

Details of genes contained in the regions shared between GWAS analysis and my overlapping regions (identified using Decipher patients)

Results of cross-checking between GWAS results and my analysis: 5 GWAS regions overlap!

Chr	Start	End	Strongest SNP-risk allele	Overlap with an overlapping region?	Gene in overlapping regions
chr8	129640852	130225011	rs987525	NO	-
chr1	209885318	210370590	rs642961	YES	6
chr10	118041396	118834991	rs7078100	NO	-
chr17	54615617	54778904	rs227731	YES	1
chr20	39255548	39282720	rs13041247	YES	0
chr1	94525623	94850443	rs560426	YES	2
chr1	18929842	18990793	rs742071	NO	-
chr2	43484556	43931176	rs7590268	NO	-
chr3	89307931	89597679	rs7632427	NO	-
chr8	82916953	88981540	rs12543318	YES	19
chr13	80440491	80874281	rs8001641	NO	-
chr15	63303416	63327533	rs1873147	NO	-

ABCA4

ATP-Binding Cassette, Sub-Family A (ABC1), Member 4

Function(s): ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (ABC1, MDR/TAP, MRP, ALD, OABP, GCN20, White). This protein is a member of the ABC1 subfamily. Members of the ABC1 subfamily comprise the only major ABC subfamily found exclusively in multicellular eukaryotes. This protein is a retina-specific ABC transporter with N-retinylidene-PE as a substrate. It is expressed exclusively in retina photoreceptor cells, indicating the gene product mediates transport of an essential molecule across the photoreceptor cell membrane.

Associated disease(s): Mutations in this gene are also associated with retinitis pigmentosa-19, cone-rod dystrophy type 3, early-onset severe retinal dystrophy, fundus flavimaculatus and macular degeneration age-related 2.

Associated syndrome(s): nothing

Publications ABCA4/cleft (OFCs): **YES**

Exploratory genotype-phenotype correlations of facial form and asymmetry in unaffected relatives of children with non-syndromic cleft lip and/or palate. Miller SF, Weinberg SM, Nidey NL, Defay DK, Marazita ML, Wehby GL, Moreno Uribe LM. J Anat. 2014 Jun;224(6):688-709. doi: 10.1111/joa.12182. Epub 2014 Apr 16.

Confirming genes influencing risk to cleft lip with/without cleft palate in a case-parent trio study. Beaty TH, Taub MA, Scott AF, Murray JC, Marazita ML, Schwender H, Parker MM, Hetmanski JB, Balakrishnan P, Mansilla MA, Mangold E, Ludwig KU, Noethen MM, Rubini M, Elcioglu N, Ruczinski I. Hum Genet. 2013 Jul;132(7):771-81. doi: 10.1007/s00439-013-1283-6. Epub 2013 Mar 20.

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ARHGAP29

Rho GTPase Activating Protein 29

Function(s): The encoded protein is a GTPase activator for the Rho-type GTPases by converting them to an inactive GDP-bound state. It has strong activity toward RHOA, and weaker activity toward RAC1 and CDC42. It may act as a specific effector of RAP2A to regulate Rho. In concert with RASIP1, it suppresses RhoA signaling and dampens ROCK and MYH9 activities in endothelial cells and plays an essential role in blood vessel tubulogenesis.

Associated disease(s): Diseases associated with this gene include mantle cell lymphoma and **cleft palate**.

Associated syndrome(s): nothing

Publications ARHGAP29/cleft (OFCs): **YES**

Exploratory genotype-phenotype correlations of facial form and asymmetry in unaffected relatives of children with non-syndromic cleft lip and/or palate. Miller SF, Weinberg SM, Nidey NL, Defay DK, Marazita ML, Wehby GL, Moreno Uribe LM. J Anat. 2014 Jun;224(6):688-709. doi: 10.1111/joa.12182. Epub 2014 Apr 16.

Expression and mutation analyses implicate ARHGAP29 as the etiologic gene for the cleft lip with or without cleft palate locus identified by genome-wide association on chromosome 1p22. Leslie EJ, Mansilla MA, Biggs LC, Schuette K, Bullard S, Cooper M, Dunnwald M, Lidral AC, Marazita ML, Beaty TH, Murray JC. Birth Defects Res A Clin Mol Teratol. 2012 Nov;94(11):934-42. doi: 10.1002/bdra.23076. Epub 2012 Sep 24.

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HSD11B1

Hydroxysteroid (11-Beta) Dehydrogenase 1

Function(s): The protein encoded by this gene is a microsomal enzyme that catalyzes the conversion of the stress hormone cortisol to the inactive metabolite cortisone. In addition, the encoded protein can catalyze the reverse.

Associated disease(s): Diseases associated with defects in this gene include cortisone reductase deficiency 2 and cortisone reductase deficiency.

Associated syndrome(s): nothing

Publications HSD11B1/cleft (OFCs): **NO**

rs642961 (chr1p)

TRAF3IP3

TRAF3 Interacting Protein 3

Function(s): The gene encodes a protein that mediates cell growth by modulating the c-Jun N-terminal kinase signal transduction pathway. The encoded protein may also interact with a large multi-protein assembly containing the phosphatase 2A catalytic subunit.

Associated disease(s): Diseases associated with defects in this gene include cerebral cavernous malformations 3 and cavernous malformation.

Associated syndrome(s): nothing

Publications TRAF3IP3/cleft (OFCs): **NO**

rs642961 (chr1p)

C1orf74

Chromosome 1 Open Reading Frame 74

Function(s): its functions are not known.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications C1orf74/cleft (OFCs): **NO**

rs642961 (chr1p)

IRF6

Interferon Regulatory Factor 6

Function(s): This gene encodes a member of the interferon regulatory transcription factor (IRF) family. The encoded protein may be a transcriptional activator (regulatory region DNA binding and sequence-specific DNA binding transcription factor activity).

Associated disease(s): Mutations in this gene can cause **van der Woude syndrome**, popliteal pterygium syndrome, **cleft palate lateral synechia syndrome** and **non-syndromic orofacial cleft (type 6)**.

Associated syndrome(s): nothing

Publications IRF6/cleft (OFCs): **YES**

Exploratory genotype-phenotype correlations of facial form and asymmetry in unaffected relatives of children with non-syndromic **cleft lip** and/or palate. Miller SF, Weinberg SM, Nidey NL, Defay DK, Marazita ML, Wehby GL, Moreno Uribe LM. J Anat. 2014 Jun;224(6):688-709. doi: 10.1111/joa.12182. Epub 2014 Apr 16.

Disrupting hedgehog and WNT signaling interactions promotes **cleft lip** pathogenesis. Kurosaka H, Lulianella A, Williams T, Trainor PA. J Clin Invest. 2014 Apr 1;124(4):1660-71. doi: 10.1172/JCI72688. Epub 2014 Mar 3.

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rs642961 (chr1p)

DIEXF

Digestive Organ Expansion Factor Homolog (Zebrafish)

Function(s): The encoded protein regulates the p53 pathway to control the expansion growth of digestive organs (by similarity).

Associated disease(s): Mutations in this gene are associated with multiple myeloma and myeloma.

Associated syndrome(s): nothing

Publications DIEXF/cleft (OFCs): **NO**

rs642961 (chr1p)

SYT14

Synaptotagmin XIV

Function(s): This gene is a member of the synaptotagmin gene family and encodes a protein similar to other family members that mediate membrane trafficking in synaptic transmission. The encoded protein is a calcium-independent synaptotagmin. It may be involved in the trafficking and exocytosis of secretory vesicles in non-neuronal tissues.

Associated disease(s): Mutations in this gene are a cause of autosomal recessive spinocerebellar ataxia-11 (SCAR11), and a t(1;3) translocation of this gene has been associated with neurodevelopmental abnormalities.

Associated syndrome(s): nothing

Publications SYT14/cleft (OFCs): **NO**

rs12543318 (chr8q)

ATP6VOD2

ATPase, H+ Transporting, Lysosomal 38kDa, V0 Subunit D2

Function(s): The encoded protein is a subunit of the integral membrane V0 complex of vacuolar ATPase. Vacuolar ATPase is responsible for acidifying a variety of intracellular compartments in eukaryotic cells, thus providing most of the energy required for transport processes in the vacuolar system. It may play a role in coupling of proton transport and ATP hydrolysis (by similarity).

Associated disease(s): Mutations in this gene are associated with osteopetrosis and renal tubular acidosis.

Associated syndrome(s): nothing

Publications ATP6VOD2/cleft (OFCs): **NO**

rs12543318 (chr8q)

CA1

Carbonic Anhydrase I

Function(s): Carbonic anhydrases (CAs) are a large family of zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (*carbonate dehydratase activity*). CA1 is closely linked to CA2 and CA3 genes on chromosome 8, and it encodes a cytosolic protein which is found at the highest level in erythrocytes. Variants of this gene have been described in some populations.

Associated disease(s): Mutations in this gene are associated with subacute thyroiditis and transient global amnesia.

Associated syndrome(s): nothing

Publications CA1/cleft (OFCs): **NO**

rs12543318 (chr8q)

CA2

Carbonic Anhydrase II

Function(s): Carbonic anhydrases (CAs) are a large family of zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (*carbonate dehydratase activity*). This gene is one of several (at least 7) isozymes of carbonic anhydrase.

Associated disease(s): Mutations in this gene are associated with osteopetrosis, autosomal recessive 3, with renal tubular acidosis, and osteopetrosis autosomal recessive 3.

Associated syndrome(s): nothing

Publications CA2/cleft (OFCs): **NO**

rs12543318 (chr8q)

CA3

Carbonic Anhydrase III, Muscle Specific

Function(s): Carbonic anhydrases (CAs) are a large family of zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (*carbonate dehydratase activity*). This gene is one of several (at least 7) isozymes of carbonic anhydrase. The expression of this gene is strictly tissue specific and present at high levels in skeletal muscle and much lower levels in cardiac and smooth muscle.

Associated disease(s): Mutations in this gene are associated with hordeolum and laryngeal disease.

Associated syndrome(s): nothing

Publications CA3/cleft (OFCs): **NO**

rs12543318 (chr8q)

CA13

Carbonic Anhydrase XIII

Function(s): Carbonic anhydrases (CAs) are a large family of zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (*carbonate dehydratase activity*). This gene is one of several (at least 7) isozymes of carbonic anhydrase.

Associated disease(s): Mutations in this gene are associated with suppurative otitis media and otitis media.

Associated syndrome(s): nothing

Publications CA13/cleft (OFCs): **NO**

rs12543318 (chr8q)

CNBD1

Cyclic Nucleotide Binding Domain Containing 1

Function(s): Its functions are not known.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications CNBD1/cleft (OFCs): **NO**

rs12543318 (chr8q)

CNGB3

Cyclic Nucleotide Gated Channel Beta 3

Function(s): Its encoded protein is a beta subunit of a cyclic nucleotide-gated ion channel. The encoded beta subunit appears to play a role in modulation of channel function in cone photoreceptors. This heterotetrameric channel is necessary for sensory transduction functions are not known.

Associated disease(s): Mutations in this gene are associated with Stargardt macular degeneration, and Stargardt disease (autosomal recessive).

Associated syndrome(s): nothing

Publications CNGB3/cleft (OFCs): **NO**

rs12543318 (chr8q)

CPNE3

Copine III

Function(s): Its encoded protein is calcium-dependent membrane-binding proteins which may regulate molecular events at the interface of the cell membrane and cytoplasm.

Associated disease(s): Mutations in this gene are associated with infertility and schizophrenia.

Associated syndrome(s): nothing

Publications CPNE3/cleft (OFCs): **NO**

rs12543318 (chr8q)

C8orf59

Chromosome 8 Open Reading Frame 59

Function(s): It is a protein-coding gene. An important paralog of this gene is ENSG00000226209. Its functions are not characterized.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications C8orf59/cleft (OFCs): **NO**

rs12543318 (chr8q)

DCAF4L2

DDB1 And CUL4 Associated Factor 4-Like 2

Function(s): It is a protein-coding gene. An important paralog of this gene is ENSG00000226209. Its functions are not characterized.

Associated disease(s): Defects in this gene are associated with **cleft palate** and **cleft lip**.

Associated syndrome(s): nothing

Publications DCAF4L2/cleft (OFCs): **YES**

Confirming genes influencing risk to cleft lip with/without cleft palate in a case-parent trio study. Beaty TH, Taub MA, Scott AF, Murray JC, Marazita ML, Schwender H, Parker MM, Hetmanski JB, Balakrishnan P, Mansilla MA, Mangold E, Ludwig KU, Noethen MM, Rubini M, Elcioglu N, Ruczinski I. Hum Genet. 2013 Jul;132(7):771-81. doi: 10.1007/s00439-013-1283-6. Epub 2013 Mar 20.

rs12543318 (chr8q)

E2F5

E2F Transcription Factor 5, P130-Binding

Function(s): The protein encoded by this gene is a member of the E2F family of transcription factors. This protein is differentially phosphorylated and is expressed in a wide variety of human tissues. Both this protein and E2F4 interact with tumor suppressor proteins p130 and p107, but not with pRB. The encoded protein is a transcriptional activator that binds to E2F sites, these sites are present in the promoter of many genes whose products are involved in cell proliferation. It may mediate growth factor-initiated signal transduction and it is likely involved in the early responses of resting cells to growth factor stimulation

Associated disease(s): Mutations in this gene are associated with retinoblastoma and choroiditis.

Associated syndrome(s): nothing

Publications E2F5/cleft (OFCs): **YES (??)**

Role of skeletal muscle in palate development. Rot I, Kablar B. Histol Histopathol. 2013 Jan;28(1):1-13. Review.

Expression of the E2F family of transcription factors during murine development. Kusek JC, Greene RM, Nugent P, Pisano MM. Int J Dev Biol. 2000 Apr;44(3):267-77.

rs12543318 (chr8q)

LOC100996348

Uncharacterized LOC100996348

Function(s): It is an RNA gene, and is affiliated with the antisense RNA class.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications LOC100996348/cleft (OFCs): **NO**

rs12543318 (chr8q)

LRRCC1

Leucine Rich Repeat And Coiled-Coil Centrosomal Protein 1

Function(s): It is required for the organization of the mitotic spindle and it maintains the structural integrity of centrosomes during mitosis.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications LRRCC1/cleft (OFCs): **NO**

rs12543318 (chr8q)

PSKH2

Protein Serine Kinase H2

Function(s): The functions of its encoded protein include protein serine/threonine kinase activity.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications PSKH2/cleft (OFCs): **NO**

rs12543318 (chr8q)

RALYL

RALY RNA Binding Protein-Like

Function(s): The functions of its encoded protein include RNA binding and nucleotide binding.

Associated disease(s): Defects in this gene are associated with include atherosclerosis and neuroblastoma.

Associated syndrome(s): nothing

Publications RALYL/cleft (OFCs): **NO**

rs12543318 (chr8q)

REXO1L2P

REX1, RNA Exonuclease 1 Homolog (S. Cerevisiae)-Like 2, Pseudogene

Function(s): It is a pseudogene. Its functions include exonuclease activity and nucleic acid binding.

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications REXO1L2P/cleft (OFCs): **NO**

rs12543318 (chr8q)

RMDN1

Regulator Of Microtubule Dynamics 1

Function(s): Its functions are not well known.

Associated disease(s): Diseases associated with this gene include chronic lymphocytic leukemia, and hepatocellular carcinoma.

Associated syndrome(s): nothing

Publications RMDN1/cleft (OFCs): **NO**

rs12543318 (chr8q)

SLC7A13

Solute Carrier Family 7 (Anionic Amino Acid Transporter), Member 13

Function(s): Its encoded protein is involved in acid transmembrane transporter activity. It mediates the transport L-aspartate and L-glutamate in a sodium-independent manner (by similarity).

Associated disease(s): nothing

Associated syndrome(s): nothing

Publications SLC7A13/cleft (OFCs): **NO**

rs12543318 (chr8q)

WWP1

WW Domain Containing E3 Ubiquitin Protein Ligase 1

Function(s): WW domain-containing proteins are found in all eukaryotes and play an important role in the regulation of a wide variety of cellular functions such as protein degradation, transcription and RNA splicing. The encoded protein belongs to a family of NEDD4-like proteins, which are E3 ubiquitin-ligase molecules and regulate key trafficking decisions, including targeting of proteins to proteosomes or lysosomes.

Associated disease(s): Defects in this gene are related to liddle syndrome and human t-cell leukemia virus type 1.

Associated syndrome(s): nothing

Publications WWP1/cleft (OFCs): **NO**

NOG*Noggin*

Function(s): The secreted polypeptide, encoded by this gene, binds and inactivates members of the transforming growth factor-beta (TGF-beta) superfamily signaling proteins, such as bone morphogenetic protein-4 (BMP4). By diffusing through extracellular matrices more efficiently than members of the TGF-beta superfamily, this protein may have a principal role in creating morphogenic gradients. The protein appears to have pleiotropic effect, both early in development as well as in later stages. It is essential for cartilage morphogenesis and joint formation and it is an Inhibitor of bone morphogenetic proteins (BMP) signaling which is required for growth and patterning of the neural tube and somite.

Associated disease(s): Defects in this gene are related to include multiple synostoses syndrome 1 and multiple synostosis syndrome 1. (Possible correlation with **cleft lip with/without palate**).

Associated syndrome(s): nothing

Publications NOG/cleft (OFCs): **YES**

Multiple tissue-specific requirements for the BMP antagonist Noggin in development of the mammalian craniofacial skeleton. Matsui M, Klingensmith J. Dev Biol. 2014 Jun 17. pii: S0012-1606(14)00302-9. doi: 10.1016/j.ydbio.2014.06.006.

Nonsyndromic cleft lip with or without cleft palate: Increased burden of rare variants within Gremlin-1, a component of the bone morphogenetic protein 4 pathway. Al Chawa T, Ludwig KU, Fier H, Pötzsch B, Reich RH, Schmidt G, Braumann B, Daratsianos N, Böhmer AC, Schuencke H, Alblas M, Fricker N, Hoffmann P, Knapp M, Lange C, Nöthen MM, Mangold E. Birth Defects Res A Clin Mol Teratol. 2014 Jun;100(6):493-8. doi: 10.1002/bdra.23244. Epub 2014 Apr 7.

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