Supplementary Information

Genome-wide meta-analyses of nonsyndromic cleft lip with or without cleft palate identify six new risk loci

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Supplementary Methods

Bonn study

Statistical analysis was identical to the analysis performed in Mangold et al. 2010[1].

Baltimore study

To ensure that genotype data from the Bonn-II and the Baltimore datasets were comparable, the following measures were undertaken: (i) for each sample-by-chromosome combination with a chromosomal anomaly and/or a missing call rate per chromosome above 5%, genotype calls were filtered out; (ii) samples with a missing call rate of > 5% were removed; (iii) SNPs with a FALSE-value for the quality flag provided in the 'SNP analysis results.csv' (part of the data distributed on dbGaP) were removed.

Meta-analyses for NSCL/P

The likelihood for the combined sample is the product of: (i) the likelihood conditional on parental genotypes (CPG-likelihood) for case-parent trio data, as previously described[2], and (ii) the likelihood for the case-control data. The key parameters in the CPG-likelihood calculation are the genotypic relative risks (RRs) for homozygous and heterozygous affected individuals (ψ_2 and ψ_1, respectively). The corresponding parameters in the likelihood calculation for case-control data are ψ_2 and ψ_1 (since controls in the Bonn-II study were unscreened for NSCL/P), along with the frequency of homozygous and heterozygous individuals in the sample populations. We assumed a multiplicative model (i.e. $\psi_2 = \psi_1^2$), resulting in an asymptotic null distribution of the likelihood ratio test (LRT) statistic of Chi^2 with a single degree of freedom (df). The genomic inflation factor was 1.041 in meta-analysis$_{Euro}$ and 1.047 in meta-analysis$_{all}$.

Imputing at genome-wide significant loci

For each of the newly identified loci, the surrounding region including adjacent recombination hotspots (maximally +/- 500 kb flanking the top SNPs) was imputed using IMPUTE2[3]. For each individual and for each SNP, the most likely predicted genotype above a threshold of 0.8 was assumed. Subsequent statistical analysis was identical to the prior analysis of genotyped SNPs. As suggested by Southam et al. (2011), post-imputation filtering excludes a substantial proportion of SNPs which were inaccurately imputed and, thus, is likely to provide spurious

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association results[4]. Accordingly, SNPs with a MAF less/equal than 5% (as estimated from controls and, in the case of trios, the non-transmitted parental alleles) were removed, as well as SNPs for which the respective LD data were not available in HapMap3 and 1000 genomes_release1.

Subgroup analysis

The NSCLO analysis included 79 European cases and 448 parent-child trios (233 Europeans, 215 Asians). The NSCLP analysis included 320 European cases and 1,013 parent-child trios (433 Europeans, 580 Asians). The same European controls were used for both analyses (n=1,318).

A heterogeneity LRT was used to test for heterogeneity of the genotypic RRs between the NSCLO and NSCLP phenotypes. We applied a general model that allowed for arbitrary genotypic RRs, resulting in an asymptotic Chi^2 null distribution with two degrees of freedom.

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Supplementary Tables

Supplementary Table 1: Asian trio data for the newly reported susceptibility loci. Transmission distortion *P*-values are reported for SNPs reaching genome-wide significance in the meta-analyses. For all markers except rs1873147, association is in the same direction as in the European case-control and European trio data.

dbSNP-ID	Chr.	Position	T	NT	P_{TDT}
rs742071	1	18,852,461	54	88	**4.33×10^{-03}**
rs7590268	2	43,393,629	75	57	1.17×10^{-01}
rs7632427	3	89,617,067	168	247	**1.05×10^{-04}**
rs12543318	8	88,937,456	328	406	**3.99×10^{-03}**
rs1575900	13	79,574,705	315	341	3.10×10^{-01}
rs9318679	13	79,588,136	304	331	2.84×10^{-01}
rs1215465	13	79,589,353	385	411	3.57×10^{-01}
rs8001641	13	79,590,812	240	199	5.04×10^{-02}
rs9545330	13	79,597,167	331	333	9.38×10^{-01}
rs942233	13	79,599,849	343	318	3.31×10^{-01}
rs1873147	15	61,099,685	197	190	7.22×10^{-01}

Chr. – chromosome, T – number of transmitted alleles, NT – number of non-transmitted alleles, TDT – transmission disequilibrium test, *P*-value in bold if nominally significant.

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Supplementary Table 2: Association results for SNPs in high linkage disequilibrium to genotyped topSNP. For each locus, SNPs with r^2-values > 0.8 (based on 1000 genomes_release 1) are depicted in descending order. GWAS top SNPs are marked in bold. For the 8q21.3 locus, no SNPs with $r^2 > 0.8$ were available, therefore, SNPs with $r^2 > 0.5$ have been chosen for this locus. Association results are based on genotyped (G) or imputed (I) SNPs (n.a. - SNP not available after QC; in bold if genome-wide significant).

Locus	SNP-ID	Position (hg18)	r^2 [a]	D' [a]	SNP type [b]	P_{meta_Euro}	P_{meta_all}
	rs742071	**18,852,461**	**1.000**	**1.000**	**G**	**2.63×10^{-07}**	**7.02×10^{-09}**
	rs11583072	18,838,594	0.967	1.000	I	1.47×10^{-05}	1.42×10^{-06}
	rs4920524	18,850,959	0.902	1.000	I	1.53×10^{-06}	**4.94×10^{-08}**
	rs9439714	18,849,076	0.872	1.000	I	2.14×10^{-06}	7.02×10^{-08}
	rs56675509	18,844,221	0.872	1.000	I	6.53×10^{-05}	1.03×10^{-05}
1p36	rs56075776	18,859,095	0.868	0.964	I	7.71×10^{-06}	2.16×10^{-06}
	rs9439713	18,845,363	0.842	1.000	I	2.11×10^{-05}	2.87×10^{-06}
	rs7364475	18,837,648	0.842	1.000	I	1.62×10^{-03}	2.77×10^{-04}
	rs1339063	18,862,162	0.835	0.929	I	1.33×10^{-06}	5.84×10^{-06}
	rs4920338	18,863,380	0.804	0.927	G	1.58×10^{-06}	8.39×10^{-07}
	rs4920339	18,863,592	0.804	0.927	I	1.99×10^{-06}	1.29×10^{-06}
	rs7590268	**43,393,629**	**1.000**	**1.000**	**G**	**4.05×10^{-08}**	**1.25×10^{-08}**
	rs13035011	43,397,621	1.000	1.000	I	6.19×10^{-08}	**3.70×10^{-08}**
	rs35338810	43,402,450	0.943	1.000	I	1.75×10^{-05}	6.44×10^{-06}
	rs6544648	43,453,562	0.895	1.000	I	1.75×10^{-06}	1.91×10^{-06}
	rs10445925	43,523,648	0.895	1.000	I	2.30×10^{-06}	1.40×10^{-06}
	rs35114568	43,528,796	0.895	1.000	I	2.87×10^{-06}	1.73×10^{-06}
2p21	rs2046916	43,539,711	0.895	1.000	I	4.60×10^{-06}	3.21×10^{-06}
	rs7600177	43,481,559	0.848	1.000	I	4.56×10^{-06}	2.65×10^{-06}
	rs6544656	43,488,647	0.848	1.000	I	3.47×10^{-06}	2.27×10^{-06}
	rs6729902	43,430,472	0.836	0.941	I	3.32×10^{-07}	2.48×10^{-07}
	rs12477823	43,473,824	0.806	1.000	I	3.19×10^{-06}	2.15×10^{-06}
	rs7596480	43,474,666	0.806	1.000	I	3.01×10^{-06}	1.99×10^{-06}
	rs6544652	43,479,716	0.806	1.000	I	3.14×10^{-06}	2.12×10^{-06}
	rs7632427	**89,617,067**	**1.000**	**1.000**	**G**	**4.20×10^{-05}**	**3.90×10^{-08}**
	rs11918555	89,624,624	0.967	1.000	I	1.16×10^{-04}	2.06×10^{-07}
	rs724972	89,664,098	0.967	1.000	I	2.07×10^{-04}	3.26×10^{-06}
	rs7652296	89,669,952	0.935	1.000	I	1.91×10^{-04}	2.39×10^{-06}
	rs7650184	89,612,747	0.934	0.966	I	2.10×10^{-04}	9.08×10^{-07}
	rs12636275	89,605,728	0.934	0.966	I	1.80×10^{-03}	7.62×10^{-06}
	rs987748	89,576,720	0.934	0.966	I	1.26×10^{-03}	2.12×10^{-04}
	rs7637670	89,575,857	0.934	0.966	G	2.56×10^{-03}	3.22×10^{-04}
	rs2117137	89,608,195	0.901	0.965	G	9.51×10^{-04}	7.76×10^{-06}
3p11.1	rs35124509	89,604,383	0.901	0.965	I	1.30×10^{-03}	9.68×10^{-06}
	rs6771054	89,572,219	0.901	0.965	I	2.48×10^{-03}	3.63×10^{-04}
	rs73153219	89,708,592	0.901	0.965	-	n.a.	n.a.
	rs6795325	89,724,744	0.901	0.965	I	4.45×10^{-04}	9.03×10^{-07}
	rs7621573	89,677,942	0.870	0.964	I	4.22×10^{-04}	3.05×10^{-07}
	rs67316928	89,564,924	0.869	0.932	-	n.a.	n.a.
	rs73145338	89,677,457	0.869	0.932	-	n.a.	n.a.
	rs10511145	89,680,369	0.869	0.932	G	4.01×10^{-04}	3.59×10^{-07}
	rs7632502	89,552,143	0.869	0.932	I	3.23×10^{-03}	1.23×10^{-03}
	rs11921985	89,550,047	0.869	0.932	I	1.45×10^{-02}	8.12×10^{-03}

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3p11.1 (continued)	rs7635916	89,715,830	0.869	0.932	I	4.44×10^{-04}	5.16×10^{-07}
	rs6551413	89,723,040	0.869	0.932	I	4.44×10^{-04}	5.82×10^{-07}
	rs1520596	89,728,232	0.869	0.932	I	4.31×10^{-04}	1.45×10^{-06}
	rs66499884	89,741,702	0.869	0.932	-	n.a.	n.a.
	rs35968370	89,549,029	0.837	0.930	I	4.28×10^{-03}	8.43×10^{-04}
	rs17027018	89,687,464	0.837	0.930	I	3.13×10^{-04}	2.96×10^{-07}
	rs3792572	89,539,245	0.837	0.930	I	8.73×10^{-03}	5.11×10^{-03}
	rs55747880	89,695,631	0.837	0.930	I	3.22×10^{-04}	1.20×10^{-06}
	rs6772953	89,534,411	0.837	0.930	I	5.21×10^{-03}	1.37×10^{-03}
	rs60243237	89,776,743	0.837	0.930	I	5.17×10^{-04}	4.99×10^{-06}
	rs11925143	89,806,374	0.837	0.930	I	4.66×10^{-04}	4.47×10^{-06}
	rs7613412	89,806,907	0.837	0.930	I	4.66×10^{-04}	4.47×10^{-06}
	rs59381722	89,784,172	0.805	0.897	I	9.34×10^{-04}	9.36×10^{-06}
	rs6551415	89,787,851	0.805	0.897	I	3.70×10^{-04}	2.39×10^{-06}
	rs6806912	89,834,043	0.805	0.897	I	3.97×10^{-04}	1.28×10^{-06}
8q21.3	**rs12543318**	**88,937,456**	**1.000**	**1.000**	**G**	$\mathbf{1.02\times10^{-06}}$	$\mathbf{1.90\times10^{-08}}$
	rs1911665	88,965,596	0.772	0.925	I	3.86×10^{-04}	3.39×10^{-04}
	rs7839686	88,994,844	0.772	0.925	I	2.60×10^{-04}	5.52×10^{-04}
	rs4400429	89,039,798	0.713	0.921	I	1.09×10^{-04}	3.75×10^{-04}
	rs6469114	89,018,858	0.647	1.000	I	9.67×10^{-04}	1.00×10^{-04}
	rs2664364	89,086,684	0.630	0.913	G	5.33×10^{-04}	2.72×10^{-03}
	rs2664366	89,093,956	0.630	0.913	G	1.24×10^{-03}	5.24×10^{-03}
	rs11786656	88,973,474	0.605	1.000	I	7.69×10^{-04}	1.13×10^{-05}
	rs1034832	88,987,447	0.595	0.912	I	1.19×10^{-03}	4.89×10^{-05}
	rs2337160	89,031,182	0.595	0.912	I	1.30×10^{-03}	1.39×10^{-04}
	rs1477915	89,050,656	0.595	0.912	G	5.35×10^{-04}	7.15×10^{-05}
	rs6995841	89,052,352	0.595	0.912	I	1.18×10^{-03}	6.46×10^{-04}
	rs2664371	89,126,078	0.508	0.791	I	1.58×10^{-03}	3.46×10^{-03}
13q31.1	**rs8001641**	**79,590,812**	**1.000**	**1.000**	**G**	$\mathbf{6.20\times10^{-10}}$	$\mathbf{2.62\times10^{-10}}$
	rs1409904	79,587,878	1.000	1.000	I	$\mathbf{9.41\times10^{-10}}$	$\mathbf{3.77\times10^{-10}}$
	rs17215941	79,596,989	1.000	1.000	I	$\mathbf{2.72\times10^{-10}}$	$\mathbf{7.98\times10^{-11}}$
	rs9601323	79,598,398	1.000	1.000	I	$\mathbf{2.00\times10^{-10}}$	$\mathbf{5.11\times10^{-11}}$
	rs11842594	79,599,077	1.000	1.000	I	$\mathbf{1.67\times10^{-10}}$	$\mathbf{3.83\times10^{-11}}$
	rs1854110	79,599,486	1.000	1.000	I	$\mathbf{9.34\times10^{-11}}$	$\mathbf{1.96\times10^{-11}}$
	rs11841646	79,577,303	0.935	1.000	I	$\mathbf{7.24\times10^{-10}}$	$\mathbf{4.71\times10^{-11}}$
	rs11617692	79,595,436	0.875	1.000	I	$\mathbf{2.66\times10^{-09}}$	8.43×10^{-08}
	rs73241018	79,581,765	0.870	0.965	-	n.a.	n.a.
15q22.2	**rs1873147**	**61,099,685**	**1.000**	**1.000**	**G**	$\mathbf{2.81\times10^{-08}}$	$\mathbf{7.92\times10^{-07}}$
	rs7179658	61,099,748	1.000	1.000	I	$\mathbf{2.13\times10^{-08}}$	6.54×10^{-07}
	rs1873149	61,099,481	1.000	1.000	I	$\mathbf{1.83\times10^{-08}}$	5.83×10^{-07}
	rs4774470	61,099,172	1.000	1.000	I	$\mathbf{2.05\times10^{-08}}$	6.34×10^{-07}
	rs4775601	61,099,033	1.000	1.000	I	$\mathbf{2.35\times10^{-08}}$	8.86×10^{-07}
	rs4775600	61,098,993	1.000	1.000	I	$\mathbf{2.17\times10^{-08}}$	6.46×10^{-07}
	rs4774469	61,098,980	1.000	1.000	I	$\mathbf{2.17\times10^{-08}}$	6.46×10^{-07}
	rs12440411	61,100,634	1.000	1.000	I	$\mathbf{1.76\times10^{-08}}$	5.65×10^{-07}
	rs12443285	61,100,649	1.000	1.000	I	$\mathbf{1.76\times10^{-08}}$	5.65×10^{-07}
	rs12443295	61,100,719	1.000	1.000	I	$\mathbf{2.05\times10^{-08}}$	6.34×10^{-07}
	rs4775599	61,098,548	1.000	1.000	I	$\mathbf{6.79\times10^{-09}}$	2.67×10^{-07}
	rs2130165	61,101,572	1.000	1.000	I	$\mathbf{1.71\times10^{-08}}$	5.83×10^{-07}
	rs4774467	61,098,478	0.954	1.000	I	$\mathbf{8.10\times10^{-09}}$	3.20×10^{-07}
	rs2899687	61,112,601	0.861	1.000	I	4.40×10^{-06}	2.46×10^{-05}

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Supplementary Table 3: List of SNPs showing $P<10^{-04}$ in either the European meta-analysis (Euro) or in the combined European/Asian meta-analysis (all).

dbSNP-ID	Alleles[1]	Chr.	Position	P_{meta_Euro}	P_{meta_all}
rs4920520	A/G	1	18802429	5.44×10^{-06}	6.45×10^{-06}
rs4920522	C/T*	1	18812967	7.41×10^{-07}	9.41×10^{-07}
rs17352100	T/C	1	18824699	5.76×10^{-06}	3.25×10^{-07}
rs766325	G/A*	1	18829045	7.51×10^{-06}	7.39×10^{-07}
rs6695765	T/C*	1	18851907	6.67×10^{-06}	1.12×10^{-06}
rs742071	T/G	1	18852461	2.63×10^{-07}	7.02×10^{-09}
rs6659735	G/A*	1	18856284	5.84×10^{-06}	1.36×10^{-06}
rs4920338	T/C	1	18863380	1.58×10^{-06}	8.39×10^{-07}
rs3748748	A/G	1	19890782	8.81×10^{-05}	4.78×10^{-04}
rs427371	T/C	1	40655853	4.66×10^{-05}	1.87×10^{-04}
rs521538	A/G	1	94298211	3.84×10^{-04}	1.25×10^{-05}
rs1191232	T/C	1	94303780	4.53×10^{-05}	8.67×10^{-06}
rs560426	G/A	1	94326026	1.02×10^{-06}	3.14×10^{-12}
rs563429	C/T	1	94326454	3.85×10^{-04}	6.33×10^{-05}
rs952499	C/T*	1	94331013	4.36×10^{-05}	7.18×10^{-08}
rs4147812	G/T	1	94347631	8.37×10^{-08}	9.90×10^{-10}
rs2297634	G/A*	1	94349556	3.15×10^{-04}	4.39×10^{-05}
rs3789451	T/C	1	94358916	6.11×10^{-05}	3.56×10^{-07}
rs11802196	C/A	1	94366631	2.53×10^{-04}	1.55×10^{-06}
rs6686599	A/G	1	94369419	3.37×10^{-04}	1.96×10^{-06}
rs1931565	T/C	1	94369455	1.51×10^{-04}	1.02×10^{-05}
rs1411701	A/G	1	94407616	1.01×10^{-06}	5.88×10^{-07}
rs6541340	C/T	1	94451100	1.01×10^{-06}	1.45×10^{-05}
rs3789688	A/G	1	94463828	1.17×10^{-06}	2.46×10^{-06}
rs11165110	A/G	1	94525057	8.81×10^{-06}	$1.02\times10-^{04}$
rs2172133	T/C	1	94575620	6.21×10^{-06}	1.61×10^{-05}
rs12057415	T/C	1	94602357	6.13×10^{-07}	2.05×10^{-06}
rs2391467	T/C	1	94623031	8.14×10^{-07}	1.10×10^{-06}
rs12047510	C/T	1	161108826	1.86×10^{-02}	5.36×10^{-05}
rs11119328	A/C	1	207951941	6.53×10^{-04}	8.12×10^{-05}
rs3765240	A/G	1	207984774	6.19×10^{-05}	8.00×10^{-06}
rs627670	G/A	1	207995922	2.34×10^{-04}	1.04×10^{-05}
rs909710	A/G	1	207997317	2.75×10^{-04}	8.79×10^{-06}
rs17015169	T/C	1	208003537	1.34×10^{-04}	8.14×10^{-09}
rs590223	G/A	1	208013330	3.48×10^{-04}	1.92×10^{-06}
rs2073485	A/G	1	208029417	9.30×10^{-02}	2.12×10^{-10}
rs861020	A/G	1	208043734	1.78×10^{-06}	3.24×10^{-12}
rs126280	A/G	1	208086447	8.42×10^{-06}	8.11×10^{-11}
rs6689839	G/A	1	208093649	1.21×10^{-02}	1.98×10^{-05}
rs2064163	T/G	1	208115442	2.37×10^{-01}	2.08×10^{-08}
rs932347	T/C	1	208122253	8.33×10^{-04}	1.38×10^{-06}
rs4844913	A/G	1	208134740	9.62×10^{-02}	7.99×10^{-07}
rs9429830	T/C	1	208177160	3.31×10^{-02}	2.20×10^{-07}
rs227178	A/G	1	208283569	8.36×10^{-02}	1.01×10^{-06}
rs2485893	A/G	1	208414778	6.50×10^{-02}	8.86×10^{-07}
rs10779526	T/C	1	208418819	6.65×10^{-02}	8.18×10^{-07}
rs12094311	G/A	1	208435759	1.88×10^{-02}	8.89×10^{-08}
rs12060567	A/G	1	208437213	1.33×10^{-02}	1.62×10^{-07}
rs6428942	C/T	1	243885338	1.37×10^{-05}	1.95×10^{-02}
rs2282381	A/C	1	243907032	2.61×10^{-05}	9.86×10^{-03}
rs4832647	G/A	2	16568877	4.64×10^{-03}	9.40×10^{-05}
rs4497881	A/C	2	16570372	2.49×10^{-04}	1.77×10^{-06}

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rs4441471	G/A	2	16578889	1.78×10^{-04}	7.70×10^{-07}
rs15653	A/G	2	16594991	3.12×10^{-04}	5.35×10^{-06}
rs4952315	G/T	2	32961969	6.90×10^{-05}	9.32×10^{-02}
rs4952316	C/A	2	32967622	1.28×10^{-05}	1.58×10^{-02}
rs4952548	A/C	2	42017719	7.82×10^{-05}	1.21×10^{-04}
rs6749927	G/A	2	43338060	1.00×10^{-04}	2.92×10^{-05}
rs7561670	A/G	2	43359763	9.33×10^{-04}	1.60×10^{-05}
rs11900952	A/G	2	43367540	4.72×10^{-05}	1.03×10^{-06}
rs7590268	G/T	2	43393629	4.05×10^{-08}	1.25×10^{-08}
rs17030752	C/T	2	43483997	1.18×10^{-04}	7.02×10^{-05}
rs9677398	A/C	2	43487639	3.77×10^{-06}	3.78×10^{-06}
rs1873555	C/T	2	43633169	1.02×10^{-04}	2.52×10^{-05}
rs6725776	G/A	2	43636645	2.56×10^{-04}	3.95×10^{-05}
rs10211106	T/C	2	43651557	3.70×10^{-04}	7.83×10^{-05}
rs11897432	A/G	2	43671009	3.41×10^{-06}	2.36×10^{-06}
rs17335631	A/C	2	43727009	6.77×10^{-05}	1.44×10^{-04}
rs7592384	G/T*	2	43779969	9.27×10^{-06}	5.27×10^{-04}
rs4952676	G/A*	2	43783487	2.09×10^{-05}	4.19×10^{-04}
rs4953002	T/C*	2	43784680	2.77×10^{-05}	5.75×10^{-04}
rs1446232	T/C	2	138164301	6.81×10^{-05}	7.67×10^{-03}
rs11680805	C/T	2	138188187	4.91×10^{-05}	5.69×10^{-02}
rs10496787	T/C	2	138200825	5.73×10^{-05}	1.09×10^{-02}
rs1446226	T/C	2	138201519	5.49×10^{-05}	1.25×10^{-02}
rs1112964	C/T	2	145816763	8.53×10^{-05}	6.75×10^{-02}
rs10445672	C/T	2	145821724	3.81×10^{-05}	3.27×10^{-02}
rs6715297	C/T	2	180105114	6.47×10^{-05}	8.13×10^{-02}
rs1400822	G/T	2	180105700	1.66×10^{-05}	4.06×10^{-02}
rs6436163	C/T	2	220312143	4.22×10^{-05}	1.51×10^{-05}
rs1364701	G/A*	2	220366080	7.69×10^{-04}	8.33×10^{-05}
rs982693	A/C*	2	220367882	5.90×10^{-04}	6.54×10^{-05}
rs719325	A/G	2	220376177	5.44×10^{-04}	5.00×10^{-05}
rs3815854	A/G*	2	220376982	4.88×10^{-05}	7.02×10^{-06}
rs992871	C/T*	2	220397828	5.48×10^{-05}	1.29×10^{-05}
rs12477147	G/T	2	221775394	1.84×10^{-03}	7.33×10^{-05}
rs4858297	G/A	3	21216152	6.97×10^{-05}	3.13×10^{-02}
rs6550573	G/T	3	21237353	3.90×10^{-05}	2.21×10^{-02}
rs6795970	A/G	3	38741679	9.01×10^{-05}	9.80×10^{-04}
rs6798015	C/T	3	38773840	1.33×10^{-05}	4.21×10^{-05}
rs7430439	G/A	3	38778643	9.10×10^{-05}	1.22×10^{-03}
rs1512912	A/G	3	89390621	9.47×10^{-05}	2.81×10^{-03}
rs1040017	C/A	3	89412322	3.12×10^{-05}	8.63×10^{-04}
rs7633500	A/G	3	89579772	2.12×10^{-03}	7.35×10^{-05}
rs2117137	C/T	3	89608195	9.51×10^{-04}	7.76×10^{-06}
rs7632427	C/T	3	89617067	4.20×10^{-05}	3.90×10^{-08}
rs6774870	T/C	3	89647581	1.65×10^{-04}	8.24×10^{-06}
rs907548	A/G	3	89657542	1.83×10^{-04}	9.84×10^{-06}
rs10511145	T/G	3	89680369	4.01×10^{-04}	3.59×10^{-07}
rs668668	C/T	3	100919114	2.31×10^{-03}	2.65×10^{-06}
rs694429	G/A	3	100942359	7.92×10^{-03}	2.23×10^{-05}
rs792829	G/A	3	100945337	2.87×10^{-03}	5.67×10^{-06}
rs792841	G/T	3	100953998	7.79×10^{-03}	3.69×10^{-05}
rs792835	T/C*	3	100958985	1.70×10^{-03}	2.82×10^{-06}
rs704570	T/C	3	100959832	3.59×10^{-03}	1.70×10^{-06}
rs704574	G/A*	3	100966463	1.87×10^{-03}	2.56×10^{-06}
rs1038294	T/C	3	100986418	7.93×10^{-03}	2.17×10^{-05}
rs793494	T/C	3	100991458	5.71×10^{-03}	2.33×10^{-05}

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rs1287283	A/G	3	100998440	1.11×10^{-02}	7.56×10^{-05}
rs813218	G/A*	3	101075286	4.49×10^{-04}	1.29×10^{-06}
rs1384062	G/T	3	101080618	2.03×10^{-03}	2.82×10^{-06}
rs793440	T/C	3	101125866	7.74×10^{-03}	3.91×10^{-05}
rs13317017	A/C	3	101148211	5.75×10^{-03}	2.39×10^{-05}
rs4244713	T/G	3	101162274	8.11×10^{-03}	3.00×10^{-05}
rs766778	C/T	3	101234170	1.70×10^{-03}	1.92×10^{-06}
rs12629505	A/G	3	101387473	6.21×10^{-03}	9.23×10^{-05}
rs9857793	T/C	3	101669652	9.68×10^{-05}	2.47×10^{-02}
rs1515496	G/A	3	190991260	9.67×10^{-05}	3.15×10^{-03}
rs3843376	C/T*	3	198298821	6.70×10^{-04}	7.85×10^{-05}
rs12632536	C/T	3	198318047	1.65×10^{-04}	5.84×10^{-05}
rs1134986	A/G	3	198349639	4.06×10^{-04}	7.42×10^{-05}
rs10489880	C/T	3	198445583	9.67×10^{-05}	6.41×10^{-05}
rs338186	T/C	3	198448009	2.63×10^{-04}	4.06×10^{-05}
rs6830734	C/T	4	4703905	9.34×10^{-05}	3.49×10^{-05}
rs1907989	C/T	4	4869826	1.24×10^{-02}	7.66×10^{-05}
rs1105886	T/C	4	41306332	5.86×10^{-05}	4.53×10^{-05}
rs6840263	A/C	4	94927934	1.89×10^{-05}	2.19×10^{-04}
rs270552	C/T	5	38074102	3.85×10^{-04}	7.38×10^{-05}
rs270550	T/C	5	38075952	1.63×10^{-04}	6.58×10^{-05}
rs4348193	T/G	5	77671476	8.01×10^{-06}	1.06×10^{-02}
rs4704506	G/T	5	77690583	1.42×10^{-05}	5.96×10^{-02}
rs4360024	C/T	5	77719962	1.85×10^{-05}	1.37×10^{-01}
rs4703516	T/G	5	80690722	3.33×10^{-04}	2.72×10^{-06}
rs388383	T/C	5	111731534	7.94×10^{-05}	1.37×10^{-04}
rs9327783	A/G	5	136671767	4.13×10^{-04}	6.62×10^{-05}
rs1981973	C/T	5	157916350	1.93×10^{-05}	1.08×10^{-03}
rs1650504	A/G	5	157962128	9.54×10^{-06}	2.75×10^{-03}
rs4242182	T/C	5	174088774	9.16×10^{-05}	4.11×10^{-05}
rs9405785	G/A	6	4860027	7.78×10^{-04}	8.30×10^{-05}
rs17763231	T/C	6	7419342	1.52×10^{-02}	8.55×10^{-05}
rs616879	G/T	6	10500486	2.20×10^{-05}	4.30×10^{-05}
rs2182337	T/C	6	11343668	3.33×10^{-05}	1.95×10^{-03}
rs2535238	T/G	6	29753017	1.44×10^{-04}	7.07×10^{-05}
rs2747457	G/T	6	29764396	1.61×10^{-04}	5.68×10^{-05}
rs3094621	G/A	6	30436732	9.44×10^{-05}	1.93×10^{-05}
rs3095314	A/G	6	31197610	2.17×10^{-05}	2.03×10^{-04}
rs1591514	T/C	6	76286674	8.50×10^{-05}	6.07×10^{-03}
rs4895890	T/C	6	130982926	3.28×10^{-03}	5.83×10^{-05}
rs538017	C/T	6	151358885	2.88×10^{-05}	7.13×10^{-03}
rs1028651	A/G	6	152979558	1.82×10^{-05}	5.44×10^{-03}
rs1028650	C/A	6	152979718	1.77×10^{-05}	6.31×10^{-03}
rs1631293	T/C	6	152981579	6.71×10^{-05}	3.05×10^{-03}
rs1744385	T/C	6	152982159	3.15×10^{-05}	6.39×10^{-03}
rs1631457	G/A	6	152988207	2.56×10^{-05}	2.76×10^{-03}
rs2758805	A/G	6	153000994	3.68×10^{-06}	1.24×10^{-02}
rs1830642	T/C	6	153005519	3.40×10^{-06}	1.19×10^{-02}
rs2758811	G/A	6	153006098	3.17×10^{-06}	1.16×10^{-02}
rs2758812	C/T	6	153007601	4.98×10^{-05}	2.10×10^{-02}
rs2258974	A/G	6	153016243	3.09×10^{-05}	3.34×10^{-04}
rs2996635	T/C	6	153052856	5.99×10^{-05}	9.65×10^{-03}
rs2038616	G/A	6	153064367	2.61×10^{-06}	4.33×10^{-03}
rs4725033	C/T	7	7820533	2.92×10^{-02}	1.40×10^{-05}
rs17218211	G/A	7	20707173	1.65×10^{-04}	8.88×10^{-05}
rs3801936	T/C	7	107323653	6.68×10^{-05}	6.48×10^{-03}

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rs2240627	G/A	7	150719581	2.30×10^{-05}	3.20×10^{-02}
rs7846606	G/A	8	77670168	7.48×10^{-04}	6.82×10^{-06}
rs7830040	T/C*	8	83079508	3.99×10^{-03}	3.47×10^{-05}
rs4529421	G/A	8	83084534	1.16×10^{-03}	1.25×10^{-05}
rs7820074	C/T	8	83091153	9.68×10^{-04}	8.55×10^{-06}
rs7819401	G/A	8	88900831	2.81×10^{-02}	7.45×10^{-06}
rs12543318	C/A	8	88937456	1.02×10^{-06}	1.90×10^{-08}
rs1477915	T/C*	8	89050656	5.35×10^{-04}	7.15×10^{-05}
rs10505528	T/C	8	129710034	3.19×10^{-05}	4.14×10^{-05}
rs10956433	C/T	8	129728946	4.56×10^{-05}	2.01×10^{-04}
rs4236736	A/C	8	129760428	1.72×10^{-05}	2.55×10^{-05}
rs7015145	A/G	8	129778467	2.30×10^{-13}	3.38×10^{-12}
rs6470648	G/A	8	129785490	5.40×10^{-07}	8.98×10^{-05}
rs9297775	A/C	8	129805894	8.14×10^{-13}	5.92×10^{-12}
rs1030608	A/G	8	129808934	7.53×10^{-12}	3.43×10^{-07}
rs1030609	A/C	8	129809059	6.72×10^{-12}	4.49×10^{-07}
rs6996786	T/G	8	129817168	7.79×10^{-12}	4.61×10^{-11}
rs4545057	C/A	8	129858316	2.49×10^{-08}	2.30×10^{-08}
rs4397367	A/G	8	129860721	8.29×10^{-07}	1.12×10^{-04}
rs2395855	T/C	8	129909921	3.17×10^{-16}	7.18×10^{-14}
rs4733653	C/T	8	129913853	2.32×10^{-12}	9.84×10^{-09}
rs11989880	T/C	8	129942164	2.77×10^{-18}	5.89×10^{-15}
rs4733532	G/A	8	129950481	1.21×10^{-15}	2.43×10^{-14}
rs1850889	A/G	8	129959587	7.07×10^{-17}	1.44×10^{-16}
rs1519850	G/A	8	129966003	7.95×10^{-16}	3.77×10^{-15}
rs1519849	A/G	8	129966149	4.05×10^{-16}	1.49×10^{-14}
rs1519847	A/G	8	129984942	3.49×10^{-20}	5.47×10^{-21}
rs1530300	C/T	8	129988640	4.90×10^{-23}	6.31×10^{-22}
rs1519841	G/A	8	129988982	5.90×10^{-20}	1.80×10^{-20}
rs12542837	C/T	8	129995843	1.25×10^{-20}	1.02×10^{-20}
rs987525	A/C	8	130015336	3.94×10^{-34}	5.12×10^{-35}
rs12548036	T/G	8	130017064	8.70×10^{-21}	2.24×10^{-21}
rs7017252	T/C	8	130020026	8.96×10^{-19}	1.81×10^{-20}
rs12547241	A/G	8	130021691	2.66×10^{-15}	9.41×10^{-17}
rs1470206	T/C*	8	130046646	1.49×10^{-14}	2.71×10^{-17}
rs882083	T/C	8	130051938	2.35×10^{-20}	6.83×10^{-23}
rs11787407	A/G*	8	130054622	1.31×10^{-16}	1.39×10^{-18}
rs12546523	G/A*	8	130055292	4.50×10^{-17}	1.19×10^{-18}
rs2004375	T/C	8	130071912	2.76×10^{-11}	2.95×10^{-11}
rs748978	T/C	8	130072298	3.83×10^{-16}	1.27×10^{-14}
rs10110974	C/A	8	130078969	5.55×10^{-07}	1.26×10^{-06}
rs2197111	T/C	8	130084897	2.35×10^{-11}	1.26×10^{-08}
rs7018275	C/T	8	130085681	2.44×10^{-11}	1.30×10^{-08}
rs10505532	A/C	8	130091143	8.88×10^{-07}	3.43×10^{-06}
rs1372452	A/G	8	130098216	9.74×10^{-12}	5.63×10^{-09}
rs12334809	T/C	8	130100188	8.27×10^{-12}	5.86×10^{-09}
rs7844734	T/C	8	130111323	2.35×10^{-07}	1.39×10^{-06}
rs4487715	T/C	8	130125163	3.07×10^{-07}	5.26×10^{-06}
rs10808576	G/T	8	130133153	6.00×10^{-07}	2.88×10^{-07}
rs11996876	C/T	8	130156354	8.35×10^{-10}	3.56×10^{-08}
rs11784932	A/C	8	130164660	9.38×10^{-07}	1.07×10^{-06}
rs4339605	C/T	8	130181350	1.13×10^{-06}	2.06×10^{-06}
rs4571700	T/C	8	130242649	7.47×10^{-06}	1.10×10^{-05}
rs3935421	C/T	8	130272321	4.00×10^{-10}	4.55×10^{-09}
rs6470706	T/C	8	130273916	8.15×10^{-05}	1.05×10^{-03}
rs4422741	C/T	8	130280510	5.52×10^{-10}	6.09×10^{-09}

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rs7819443	A/G	8	130287862	8.88×10^{-06}	1.60×10^{-03}
rs4613964	A/G	8	130290041	7.27×10^{-06}	1.70×10^{-03}
rs7822386	G/A	8	130293903	1.28×10^{-09}	3.33×10^{-07}
rs7826688	A/G	8	130294193	1.20×10^{-09}	3.22×10^{-07}
rs3780136	A/C	9	36835973	9.62×10^{-05}	3.65×10^{-04}
rs9410321	C/T	9	91220006	1.20×10^{-05}	6.09×10^{-06}
rs4132699	C/A	9	91226247	3.52×10^{-05}	5.20×10^{-07}
rs11265876	G/T	9	91229236	2.58×10^{-05}	1.91×10^{-05}
rs10512197	A/G	9	91230295	7.57×10^{-03}	4.49×10^{-05}
rs11999884	G/A	9	91260211	1.86×10^{-02}	5.67×10^{-05}
rs2031970	T/C	9	91393992	2.00×10^{-04}	1.95×10^{-05}
rs7871395	T/C	9	91399407	9.78×10^{-06}	1.75×10^{-05}
rs1475537	T/C	9	91402570	3.25×10^{-05}	2.01×10^{-05}
rs3138512	A/G	9	91412273	2.10×10^{-06}	2.22×10^{-06}
rs3138513	T/C	9	91412315	3.15×10^{-05}	3.45×10^{-05}
rs17539995	A/G	9	91431667	1.23×10^{-03}	7.30×10^{-05}
rs1109998	C/T	9	91467030	1.15×10^{-05}	3.22×10^{-04}
rs4877120	G/T	9	91469268	2.81×10^{-05}	1.06×10^{-04}
rs12352804	A/G	9	92770879	3.03×10^{-03}	7.96×10^{-05}
rs3814127	C/T	9	128305563	9.07×10^{-04}	4.61×10^{-05}
rs10819174	T/C	9	128307886	1.09×10^{-03}	7.08×10^{-05}
rs12356363	T/C	10	20488292	1.19×10^{-04}	8.59×10^{-05}
rs16928239	A/G	10	72420642	8.80×10^{-05}	1.08×10^{-04}
rs17542297	A/G	10	72444914	2.60×10^{-04}	7.84×10^{-05}
rs780689	A/G	10	72796833	1.15×10^{-05}	6.13×10^{-02}
rs2755427	T/C	10	89407452	1.79×10^{-03}	3.54×10^{-05}
rs11197843	T/G	10	118631386	2.02×10^{-05}	2.97×10^{-05}
rs2257791	G/A	10	118633660	1.25×10^{-04}	3.56×10^{-05}
rs10886031	C/T	10	118794983	1.32×10^{-06}	1.89×10^{-06}
rs7078160	A/G	10	118817550	2.81×10^{-08}	3.96×10^{-11}
rs1898355	A/G	10	118818359	2.49×10^{-06}	7.46×10^{-06}
rs4752028	C/T	10	118824981	1.54×10^{-08}	1.71×10^{-10}
rs1393878	G/A	11	13869322	5.40×10^{-02}	9.94×10^{-05}
rs11603089	G/A	11	18238627	2.81×10^{-05}	1.04×10^{-02}
rs1365425	A/G	11	83811667	8.90×10^{-05}	3.35×10^{-03}
rs7950069	A/G	11	114645763	5.90×10^{-03}	5.03×10^{-06}
rs617320	C/A	11	119466904	5.29×10^{-03}	1.54×10^{-05}
rs923811	G/T	11	128920427	7.52×10^{-02}	6.95×10^{-05}
rs722097	A/G	12	585103	2.02×10^{-04}	1.78×10^{-05}
rs3136560	T/C	12	9807813	8.75×10^{-05}	1.48×10^{-04}
rs1554255	G/A	12	41363753	3.36×10^{-05}	1.62×10^{-05}
rs7304375	C/T	12	41376968	2.01×10^{-05}	1.27×10^{-05}
rs727266	T/C	12	51642678	1.49×10^{-03}	9.82×10^{-05}
rs1867445	A/G	12	68327389	3.16×10^{-03}	1.22×10^{-05}
rs1373453	C/T	12	68341177	8.30×10^{-04}	2.47×10^{-06}
rs17106937	G/A	12	68352547	2.95×10^{-03}	1.60×10^{-05}
rs12322558	G/A	12	68366420	3.78×10^{-03}	7.84×10^{-05}
rs6539264	A/G	12	105215707	2.89×10^{-04}	3.33×10^{-06}
rs1532586	G/A	12	105224714	1.61×10^{-03}	2.25×10^{-05}
rs17475847	T/C	13	19806370	8.68×10^{-06}	2.24×10^{-05}
rs4769376	T/G	13	24092771	1.01×10^{-01}	2.91×10^{-05}
rs941823	A/G	13	39911977	8.38×10^{-04}	5.92×10^{-05}
rs9530556	C/T	13	75999906	2.45×10^{-03}	5.07×10^{-05}
rs10492453	C/T	13	76021534	4.45×10^{-03}	9.90×10^{-05}
rs4885678	T/G	13	79338492	9.12×10^{-05}	4.49×10^{-04}
rs9574565	T/C	13	79566875	7.67×10^{-06}	3.80×10^{-05}

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rs9601318	T/C	13	79571192	5.25×10^{-05}	5.84×10^{-06}
rs1575900	G/T	13	79574705	4.87×10^{-09}	1.74×10^{-07}
rs1327314	A/G	13	79581626	1.00×10^{-06}	2.46×10^{-05}
rs9318679	A/C	13	79588136	2.08×10^{-08}	4.08×10^{-07}
rs1215465	A/G	13	79589353	5.62×10^{-10}	7.69×10^{-08}
rs8001641	A/G	13	79590812	6.20×10^{-10}	2.62×10^{-10}
rs9545330	G/A	13	79597167	3.48×10^{-10}	2.17×10^{-06}
rs942233	G/A	13	79599849	1.69×10^{-08}	3.34×10^{-07}
rs4146682	G/A	13	79600066	3.77×10^{-06}	3.86×10^{-07}
rs1755254	G/A	13	79772282	3.43×10^{-05}	2.78×10^{-03}
rs13542	A/G	13	99436393	1.95×10^{-05}	1.28×10^{-06}
rs2518659	T/C	14	30341238	9.49×10^{-05}	1.09×10^{-05}
rs2213951	C/T	14	30345865	1.19×10^{-03}	7.55×10^{-05}
rs8009619	G/T	14	77470073	7.83×10^{-06}	8.08×10^{-05}
rs10134056	A/G	14	80989149	3.67×10^{-05}	1.47×10^{-03}
rs11160835	T/C	14	104658689	1.98×10^{-05}	1.72×10^{-02}
rs3097531	C/A	15	25584546	4.84×10^{-05}	6.74×10^{-01}
rs17673470	C/T	15	25586078	3.01×10^{-05}	6.50×10^{-01}
rs1919360	T/C	15	30830747	7.86×10^{-05}	9.85×10^{-04}
rs1919362	T/C	15	30830949	2.35×10^{-06}	2.80×10^{-05}
rs1258763	G/A*	15	30837715	5.36×10^{-07}	1.81×10^{-06}
rs3812929	G/T	15	30846355	6.91×10^{-05}	2.51×10^{-03}
rs3743106	T/G	15	30851101	5.35×10^{-06}	2.34×10^{-06}
rs11635135	G/A	15	31000565	4.32×10^{-04}	3.61×10^{-05}
rs2280065	T/C	15	55550032	9.80×10^{-05}	2.05×10^{-03}
rs1906779	A/G	15	61090469	8.86×10^{-06}	3.28×10^{-03}
rs8029221	T/C	15	61095636	4.47×10^{-07}	5.58×10^{-05}
rs1873147	C/T	15	61099685	2.81×10^{-08}	7.92×10^{-07}
rs12595658	A/G	15	61100439	1.87×10^{-05}	3.79×10^{-03}
rs6494383	G/A*	15	61103265	2.15×10^{-05}	4.04×10^{-05}
rs11071718	A/C	15	61114586	3.50×10^{-05}	5.21×10^{-04}
rs8049367	C/T	16	3920446	4.47×10^{-05}	8.74×10^{-05}
rs1003677	T/C	16	6396764	7.95×10^{-02}	8.61×10^{-05}
rs12927233	C/T	16	32045466	4.00×10^{-04}	5.21×10^{-05}
rs4435250	T/C	16	53414172	1.25×10^{-05}	1.64×10^{-04}
rs11078772	A/C	17	8812267	1.51×10^{-04}	3.23×10^{-05}
rs2872615	C/T	17	8855418	7.40×10^{-06}	4.73×10^{-07}
rs9788972	A/G	17	8860355	5.07×10^{-04}	2.49×10^{-07}
rs1880646	C/T	17	8870570	3.83×10^{-06}	3.96×10^{-06}
rs9674710	A/G	17	8881934	3.89×10^{-05}	3.03×10^{-02}
rs8076457	T/C	17	8884654	4.67×10^{-07}	2.17×10^{-07}
rs8069536	T/G	17	8897010	1.54×10^{-04}	1.28×10^{-06}
rs8081823	A/G	17	8906276	3.36×10^{-03}	7.49×10^{-05}
rs17760296	G/T	17	51970616	9.91×10^{-05}	2.65×10^{-04}
rs12936596	G/T	17	52098098	6.71×10^{-05}	6.56×10^{-04}
rs12451251	C/T	17	52104557	5.45×10^{-05}	5.62×10^{-04}
rs12951993	A/G	17	52115613	5.75×10^{-07}	3.94×10^{-07}
rs1029723	C/T	17	52122547	4.10×10^{-06}	1.44×10^{-05}
rs227731	C/A	17	52128237	4.26×10^{-08}	1.78×10^{-08}
rs227730	G/A	17	52128950	9.56×10^{-07}	6.27×10^{-06}
rs227723	A/G	17	52133903	1.33×10^{-06}	2.88×10^{-06}
rs8071332	G/A	17	58495685	4.90×10^{-05}	5.30×10^{-05}
rs9908143	T/C	17	60185048	2.60×10^{-05}	5.07×10^{-05}
rs2007530	A/G	17	60194509	5.25×10^{-06}	4.46×10^{-06}
rs1808191	G/T	17	60214490	2.94×10^{-06}	4.56×10^{-06}
rs2305529	C/T	17	71213848	1.09×10^{-04}	4.78×10^{-05}

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rs3744000	C/T	17	71215928	1.43×10^{-04}	5.48×10^{-05}
rs4789817	G/A	17	78201278	2.03×10^{-03}	4.93×10^{-05}
rs522402	G/A	18	7028462	1.75×10^{-06}	1.90×10^{-05}
rs7238012	C/T	18	30147038	7.40×10^{-05}	1.81×10^{-01}
rs903736	C/A	18	32355674	5.78×10^{-05}	2.31×10^{-05}
rs1565978	G/A	18	32402506	6.58×10^{-05}	2.19×10^{-03}
rs2852945	G/A	18	43573552	4.14×10^{-03}	5.77×10^{-05}
rs880183	A/G	19	2000314	7.92×10^{-06}	2.97×10^{-03}
rs3746101	T/G	19	2001823	7.61×10^{-06}	4.59×10^{-03}
rs6510337	T/C	19	38237541	1.44×10^{-02}	3.85×10^{-05}
rs6029228	T/G	20	38688962	7.18×10^{-03}	4.76×10^{-06}
rs6072081	A/G	20	38694468	1.59×10^{-03}	9.13×10^{-08}
rs6065259	A/G	20	38695393	1.28×10^{-03}	1.40×10^{-07}
rs6102074	G/T	20	38701599	6.64×10^{-03}	6.90×10^{-06}
rs17820943	T/C	20	38701930	9.42×10^{-04}	1.09×10^{-08}
rs13041247	C/T	20	38702488	7.41×10^{-04}	6.17×10^{-09}
rs11696257	T/C	20	38704230	9.00×10^{-04}	8.02×10^{-09}
rs6072087	C/T	20	38709306	8.79×10^{-04}	3.70×10^{-05}
rs6102085	G/A	20	38715043	1.75×10^{-02}	6.90×10^{-08}
rs6016404	A/C	20	38716134	1.57×10^{-02}	1.22×10^{-05}
rs2064278	T/G	20	48796589	2.82×10^{-03}	2.79×10^{-05}
rs6122972	G/A	20	48808649	1.44×10^{-02}	9.82×10^{-05}
rs2834132	G/A	21	33477703	3.52×10^{-04}	9.96×10^{-05}
rs5765956	C/T	22	43529323	1.18×10^{-05}	2.13×10^{-06}

[1] - Minor allele first, based on European data (meta_Euro). SNPs for which the minor allele changes in the European/Asian combined analysis (meta_all) are marked with *. Chr. - chromosome.

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Supplementary Table 4: SNPs with genome-wide significance in at least one subgroup analysis. *P*-values from the meta-analysis in Europeans (P_{meta_Euro}) and the combined analysis of Europeans and Asians (P_{meta_all}) are presented if they reached genome-wide significance, for the subgroups NSCLO (nonsyndromic cleft lip only) and NSCLP (nonsyndromic cleft lip and palate). Both groups are combined in NSCL/P (cleft lip with or without cleft palate). '-' indicates non-genome-wide significant values. Grey shading indicates SNPs for which *P*-values were lower in the subgroup analyses compared to the overall NSCL/P sample.

dbSNP-ID	Locus	NSCL/P		NSCLP		NSCLO	
		P_{meta_Euro}	P_{meta_all}	P_{meta_Euro}	P_{meta_all}	P_{meta_Euro}	P_{meta_all}
rs560426	1p22.1	-	3.14×10^{-12}	-	5.44×10^{-10}	-	-
rs7015145	8q24	2.30×10^{-13}	3.38×10^{-12}	2.27×10^{-10}	5.72×10^{-10}	-	-
rs9297775	8q24	8.14×10^{-13}	5.92×10^{-12}	2.30×10^{-09}	2.89×10^{-09}	-	-
rs1030608	8q24	7.53×10^{-12}	-	2.59×10^{-09}	-	-	-
rs1030609	8q24	6.72×10^{-12}	-	1.99×10^{-09}	-	-	-
rs6996786	8q24	7.79×10^{-12}	4.61×10^{-11}	1.24×10^{-08}	1.45×10^{-08}	-	-
rs2395855	8q24	3.17×10^{-16}	7.18×10^{-14}	9.32×10^{-12}	2.57×10^{-09}	-	-
rs4733653	8q24	2.32×10^{-12}	9.84×10^{-09}	4.66×10^{-09}	-	-	-
rs11989880	8q24	2.77×10^{-18}	5.89×10^{-15}	4.33×10^{-12}	4.41×10^{-10}	5.99×10^{-09}	-
rs4733532	8q24	1.21×10^{-15}	2.43×10^{-14}	4.78×10^{-11}	7.79×10^{-10}	-	-
rs1850889	8q24	7.07×10^{-17}	1.44×10^{-16}	8.44×10^{-12}	5.07×10^{-11}	-	-
rs1519850	8q24	7.95×10^{-16}	3.77×10^{-15}	1.42×10^{-11}	8.41×10^{-11}	-	-
rs1519849	8q24	4.05×10^{-16}	1.49×10^{-14}	3.29×10^{-11}	7.08×10^{-10}	-	-
rs1519847	8q24	3.49×10^{-20}	5.47×10^{-21}	1.71×10^{-16}	1.33×10^{-17}	-	-
rs1530300	8q24	4.9×10^{-23}	6.31×10^{-22}	7.03×10^{-18}	7.00×10^{-18}	-	-
rs1519841	8q24	5.9×10^{-20}	1.80×10^{-20}	2.26×10^{-16}	1.97×10^{-17}	-	-
rs12542837	8q24	1.25×10^{-20}	1.02×10^{-20}	6.37×10^{-17}	9.48×10^{-18}	-	-
rs987525	8q24	3.94×10^{-34}	5.12×10^{-35}	1.79×10^{-26}	1.42×10^{-26}	1.20×10^{-10}	1.96×10^{-11}
rs12548036	8q24	8.7×10^{-21}	2.24×10^{-21}	3.73×10^{-17}	1.79×10^{-17}	-	-
rs7017252	8q24	8.96×10^{-19}	1.81×10^{-20}	6.29×10^{-15}	3.41×10^{-16}	-	-
rs12547241	8q24	2.66×10^{-15}	9.41×10^{-17}	6.26×10^{-11}	2.81×10^{-12}	-	-
rs1470206	8q24	1.49×10^{-14}	2.71×10^{-17}	2.51×10^{-10}	1.39×10^{-12}	-	-
rs882083	8q24	2.35×10^{-20}	6.83×10^{-23}	1.98×10^{-16}	2.47×10^{-18}	-	-
rs11787407	8q24	1.31×10^{-16}	1.39×10^{-18}	5.60×10^{-12}	1.46×10^{-13}	-	-
rs12546523	8q24	4.5×10^{-17}	1.19×10^{-18}	2.31×10^{-12}	1.12×10^{-13}	-	-
rs748978	8q24	3.83×10^{-16}	1.27×10^{-14}	1.28×10^{-11}	1.39×10^{-09}	-	-
rs2197111	8q24	2.35×10^{-11}	1.26×10^{-08}	3.74×10^{-08}	-	-	-
rs7018275	8q24	2.44×10^{-11}	1.30×10^{-08}	3.85×10^{-08}	-	-	-
rs1372452	8q24	9.74×10^{-12}	5.63×10^{-09}	1.35×10^{-08}	-	-	-
rs12334809	8q24	8.27×10^{-12}	5.86×10^{-09}	1.44×10^{-08}	-	-	-
rs7078160	10q25	2.81×10^{-08}	3.96×10^{-11}	-	5.68×10^{-10}	-	-
rs4752028	10q25	1.54×10^{-08}	1.71×10^{-10}	-	1.21×10^{-08}	-	-
rs1575900	13q31.1	4.87×10^{-09}	-	3.77×10^{-10}	-	-	-
rs9318679	13q31.1	2.08×10^{-08}	-	2.60×10^{-08}	-	-	-
rs1215465	13q31.1	5.62×10^{-10}	-	3.21×10^{-10}	2.32×10^{-08}	-	-
rs8001641	13q31.1	6.2×10^{-10}	2.62×10^{-10}	6.51×10^{-11}	8.87×10^{-11}	-	-
rs9545330	13q31.1	3.48×10^{-10}	-	9.22×10^{-10}	-	-	-
rs942233	13q31.1	1.69×10^{-08}	-	7.81×10^{-09}	-	-	-

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Supplementary Table 5: Subgroup analysis of SNPs at chromosome 13q31.1. Analysis is depicted for the European sample (**a**) and the combined European/Asian sample (**b**). Bold-type indicates genome-wide significance in the meta-analysis or nominal significance in the homogeneity likelihood ratio test (P_{homog}).

(**a**)

dbSNP-ID	Position	Alleles	NSCLO			NSCLP			P_{homog}
			P_{meta_Euro}	RR het (95% CI)	RR hom (95% CI)	P_{meta_Euro}	RR het (95% CI)	RR hom (95% CI)	
rs1575900	79,574,705	G/T	0.258	0.916 (0.689 - 1.216)	0.744 (0.454 - 1.219)	**3.77×10^{-10}**	0.593 (0.493 - 0.714)	0.447 (0.321 - 0.623)	**0.024**
rs9318679	79,588,136	A/C	0.065	0.799 (0.601 - 1.062)	0.674 (0.400 - 1.134)	**2.60×10^{-10}**	0.688 (0.573 - 0.827)	0.410 (0.283 - 0.595)	0.28
rs1215465	79,589,353	A/G	0.622	0.772 (0.578 - 1.031)	0.704 (0.456 - 1.086)	**3.21×10^{-10}**	0.674 (0.562 - 0.808)	0.404 (0.296 - 0.553)	0.113
rs8001641	79,590,812	A/G	0.163	1.149 (0.818 - 1.615)	1.329 (0.887 - 1.990)	**6.51×10^{-11}**	1.631 (1.285 - 2.071)	2.415 (1.842 - 3.166)	**0.041**
rs9545330	79,597,167	G/A	0.025	0.747 (0.558 - 0.999)	0.619 (0.349 - 1.097)	**9.22×10^{-10}**	0.637 (0.529 - 0.768)	0.356 (0.229 - 0.553)	0.282
rs942233	79,599,849	G/A	0.127	0.834 (0.629 - 1.105)	0.739 (0.479 - 1.140)	**7.81×10^{-09}**	0.683 (0.567 - 0.822)	0.450 (0.335 - 0.604)	0.144

(**b**)

SNP-ID	Position	Alleles	NSCLO			NSCLP			P_{homog}
			P_{meta_all}	RR het (95% CI)	RR hom (95% CI)	P_{meta_all}	RR het (95% CI)	RR hom (95% CI)	
rs1575900	79,574,705	G/T	0.109	0.987 (0.769 - 1.267)	0.725 (0.507 - 1.037)	1.66×10^{-07}	0.625 (0.531 - 0.736)	0.577 (0.462 - 0.720)	**0.0055**
rs9318679	79,588,136	A/C	0.109	0.827 (0.663 - 1.032)	0.807 (0.536 - 1.217)	3.66×10^{-07}	0.765 (0.664 - 0.882)	0.530 (0.401 - 0.701)	0.240
rs1215465	79,589,353	A/G	0.154	0.826 (0.657 - 1.037)	0.820 (0.588 - 1.143)	**2.32×10^{-08}**	0.738 (0.640 - 0.851)	0.559 (0.448 - 0.696)	0.139
rs8001641	79,590,812	A/G	0.088	1.204 (0.925 - 1.568)	1.349 (0.948 - 1.919)	**8.87×10^{-11}**	1.354 (1.141 - 1.607)	2.111 (1.686 - 2.641)	0.062
rs9545330	79,597,167	G/A	0.058	0.787 (0.628 - 0.987)	0.788 (0.517 - 1.200)	5.89×10^{-06}	0.763 (0.661 - 0.879)	0.594 (0.448 - 0.788)	0.527
rs942233	79,599,849	G/A	0.062	0.923 (0.721 - 1.181)	0.720 (0.514 - 1.009)	8.12×10^{-07}	0.706 (0.600 - 0.831)	0.589 (0.475 - 0.730)	0.167

NSCLO – nonsyndromic cleft lip only. NSCLP – nonsyndromic cleft lip with cleft palate. RR – relative risk. het – heterozygous. hom – homozygous. CI – confidence interval.

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Supplementary Table 6: Comparison of genotypic relative risks for markers achieving genome-wide significance in one of the two subgroups NSCLO and NSCLP. *P*-values are typed in bold if nominally significant.

dbSNP-ID	Locus	$P_{homogeneity}$ *Europeans*	$P_{homogeneity}$ *Europeans and Asians*
rs560426	1p22.1	0.954	0.847
rs7015145	8q24	0.742	0.853
rs9297775	8q24	0.876	0.920
rs1030608	8q24	0.968	0.893
rs1030609	8q24	0.982	0.873
rs6996786	8q24	0.866	0.941
rs2395855	8q24	0.427	0.234
rs4733653	8q24	0.922	0.613
rs11989880	8q24	0.189	0.507
rs4733532	8q24	0.838	0.749
rs1850889	8q24	0.573	0.419
rs1519850	8q24	0.989	0.936
rs1519849	8q24	0.822	0.744
rs1519847	8q24	0.755	0.504
rs1530300	8q24	0.911	0.746
rs1519841	8q24	0.749	0.457
rs12542837	8q24	0.750	0.373
rs987525	8q24	0.724	0.883
rs12548036	8q24	0.621	0.597
rs7017252	8q24	0.803	0.775
rs12547241	8q24	0.408	0.683
rs1470206	8q24	0.806	0.869
rs882083	8q24	0.836	0.869
rs11787407	8q24	0.842	0.926
rs12546523	8q24	0.726	0.870
rs748978	8q24	0.676	0.308
rs2197111	8q24	0.491	0.109
rs7018275	8q24	0.490	0.109
rs1372452	8q24	0.565	0.145
rs12334809	8q24	0.567	0.136
rs7078160	10q25	0.903	0.614
rs4752028	10q25	0.749	0.671
rs1575900	13q31.1	**0.024**	**0.006**
rs9318679	13q31.1	0.280	0.240
rs1215465	13q31.1	0.113	0.139
rs8001641	13q31.1	**0.041**	0.062
rs9545330	13q31.1	0.282	0.527
rs942233	13q31.1	0.144	0.167

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Supplementary Table 7: Subgroup-specific re-analysis of SNPs at the 13q31.1 locus in the EuroCran sample (Mangold et al. 2010).

SNP	Pos	TDT NSCL/P [a]			TDT NSCLP			TDT NSCLO		
		T	NT	*P*	T	NT	*P*	T	NT	*P*
rs9574565	79.566.875	227	177	**0.0129**	156	110	**4.80×10^{-03}**	71	67	0.733
rs1215465	79.589.353	268	314	0.0566	168	217	**0.0125**	100	97	0.831
rs8001641	79.590.812	275	266	0.699	198	174	0.213	77	92	0.249

NSCL/P (nonsyndromic cleft lip with or without cleft palate); NSCLO (nonsyndromic cleft lip without cleft palate); NSCLP (nonsyndromic cleft lip with cleft palate). TDT- transmission disequilibrium test, with transmitted (T) and non-transmitted (NT) alleles. [a]- data are retrieved from [1]. *P*-values are typed in bold if nominally significant.

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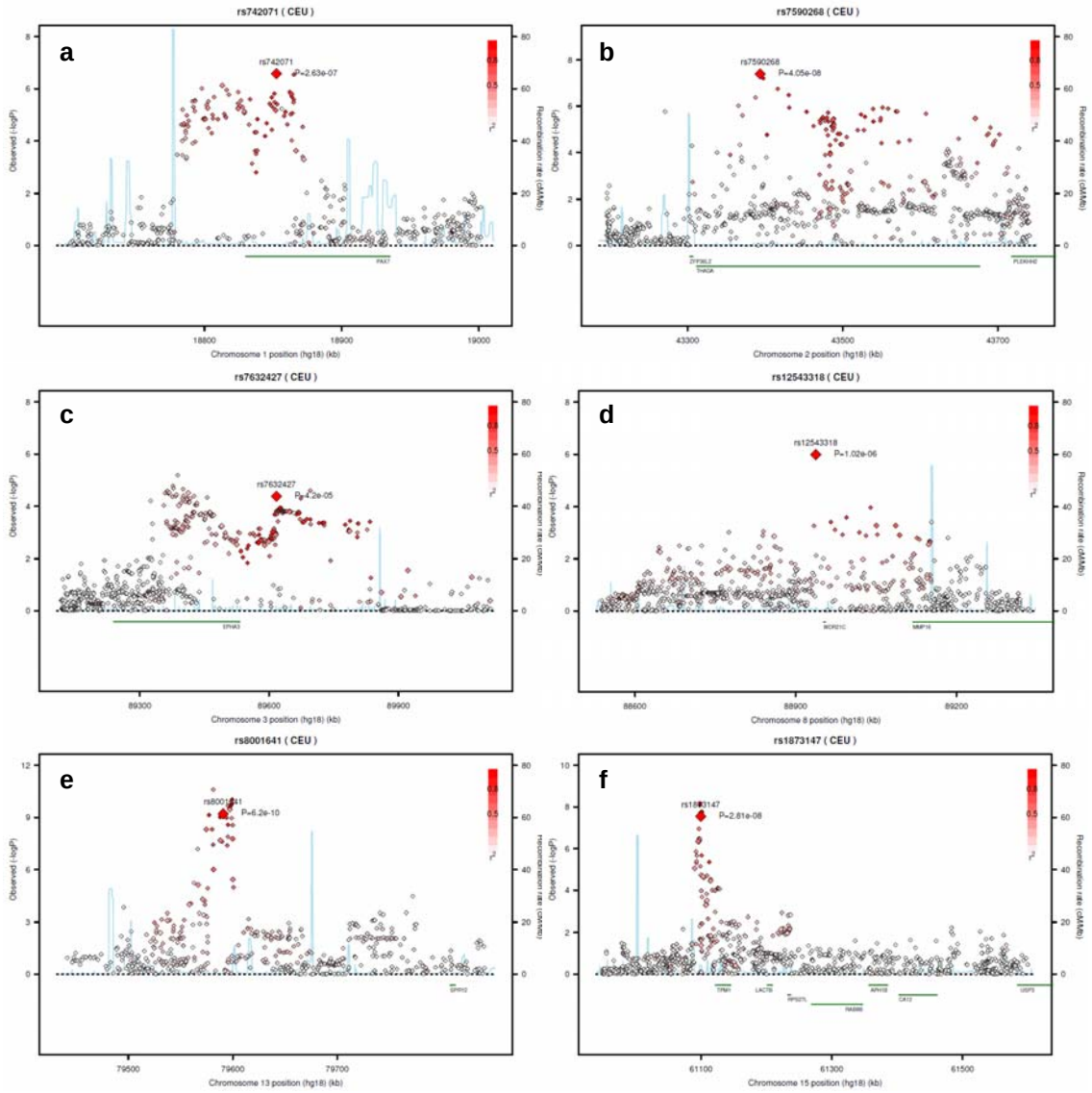
Supplementary Figures



Supplementary Figure 1: Regional association plots for the new genome-wide significant loci in the European sample ($meta_{Euro}$), based on imputed data. For each of the loci in (a) to (f), single-marker association statistics (as $-\log_{10} P$; left *y* axis) are shown. Color-codes demonstrate LD estimates to the most strongly associated genotyped SNP, and recombination rates across each region are shown in light blue (right y axis; both based on 1000genomes_release1). The chromosomal locations and relative positions of genes according to hg18 are shown (*x* axis). Windows have been chosen to include adjacent recombination hotspots, with a maximum of 500 kb either side of the top SNP. Note the different scaling of the y-axes, and the lack of genome-wide significance in (a), (c), and (d). For these three loci, genome-wide significance was achieved after adding the Asian data ($meta_{all}$).

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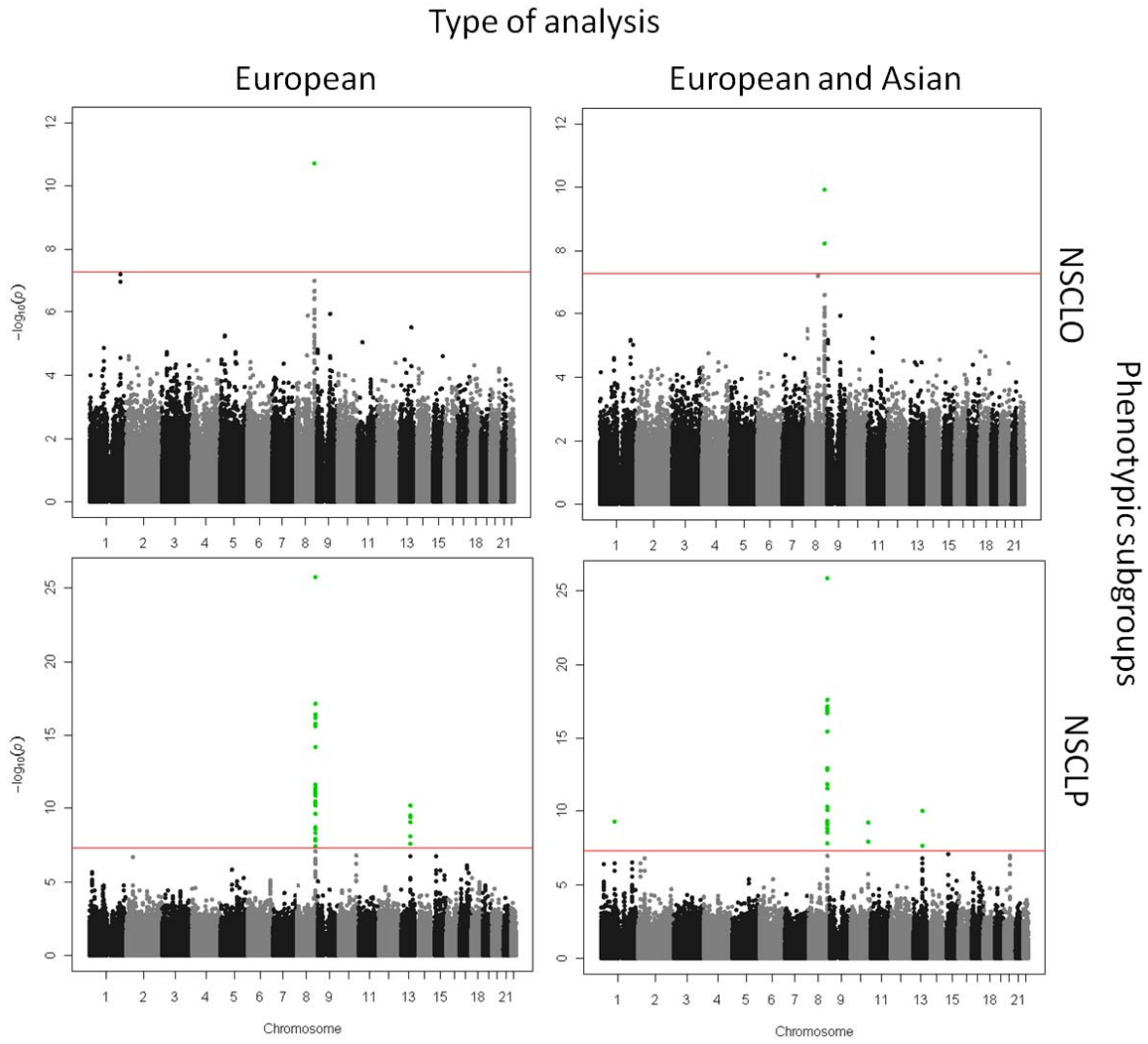

Supplementary Figure 2: Results of the genome-wide meta-analyses for the NSCL/P subgroups for both types of analyses (Europeans and combined sample). Negative $\log_{10}$ *P*-values are shown for all SNPs that passed quality control. Genome-wide significance ($P < 5\times10^{-08}$) is indicated by the red line. SNPs passing this threshold are shown in green. Note the different scaling of the y-axis in the NSCLP and NSCLO groups.

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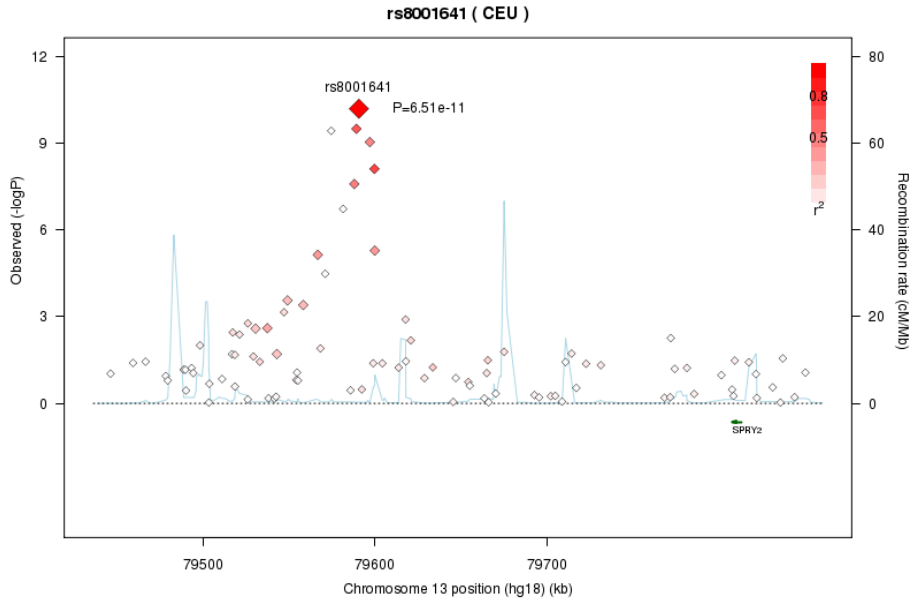

Supplementary Figure 3: Details of the 13q31 locus that showed genome-wide significant association with NSCLP in the European sample. Single-marker association statistics (as $-\log_{10} P$; left *y* axis) are shown, with color-coding to demonstrate linkage disequilibrium estimates (HapMap3 CEU) to the most strongly associated SNP rs8001641. Recombination rates across each region in HapMap CEU are shown in light blue (right *y* axis). The chromosomal locations and relative positions of genes according to hg18 are shown (*x* axis).

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Supplementary Note

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References

1. Mangold, E. et al. Genome-wide association study identifies two susceptibility loci for nonsyndromic cleft lip with or without cleft palate. *Nat Genet* **42**, 24-6 (2010).
2. Schaid, D.J. & Sommer, S.S. Genotype relative risks: methods for design and analysis of candidate-gene association studies. *Am J Hum Genet* **53**, 1114-26 (1993).
3. Howie, B.N., Donnelly, P. & Marchini, J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet* **5**, e1000529 (2009).
4. Southam, L. et al. The effect of genome-wide association scan quality control on imputation outcome for common variants. *Eur J Hum Genet* **19**, 610-4 (2011).

Nature Genetics: doi:10.1038/ng.2360