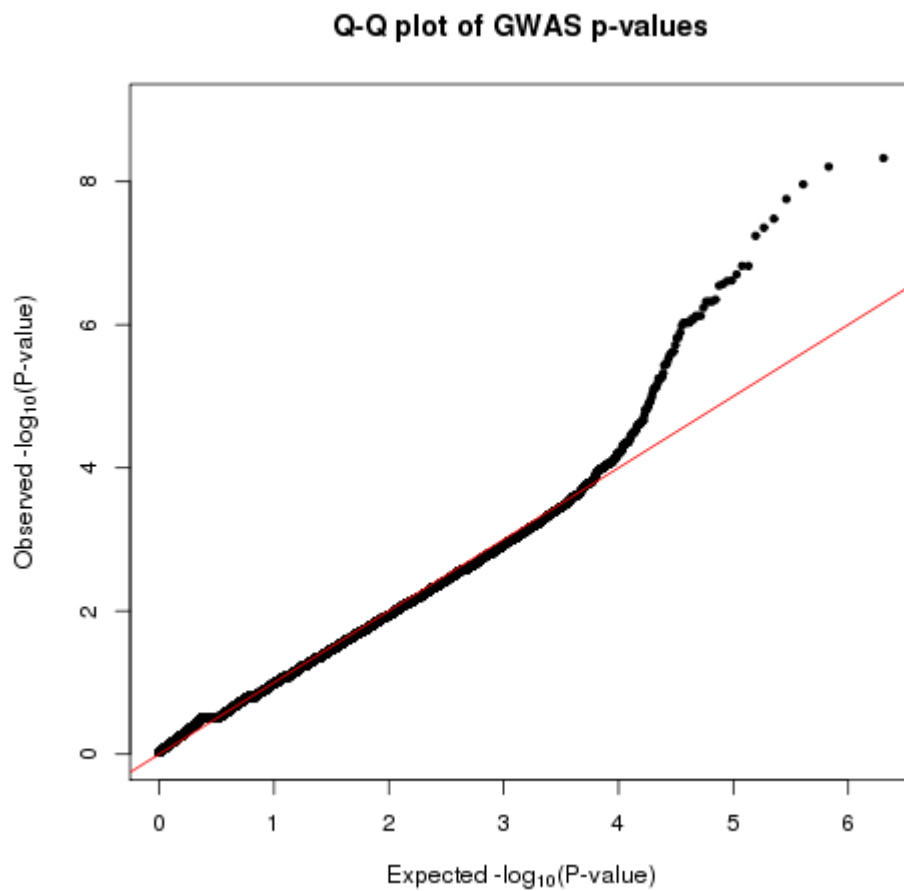


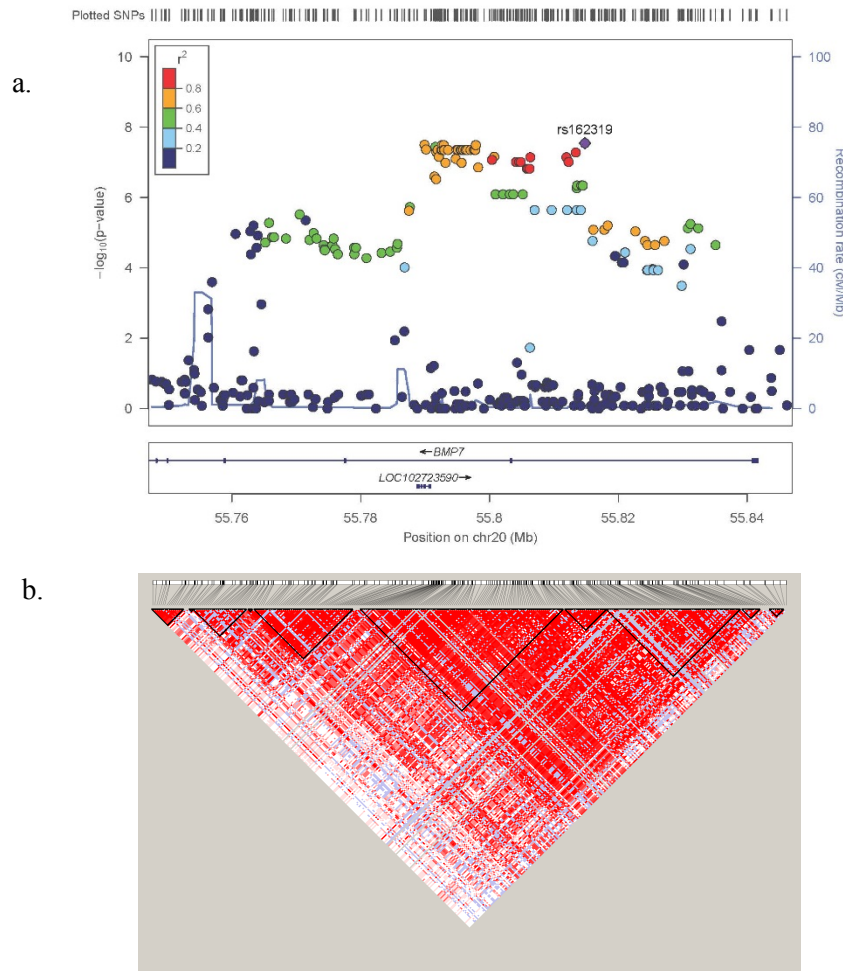
Supplementary Materials

Figure S1. The quantile-quantile (Q-Q) plot showing the observed distribution of $-\log_{10}(P)$ values), obtained from the GWAS, in black, against the expected distribution under the null hypothesis of no association (diagonal line, in red).



GWAS, genome-wide association study.

Figure S2. Regional association plot and LD plot for imputed region on chromosome 20 (± 50 kb from rs6127972). **(a)** P -values ($-\log_{10}$) are plotted against the genomic position of each SNP, with the genes in the region depicted below. The LD (r^2) between rs6127972 and other SNPs are indicated with different colors. Recombination rate in cM per Mb using HapMap controls. The most significant association was for rs162319 ($P = 2.86 \times 10^{-8}$). **(b)** LD plot (r^2) based on genotyped and imputed SNPs in this region for 215 NHW case-parent trios.



cM centimorgan; LD, linkage disequilibrium; Mb, megabase; NHW, non-Hispanic White; SNP, single nucleotide polymorph

Table S1. Association results for χ^2 test for case/control study for 194 (148 males and 46 females) cases and 333 controls (253 males and 80 females). Each sample represents a different set of female controls in the analysis.

CHR	SNP	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10
		P	P	P	P	P	P	P	P	P	P
2	rs2860732	0.1117	0.0919	0.1228	0.12300	0.1117	0.13500	0.0919	0.07498	0.13480	0.24580
5	rs4976789	0.1879	0.2131	0.2131	0.31120	0.1879	0.55030	0.2405	0.34600	0.55030	0.74290
7	rs1983511	0.0606	0.0687	0.0776	0.09819	0.0874	0.17740	0.0982	0.09819	0.13680	0.20610
7	rs10254116	0.0036	0.0043	0.0050	0.00678	0.0050	0.01010	0.0056	0.00648	0.00648	0.02299
7	rs10262453	0.00007	0.00009	0.00011	0.00030	0.00011	0.00042	0.00017	0.00028	0.00025	0.00114
7	rs4723276	0.00008	0.00010	0.00013	0.00023	0.00012	0.00022	0.00019	0.00014	0.00023	0.00098
7	rs10251775	0.1400	0.1557	0.1725	0.21040	0.1907	0.26560	0.1907	0.14760	0.27730	0.30330
8	rs6992848	0.4841	0.4346	0.4841	0.55410	0.4346	0.46610	0.4194	0.37410	0.62920	0.53580
9	rs55917620	0.6892	0.6715	0.6277	0.51860	0.6715	0.79940	0.6715	0.79940	0.89380	0.99130
9	rs7853336	0.5626	0.5794	0.5794	0.73740	0.5432	0.74160	0.5081	0.71530	0.57940	0.60260
10	rs17476559	0.8833	0.9310	0.8833	0.71950	0.9310	0.49980	0.8833	0.76660	0.82740	0.76660
11	rs936460	0.8505	0.8097	0.8266	0.63570	0.9086	0.44890	0.8266	0.48190	0.47360	0.44890
15	rs1873150	0.5298	0.5298	0.5839	0.47800	0.6398	0.52980	0.5839	0.52980	0.69750	0.58390
17	rs1467288	0.2331	0.2331	0.2331	0.10950	0.2331	0.13490	0.2331	0.27520	0.12690	0.21830
17	rs17688881	0.7032	0.7395	0.7032	0.95490	0.7120	0.97740	0.5990	0.81380	0.92850	0.79500
18	rs12458289	0.7534	0.7534	0.6961	0.49000	0.7534	0.44500	0.7534	0.64100	0.64100	0.53780
20	rs1884302	0.0278	0.0316	0.0278	0.02236	0.0316	0.02236	0.0214	0.02236	0.02667	0.03179
20	rs230191	0.0427	0.0301	0.0478	0.04790	0.0301	0.09093	0.0236	0.03811	0.06664	0.05963
20	rs230217	0.0134	0.0076	0.0117	0.00642	0.0076	0.00463	0.0057	0.00408	0.00968	0.00839
20	rs145473835	0.1878	0.1878	0.1878	0.44740	0.1878	0.44740	0.1878	0.28240	0.18780	0.18710
20	rs6127972	0.0088	0.0050	0.0064	0.00416	0.0050	0.00406	0.0037	0.00416	0.00864	0.00561
20	rs115085047	0.6975	0.6975	0.6975	0.19010	0.6975	0.19010	0.6975	0.18950	0.69750	0.18950
20	rs6014954	0.0071	0.0039	0.0061	0.00514	0.0039	0.00501	0.0028	0.00430	0.00801	0.00441
20	rs230218	0.0029	0.0015	0.0025	0.00130	0.0015	0.00109	0.0011	0.00109	0.00295	0.00176
20	rs17404303	0.0410	0.0262	0.0410	0.06010	0.0289	0.06852	0.0325	0.05869	0.09861	0.03584
20	rs162316	0.8284	0.6625	0.8284	0.78570	0.7857	0.82840	0.7026	0.74370	0.66250	0.82840
20	rs13038779	0.1750	0.1750	0.1750	0.19160	0.1318	0.18150	0.1595	0.16560	0.27920	0.18150
20	rs12480759	0.5754	0.5862	0.6217	0.68380	0.5862	0.56450	0.5517	0.49730	0.46530	0.60200
21	rs9977003	0.0733	0.0733	0.0814	0.04716	0.0752	0.02748	0.0658	0.07524	0.02359	0.03022
X	rs4831031	0.4896	0.5369	0.4029	0.58660	0.4449	0.88730	0.5369	0.63870	0.58660	0.38640
X	rs6629161	0.6822	0.5864	0.5864	0.65670	0.6822	0.73130	0.6087	0.70650	0.51810	0.60870
X	rs7061921	0.9989	0.9178	0.8944	0.87160	0.8944	0.95930	0.8419	0.65830	0.65470	0.88790
X	rs5926995	0.3336	0.3336	0.3336	0.28140	0.3336	0.35920	0.3336	0.25210	0.20990	0.37540
X	rs7888988	0.9929	0.9929	0.9929	0.96930	0.9236	0.83310	0.9929	0.91940	0.96110	0.85190
X	rs5908293	0.4753	0.4326	0.3921	0.76730	0.4753	0.82980	0.4326	0.87370	0.84760	0.93600
X	rs66603953	0.6716	0.7281	0.7281	0.56550	0.6174	0.97000	0.7281	0.72810	0.96710	0.84080
X	rs56248124	0.4890	0.6663	0.4890	0.43710	0.5446	0.28250	0.5446	0.52960	0.25700	0.50000
X	rs41313408	0.5409	0.6010	0.5409	0.21860	0.6010	0.28730	0.6010	0.37100	0.54090	0.66460
X	rs5984388	0.4872	0.5247	0.4309	0.39710	0.5635	0.53580	0.4872	0.45110	0.51930	0.28370
X	rs34360385	0.0542	0.0366	0.0320	0.02422	0.0418	0.04498	0.0477	0.05818	0.04498	0.04837
X	rs2573826	0.4346	0.4663	0.5137	0.44830	0.5480	0.38760	0.4483	0.33200	0.65700	0.23850
X	rs7472191	0.5868	0.5472	0.5472	0.52440	0.5089	0.95630	0.6275	0.90810	0.84370	0.97600
X	rs67804731	0.4608	0.4608	0.3932	0.66750	0.4608	0.60840	0.4261	0.43290	0.49010	0.25800
X	rs17149475	0.8271	0.8351	0.8351	0.89310	0.8351	0.92330	0.7506	0.92330	0.83510	0.90710

Table S2. Genotypic transmission disequilibrium test analysis results under an additive, dominant, and recessive models for SNPs with a GWAS allelic transmission disequilibrium test P -value $< 5 \times 10^{-8}$.

CHR	SNP	BP (hg19)	Allelic		Additive		Dominant		Recessive	
			OR	P	OR	P	OR	P	OR	P
20	rs6127972	55797057	2.17	4.41×10^{-8}	2.17	9.38×10^{-8}	2.25	0.0003	2.57	7.10×10^{-6}
25	rs6259097	89022047	0.34	6.22×10^{-9}	0.34	2.98×10^{-8}	0.33	1.8×10^{-7}	0.18	0.0182
25	rs2522623	91626534	0.45	1.76×10^{-8}	0.45	4.14×10^{-8}	0.55	0.0008	0.13	2.91×10^{-6}
25	rs2573826	91628577	0.45	3.31×10^{-8}	0.45	7.36×10^{-8}	0.56	0.0012	0.14	3.22×10^{-6}
25	rs2754857	91632746	0.44	1.09×10^{-8}	0.44	2.73×10^{-8}	0.53	0.0005	0.14	3.22×10^{-6}
25	rs781716	154994995	2.44	4.71×10^{-8}	2.44	1.45×10^{-8}	2.67	2.19×10^{-6}	2.73	0.0002

BP, base pair; CHR, chromosome; GWAS, genome-wide association study; OR, odds ratio; SNP, single nucleotide polymorphism.

Table S3. Candidate gene list and number of SNPs from array found in each gene region.

Gene ^a	Number of SNPs ^b
<i>ALPL</i>	37
<i>ALX3</i>	2
<i>ALX4</i>	16
<i>BBS9</i>	52
<i>BMP2</i>	3
<i>BMP4</i>	7
<i>BMP7</i>	12
<i>BMPER</i>	42
<i>CDC45</i>	5
<i>ESCO2</i>	4
<i>FAM20C</i>	13
<i>FBN1</i>	10
<i>FGF9</i>	6
<i>FGFR1</i>	13
<i>FGFR2</i>	39
<i>FREM1</i>	79
<i>GLI3</i>	48
<i>IFT122</i>	1
<i>IFT140</i>	7
<i>IFT43</i>	9
<i>IGF1R</i>	104
<i>IL11RA</i>	4
<i>IMPAD1</i>	2
<i>IRX5</i>	1
<i>KRAS</i>	2
<i>MASP1</i>	20
<i>MEGF8</i>	1
<i>MSX2</i>	1
<i>NTRK2</i>	79
<i>POR</i>	16
<i>POSTN</i>	4
<i>RAB23</i>	1
<i>RECOL4</i>	1
<i>RUNX2</i>	20
<i>SCARF2</i>	3
<i>SFRP2</i>	3
<i>SKI</i>	15
<i>SMAD6</i>	15
<i>SMO</i>	4
<i>SMURF1</i>	6
<i>SPRY1</i>	1
<i>SPRY4</i>	3
<i>STAT3</i>	12
<i>TCF12</i>	16
<i>TGFBR1</i>	7
<i>TGFBR2</i>	52
<i>WDR19</i>	6
<i>WDR35</i>	4

SNP, single nucleotide polymorphism

^atranscript including untranslated regions obtained from

www.genome.ucsc.edu, GRCh37/hg19

^bonly SNPs with a minor allele frequency >15% and missing in <5 individuals were considered.

Table S4. Discovery study, replication study and meta-analysis results.

CHR	SNP ^a	BP (hg19)	Location	Alleles ^b	Discovery			Replication				Meta-analysis		
					OR	P	RAF	Cases	Controls	OR	P	OR	P	P ^{het}
5	rs4976789	177,968,840	<i>COL23A1</i>	G/A	2.83	7.56x10 ⁻⁶	0.14	193	329	1.20	0.3112	1.63	0.0008	0.0046
7	rs10254116 ^c	33,237,489	<i>BBS9</i>	C/T	1.71	0.0002	0.35	186	331	1.44	0.0068	1.56	6.53x10 ⁻⁶	0.3722
7	rs10262453 ^c	33,256,039	<i>BBS9</i>	C/A	1.79	4.48x10 ⁻⁵	0.34	184	318	1.62	0.0003	1.70	7.46x10 ⁻⁸	0.6296
7	rs4723276 ^c	33,259,793	<i>BBS9</i>	C/T	1.80	1.88x10 ⁻⁵	0.34	188	332	1.63	0.0002	1.72	2.79x10 ⁻⁸	0.5373
18	rs12458289	60,978,586	<i>BCL2</i>	T/G	3.38	5.58x10 ⁻⁶	0.11	193	330	0.86	0.4900	1.40	0.0468	0.0001
20	rs230191	55,772,683	<i>BMP7</i>	C/T*	1.87	9.30x10 ⁻⁶	0.49	191	324	0.77	0.0479	1.15	0.1437	5.11x10 ⁻⁶
20	rs230217	55,796,517	<i>BMP7</i>	G/C	2.20	4.41x10 ⁻⁸	0.40	188	324	1.43	0.0064	1.72	2.24x10 ⁻⁸	0.0315
20	rs6127972	55,797,057	<i>BMP7</i>	T/G	2.17	4.41x10 ⁻⁸	0.40	189	330	1.45	0.0042	1.74	1.27x10 ⁻⁸	0.0379
20	rs6014954	55,797,585	<i>BMP7</i>	T/G	2.17	4.41x10 ⁻⁸	0.39	188	324	1.44	0.0051	1.72	2.40x10 ⁻⁸	0.0305
20	rs230218	55,797,797	<i>BMP7</i>	A/G	2.17	4.41x10 ⁻⁸	0.40	188	326	1.52	0.0013	1.78	2.61x10 ⁻⁹	0.0676
20	rs17404303	55,803,687	<i>BMP7</i>	T/C	0.52	2.37x10 ⁻⁶	0.40	190	328	0.78	0.0601	0.64	5.42x10 ⁻⁶	0.0375
20	rs13038779	55,809,657	<i>BMP7</i>	A/G	0.49	3.05x10 ⁻⁶	0.30	191	331	0.83	0.1916	0.65	4.92x10 ⁻⁵	0.0134
X	rs5984388	89,000,953	<i>CPXCR1,TGIF2LX</i>	T/C	0.46	12.71x10 ⁻⁷	0.25	186	323	0.40	0.7172	0.72	0.0027	3.92x10 ⁻⁵
X	rs34360385	90,407,072	<i>TGIF2LX,PABPC5</i>	T/C	0.44	5.81x10 ⁻⁷	0.26	191	326	0.69	0.0242	0.56	6.27x10 ⁻⁷	0.0504
X	rs2573826	91,628,577	<i>PCDH11X</i>	G/A	0.45	3.31x10 ⁻⁸	0.32	190	331	1.11	0.4483	0.72	0.0014	1.06x10 ⁻⁵
X	rs7472191	92,245,578	<i>PCDH11X,NAP1L3</i>	A/G	0.47	2.70x10 ⁻⁶	0.26	190	332	1.11	0.5244	0.74	0.0069	0.0002
X	rs67804731	154,995,079	<i>TMLHE,SPRY3</i>	G/A	0.93	0.7449	0.19	188	324	0.93	0.6675	0.93	0.5900	0.9978
X	rs17149475	154,995,314	<i>TMLHE,SPRY3</i>	G/A	4.26	0.0390	0.04	193	331	1.04	0.8931	1.36	0.2559	0.1047

CHR, chromosome; SNP, single nucleotide polymorphism; BP, base pairs; RAF, risk allele frequency calculated from replication study controls;

OR, odds ratio; P^{het}, test of homogeneity of the odds ratios

^aSNPs in red font are those that were imputed in the 215 NHW trios discovery sample, and are in linkage disequilibrium to associated SNP

^bMinor allele/major allele, * indicates where minor allele differed between discovery and replication samples.

^cSNP associated with sNCS

Table S5. GWAS TDT analysis results for the top associations identified in the mNCS and sNCS GWAS, and meta-analysis results.

SNP	GWAS mNCS							GWAS sNCS							Meta-analysis	
	A1	A2	T	U	MAF	OR	<i>P</i>	A1	A2	T	U	MAF	OR	<i>P</i>	Meta-P	<i>P</i> ^{het}
rs6127972	T	G	150	69	0.45	2.17	4.41x10 ⁻⁸	T	G	62	54	0.41	1.15	0.4576	1.16 x 10 ⁻⁶	0.0088
rs1884302	C	T	86	94	0.30	0.91	0.5510	C	T	119	26	0.5	4.58	1.13x10 ⁻¹⁴	2.42 x 10 ⁻⁶	7.95x10 ⁻¹⁰
rs10262453	C	A	134	75	0.38	1.79	4.48x10 ⁻⁵	C	A	15	76	0.26	0.20	1.61x10 ⁻¹⁰	0.9081	3.32x10 ⁻¹⁴

GWAS, genome-wide association study; TDT, transmission disequilibrium test; mNCS, metopic nonsyndromic craniosynostosis; sNCS, sagittal nonsyndromic craniosynostosis; SNP, single nucleotide polymorphism; A1, minor allele; A2, major allele; T, transmitted; U, untransmitted; MAF, minor allele frequency; OR, odds ratio; *P*^{het}, Cochran's Q test of heterogeneity.