctggttgg       480

acttttgtct caaatgaaat tgttaaagga acccacattt tacaaatat gtggtatgtg       540

gtggaaaaaa cttccttcca tgagtctctt ttccagggta tatgggagat aaggaggga       600

agaccagggc tttaggccc ggctcttcct ggtgctgaga tactggaaga ctgccttgta      660

aagcatctag ggatgtaaat tcaggaaaag ttctttaagc attagaccaa agctgagtga      720

gctgggagat tatggatctc gcatgtagac ctgataacgg gcatcggtag gatcttaatc      780

cttggagagc caggtgcctc cctctgccca catgatgtgc atgcaagtaa aaaagaaaca      840

tggaactaaa ttatctccca gttttcctc ctccgcagtc ccctccagct ctatccttcc       900

tttctaccaa gagcagagcc acttagagga caaggtactc aycacgtctg gctcaggtcc       960

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<213> ORGANISM: Homo sapiens

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cagcatatgg aaaaatgaaa gcgctagttt tgagttagaa gcatctttta tctacttcca      120

ctccctccac tttctggtca atattagata cataatcaga gaaatgctta aatttcacca      180
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aaggcttgct tgagttggaa gcttgatttt tttttttagaa gaaattcccc accatccatt     240

ctactgcaaa gattttcttt ctcaagtgct ttcacctgtc aaaagccctc tgtccagata     300

yttagcagat ccctccactc tctcattctg caaggcagag ggaagaggag gctacattga     360

gtgagtgtct accatgaacc aggctcagac acagacatct ggcatctcat gccggcctct     420

cagaggggct gcgaggacag tgggctgccc acgggctctc gggttcagag aggcagtgag     480

cctggctgaa gggcaccagc taggaaatgg cagagccaga ttctgcacat ccccaaagcc     540

caagacacct ccctacctcc cagacttctc catttgagta tatgcgccct gacgaaaagc     600

a                                                                      601
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 16

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acagacttag tggagccttc tctgttgaat tgaatcatat gattcactat tagctggaca     120

tttaatacta tatcgtcttt atattgttca ggattcttct cagttctttt atttgcactt     180

tggaaatgtc tcaggagaag aaattgaaag atgatagttc tttcaaataa ttattccctg     240

tcccaggaag rtagtgtttt aaagacaatt atttaaacaa aatatactac cattttctaa     300

ttcttttttga tttaagctcc ctacaataat gaatgagaag aatgagaatt aagcggttta     360

gaaaacaatg tggttttttgg caaaatcaaa atattttttaa aaatcccttta agatcatcag     420

tgcataccac atgttttgtg aagctttttgt agaatctctg aggtgtccac ctctcttatt     480

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<210> SEQ ID NO 17
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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 17

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gagggaagct atgtagactc tggaagcctt gaagcttagg agcataggaa ttacagctct     120

gtctggttgg cttaaccaca tccaggcatg gaggcaagga aaaaaaaaa aactcaaagc     180

tttgtttgga ggatggtact aggaaagaac taggaaacta gtgagagaag gtaccaagct     240

atgcctttgt ccacccacta ttcaatttac aaatatttct tggtcctata tcaggcactc     300

yattgggtac taggaataaa tacgcagatg aatgaggcat ggctctttcc ccaaaaagga     360

cttatatgtg ctcaaaatgt gttacagaaa tcccatgagg attcttggat attccaagag     420

ggtcaaattt cattgctctg ttttttcatac ctgggactgg gctttagtag actctctctg     480

gtttcctgaa gcttcatacc ccacatctgc cctactgtga gagtccaacc ccagggctct     540

agctggcttc tctcaactgt tctacagttt tctaggccac agcttgagat gtgacagaaa     600

g                                                                      601
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<210> SEQ ID NO 18
<211> LENGTH: 801

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<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

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tacccaacgg ggccactggc ctagaatggt aataaataga attgggtgac aaccttgaag     120

gtcacccgtg gttcagctct ggaggtgtcc ttgtttgtac tcactttgag taaccatcaa     180

cttataaata gcctcaggcc aattgcccag tgatgatttt gactgtcgct tgccaggggc     240

ctgggcttgt ggtttggttg tgagtctgtc atggtctctg tgacctcaga ggaggaggaa     300

ggaagatgat gatggatgct tctagtgatg caagcaacaa acatttttgg acaatgtgcc     360

caataccatt ctctgtactc tgcatgagtt aacccttcag kcttcaaaca acgctttgag     420

gtaggtgagg agactgagca ctaaaaaggt gaatgcggag ccagtgtgag cacaaaaggc     480

ctggttccct gctagaccgt gcctcctctt ggctggagct ctatggaaag agttggaacc     540

agggagcctt ggttaaaata tcagctccat cccttatgac cttgggcaac ttacaaatct     600

ccaaatctgt attttcacct tttaactaga ataatgtatg tcaattatag ggtgttagga     660

ttaaatgaga aaatgtacat aaaacttttg gggcattgtc tggcactggg taagtactca     720

atgaaaaaag gtaatggttt tttaacttgt ttaatgtttc taagccttag gttttccact     780

tataaaatga aagcgtcatt a                                               801
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1. A method of determining a high risk relative to a normal subject of non-responsiveness to treatment with an anti tumor necrosis factor alpha (TNFα) therapy in an individual, comprising:

obtaining a sample from the individual;

assaying the sample for the presence or absence of one or more genetic and/or serological risk factors; and

determining the high risk relative to a normal subject of non-responsiveness to the anti TNFα therapy based on the presence of one or more risk factors carried by the individual.

2. The method of claim 1, wherein the presence of each genetic and/or serological risk factor has an additive effect on increasing the risk of non-responsiveness in the individual.

3. The method of claim 1, wherein the individual is diagnosed with inflammatory bowel disease (IBD).

4. The method of claim 1, wherein the individual is diagnosed with ulcerative colitis (UC).

5. The method of claim 1, wherein the individual is a child.

6. The method of claim 1, wherein the one or more genetic risk factors comprise genetic variants at the loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1).

7. The method of claim 1, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 1, SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID NO.: 4, SEQ. ID. NO.: 5 and/or SEQ. ID. NO.: 6.

8. The method of claim 1, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 7, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, SEQ. ID. NO.: 10, SEQ. ID. NO.: 11, SEQ. ID. NO.: 12, SEQ. ID. NO.: 13, SEQ. ID. NO.: 14, SEQ. ID. NO.: 15, and/or SEQ. ID. NO.: 16.

9. The method of claim 1, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 17, SEQ. ID. NO.: 8, SEQ. ID. NO.: 19, and/or SEQ. ID. NO.: 6.

10. The method of claim 1, wherein the one or more genetic risk factors comprise genetic variants at the loci of ATG16, Orf13, inducible T-cell co-stimulator ligand (ICOSLG) and/or major histocompatibility complex class II DQ alpha 1 (HLADQA1).

11. The method of claim 1, wherein one of the one or more serological risk factors comprise perinuclear anti-neutrophil cytoplasmic antibody (pANCA).

12. The method of claim 1, wherein the anti TNFα therapy comprises infliximab.

13. The method of claim 1, wherein the anti TNFα therapy comprises cyclosporin.

14. A method of determining a significant likelihood of responsiveness to treatment with anti tumor necrosis factor alpha (TNF-α) therapy in an individual, comprising:

obtaining a sample from the individual;

assaying the sample for the presence of one or more serological markers associated with responsiveness to anti TNFα therapy; and

determining a significant likelihood of responsiveness based on the presence of one or more serological markers associated with responsiveness to anti TNFα therapy.

15. The method of claim 14, wherein the individual is diagnosed with inflammatory bowel disease (IBD).

16. The method of claim 14, wherein the individual is diagnosed with ulcerative colitis (UC).

17. The method of claim 14, wherein the individual is a child.

18. The method of claim 14, wherein one of the one or more serological markers comprises anti-*saccharomyces cerevisiae* antibodies (ASCA).

19. A method of predicting a high risk relative to a normal subject of non-responsiveness to anti tumor necrosis factor alpha (TNF-α) therapy in an individual with inflammatory bowel disease (IBD), comprising;

determining the presence or absence of one or more non-responsive genetic risk variants;

determining the presence or absence of positive expression of perinuclear anti-neutrophil cytoplasmic antibody (pANCA);

determining the presence or absence of an ulcerative colitis phenotype; and

predicting a high risk relative to a normal subject of non responsiveness to anti TNF-α therapy based on the presence of one or more responsive risk variants, the presence of positive expression of pANCA, and/or the presence of the ulcerative colitis phenotype.

20. The method of claim 19, wherein one of the one or more nonresponsive genetic risk variants comprise variants at the genetic loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1).

21. The method of claim 19, wherein the high risk relative to a normal subject of non-responsiveness comprises a range of 7 to 10 fold increase in risk of non-responsiveness to treatment with anti TNFα therapy.

22. A method of diagnosing an inflammatory bowel disease (IBD) subtype in an individual, comprising:

obtaining a sample from the individual;

assaying the sample for the presence or absence of one or more genetic and/or serological risk factors of nonresponsiveness to anti TNFα therapy; and

diagnosing the IBD subtype based upon the presence of one or more genetic and/or serological risk factors of nonresponsiveness to anti TNFα therapy.

23. The method of claim 22, wherein the individual is a child.

24. The method of claim 22, wherein the one or more genetic risk factors comprise genetic variants at the loci of tachykinin receptor 1 (TACR1), family with sequence similarity 19 member A4 (FAM19A4), phosphatase and actin regulator 3 (PHACTR3) and/or bromodomain and WD repeat domain containing 1 (BRWD1).

25. The method of claim 22, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 1, SEQ. ID. NO.: 2, SEQ. ID. NO.: 3, SEQ. ID NO.: 4, SEQ. ID. NO.: 5 and/or SEQ. ID. NO.: 6.

26. The method of claim 22, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 7, SEQ. ID. NO.: 8, SEQ. ID. NO.: 9, SEQ. ID. NO.: 10, SEQ. ID. NO.: 11, SEQ. ID. NO.: 12, SEQ. ID. NO.: 13, SEQ. ID. NO.: 14, SEQ. ID. NO.: 15, and/or SEQ. ID. NO.: 16.

27. The method of claim 22, wherein the one or more genetic risk factors comprise SEQ. ID. NO.: 17, SEQ. ID. NO.: 8, SEQ. ID. NO.: 19, and/or SEQ. ID. NO.: 6.

28. The method of claim 22, wherein one of the one or more serological risk factors comprise perinuclear anti-neutrophil cytoplasmic antibody (pANCA).

29. A method of treating an individual, comprising:

diagnosing the individual as susceptible to non-responsiveness to anti tumor necrosis factor alpha (TNF-α) therapy; and

treating the individual.

30. The method of claim 29, wherein treating the individual comprises administering a therapeutically effective dosage of natalizumab.

31. The method of claim 29, wherein the individual has inflammatory bowel disease (IBD).

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