

Whole-genome Sequencing reveals *de-novo* mutations associated with Nonsyndromic Cleft Lip/Palate

Waheed Awotoye^{1,2*}, Peter A. Mossey³, Jacqueline B. Hetmanski⁴, Lord J.J. Gowans⁵, Mekonen A. Eshete⁶, Wasiu L. Adeyemo⁷, Azeez Alade^{2,8}, Erliang Zeng⁹, Olawale Adamson⁷, Thirona Naicker¹⁰, Deepti Anand¹¹, Chinyere Adeleke², Tamara Busch², Mary Li², Aline Petrin^{1, 12}, Babatunde S. Aregbesola¹³, Ramat O. Braimah¹³, Fadekemi O. Oginni¹³, Ayodeji O. Oladele¹³, Abimbola Oladayo², Sami Kayali², Joy Olotu¹⁴, Mohaned Hassan², John Pape², Peter Donkor¹⁵, Fareed K.N. Arthur⁵, Solomon Obiri-Yeboah¹⁶, Daniel K. Sabbah¹⁷, Pius Agbenorku¹⁵, Gyikua Plange-Rhule¹⁸, Alexander Acheampong Oti¹⁶, Rose A. Gogal¹⁹, Terri H. Beaty⁴, Margaret Taub⁴, Mary L. Marazita²⁰, Michael J. Schnieders¹⁹, Salil A. Lachke^{11,21}, Adebawale A. Adeyemo²², Jeffrey C. Murray²³, Azeez Butali^{1,2*}

¹Iowa Institute for Oral Health Research, University of Iowa, Iowa City, IA, USA

²Department of Oral Pathology, Radiology and Medicine, College of Dentistry, University of Iowa, Iowa City, IA, USA

³Department of Orthodontics, University of Dundee, Dundee, UK

⁴Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

⁵Department of Biochemistry and Biotechnology, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

⁶Addis Ababa University, School Medicine, Surgical Department, Addis Ababa, Ethiopia

⁷Department of Oral and Maxillofacial Surgery, University of Lagos, Lagos Nigeria

⁸Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, IA, USA.

⁹Division of Biostatistics and Computational Biology, College of Dentistry, University of Iowa, Iowa City, IA, USA

¹⁰Department of Pediatrics, University of KwaZulu-Natal, South Africa

¹¹Department of Biological Sciences, University of Delaware

¹²Department of Orthodontics, University of Iowa, Iowa City, IA, USA

¹³Department of Oral and Maxillofacial Surgery, Obafemi Awolowo University, Ile-Ife, Osun A234, Nigeria

¹⁴Department of Anatomy, University of Port Harcourt

¹⁵Department of Surgery, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

¹⁶Department of Maxillofacial Sciences, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

¹⁷Department of Child Oral Health and Orthodontics, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

¹⁸Department of Child Health, School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

¹⁹Center for Biocatalysis and Bioprocessing (CBB), University of Iowa

²⁰Center for Craniofacial and Dental Genetics, Department of Oral and Craniofacial Sciences, School of Dental Medicine, and Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

²¹Center for Bioinformatics and Computational Biology, University of Delaware

²²National Human Genomic Research Institute, Bethesda, MD, USA

²³Department of Pediatrics, University of Iowa, Iowa City, IA, USA

Correspondence:

Azeez Butali, Department of Oral Pathology, Radiology and Medicine, College of Dentistry, University of Iowa, Iowa City, IA, USA Email: Azeez-butali@uiowa.edu

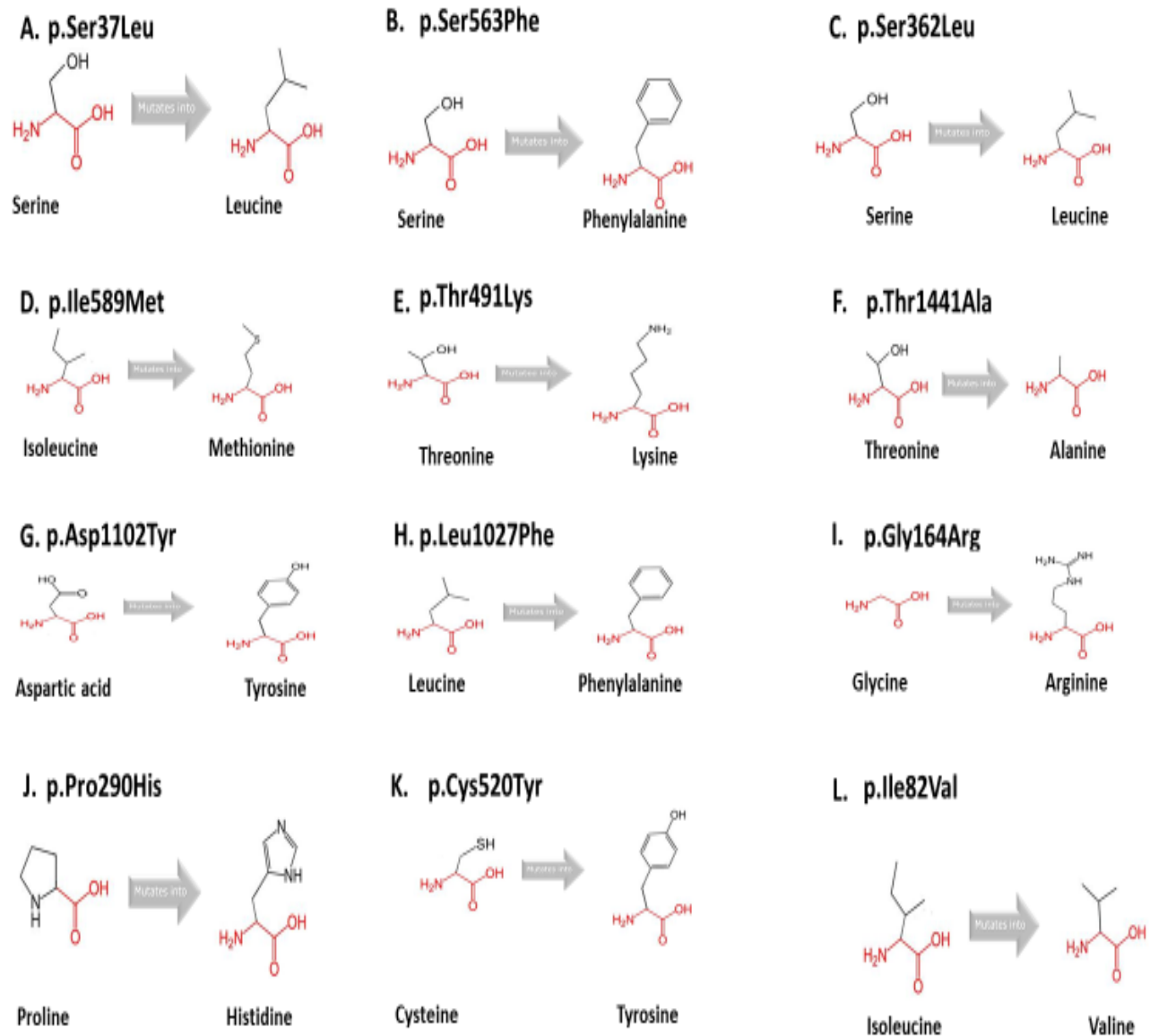
Chromosome Location	Ref/Alt	Gene Names	HGVS c.	HGVS p.	Effect
1:12617239	G/A	<i>DHRS3</i>	c.110C>T	p.Ser37Leu	Missense
1:22863094	C/A	<i>EPHB2</i>	c.869C>A	p.Pro290His	Missense
1:24458944	A/G	<i>NIPAL3</i>	c.830A>G	p.Tyr277Cys	Missense
1:25446845	T/G	<i>MACO1</i>	c.164T>G	p.Leu55Arg	Missense
1:52698320	C/A	<i>COA7</i>	c.7G>T	p.Gly3Cys	Missense
1:62555824	C/T	<i>DOCK7</i>	c.2596+1G>A		LoF
1:92245604	T/C	<i>C1orf146</i>	c.473T>C	p.Ile158Thr	Missense
2:108766258	A/G	<i>RANBP2</i>	c.5719A>G	p.Asn1907Asp	Missense
2:112659645	A/G	<i>SLC20A1</i>	c.1490A>G	p.Asn497Ser	Missense
2:11618333	C/T	<i>GREB1</i>	c.3458C>T	p.Pro1153Leu	Missense
2:178738241	G/A	<i>TTN</i>	c.14212C>T	p.Arg4738Ter	LoF
2:178747180	A/G	<i>TTN</i>	c.11312-5259T>C		Missense
2:200573408	C/G	<i>SGO2</i>	c.3062C>G	p.Ser1021Cys	Missense
2:21142968	T/C	<i>TDRD15</i>	c.5501T>C	p.Val1834Ala	Missense
2:214410244	G/A	<i>SPAG16</i>	c.1825G>A	p.Val609Ile	Missense
2:235883447	C/T	<i>AGAP1</i>	c.1153C>T	p.His385Tyr	Missense
2:24821592	C/T	<i>ADCY3</i>	c.3055G>A	p.Asp1019Asn	Missense
2:27581847	T/C	<i>C2orf16</i>	c.5275T>C	p.Cys1759Arg	Missense
2:47029351	A/G	<i>TTC7A</i>	c.1769A>G	p.Asn590Ser	Missense
2:88627076	C/T	<i>EIF2AK3</i>	c.199G>A	p.Ala67Thr	Missense
2:96193078	C/T	<i>STARD7</i>	c.743G>A	p.Arg248His	Missense
3:12557158	C/T	<i>MKRN2</i>	c.8C>T	p.Thr3Ile	Missense
3:129315334	G/A	<i>H1-10</i>	c.569C>T	p.Ala190Val	Missense
3:134561462	G/A	<i>CEP63</i>	c.2039G>A	p.Arg680His	Missense
3:179563094	T/G	<i>ACTL6A</i>	c.2T>G	p.Met1Arg	LoF
3:189894226	C/G	<i>TP63</i>	c.1767C>G	p.Ile589Met	Missense
3:195725943	C/T	<i>MUC20</i>	c.1340C>T	p.Thr447Met	Missense
3:195782050	A/G	<i>MUC4</i>	c.9530T>C	p.Val3177Ala	Missense
3:195786568	G/A	<i>MUC4</i>	c.5012C>T	p.Ser1671Phe	Missense
3:31990509	C/G	<i>ZNF860</i>	c.1430C>G	p.Thr477Ser	Missense
3:36830891	G/A	<i>TRANK1</i>	c.8692C>T	p.Arg2898Trp	Missense
3:50302157	G/A	<i>HYAL1</i>	c.800C>T	p.Ala267Val	Missense
3:51984131	C/T	<i>ACY1</i>	c.67C>T	p.Arg23Cys	Missense
4:121164073	G/A	<i>TNIP3</i>	c.53C>T	p.Thr18Met	Missense
4:147875102	C/T	<i>ARHGAP10</i>	c.784C>T	p.Arg262Ter	LoF
4:48382595	C/T	<i>SLAIN2</i>	c.890C>T	p.Thr297Met	Missense
4:48561507	C/T	<i>FRYL</i>	c.3826G>A	p.Ala1276Thr	Missense
4:52029703	A/G	<i>SGCB</i>	c.404T>C	p.Leu135Ser	Missense
4:5841335	C/T	<i>CRMP1</i>	c.1126G>A	p.Asp376Asn	Missense

5:13919284	G/C	<i>DNAH5</i>	c.867C>G	p.His289Gln	Missense
5:73866000	G/T	<i>ARHGEF28</i>	c.2139G>T	p.Gln713His	Missense
5:77039595	G/A	<i>AGGF1</i>	c.746G>A	p.Arg249His	Missense
6:113953409	C/G	<i>HDAC2</i>	c.507G>C	p.Gln169His	Missense
6:113953410	T/G	<i>HDAC2</i>	c.506A>C	p.Gln169Pro	Missense
6:158493629	C/T	<i>TULP4</i>	c.1688C>T	p.Ser563Phe	Missense
6:161106684	T/C	<i>MAP3K4</i>	c.4027T>C	p.Trp1343Arg	Missense
6:26107744	G/A	<i>H1-6</i>	c.350C>T	p.Pro117Leu	Missense
6:30986727	G/C	<i>MUC21</i>	c.552G>C	p.Glu184Asp	Missense
6:30986737	G/A	<i>MUC21</i>	c.562G>A	p.Val188Met	Missense
6:32530209	G/A	<i>HLA-DRB5</i>	c.16C>T	p.Leu6Phe	Missense
6:32584273	A/T	<i>HLA-DRB1</i>	c.206T>A	p.Phe69Tyr	Missense
6:54940571	C/T	<i>FAM83B</i>	c.1600C>T	p.Leu534Phe	Missense
6:98836046	A/T	<i>POU3F2</i>	c.1173A>T	p.Leu391Phe	Missense
7:121996450	G/A	<i>PTPRZ1</i>	c.997G>A	p.Glu333Lys	Missense
7:128866780	C/T	<i>ATP6V1FNB</i>	c.371C>T	p.Thr124Met	Missense
7:134947749	G/A	<i>CALD1</i>	c.1774G>A	p.Asp592Asn	Missense
7:149826185	G/A	<i>SSPOP</i>	c.14369G>A	p.Arg4790Gln	Missense
7:151023204	T/C	<i>ATG9B</i>	c.662A>G	p.Gln221Arg	Missense
7:155803204	G/A	<i>SHH</i>	c.1085C>T	p.Ser362Leu	Missense
7:78343861	C/T	<i>MAGI2</i>	c.1325G>A	p.Gly442Asp	Missense
7:80828605	T/C	<i>SEMA3C</i>	c.244A>G	p.Ile82Val	Missense
7:93134086	C/T	<i>SAMD9L</i>	c.1886G>A	p.Arg629Gln	Missense
7:97007691	G/C	<i>DLX6</i>	c.490G>C	p.Gly164Arg	Missense
8:10607950	G/A	<i>RP1L1</i>	c.6148C>T	p.Pro2050Ser	Missense
8:125083835	C/A	<i>WASHC5</i>	c.64G>T	p.Gly22Cys	Missense
8:143924216	C/T	<i>PLEC</i>	c.5794G>A	p.Glu1932Lys	Missense
8:144512000	C/A	<i>RECQL4</i>	c.3304G>T	p.Asp1102Tyr	Missense
8:144722489	T/C	<i>ZNF251</i>	c.1171A>G	p.Ser391Gly	Missense
9:121021568	C/T	<i>C5</i>	c.1243G>A	p.Asp415Asn	Missense
9:131128358	C/G	<i>NUP214</i>	c.268C>G	p.Pro90Ala	Missense
9:134887404	C/T	<i>FCN2</i>	c.931C>T	p.Arg311Ter	LoF
9:33796675	G/A	<i>PRSS3</i>	c.244G>A	p.Val82Ile	Missense
9:89381234	C/T	<i>SEMA4D</i>	c.1559G>A	p.Cys520Tyr	Missense
10:100989673	A/C	<i>TWINK</i>	c.1273A>C	p.Ile425Leu	Missense
10:110821608	G/A	<i>RBM20</i>	c.2989G>A	p.Val997Met	Missense
10:26021561	C/G	<i>MYO3A</i>	c.644C>G	p.Ser215Cys	Missense
10:5937203	C/T	<i>FBH1</i>	c.3208C>T	p.Gln1070Ter	LoF
10:69572797	T/C	<i>NEUROG3</i>	c.247A>G	p.Ser83Gly	Missense
10:71730574	A/T	<i>CDH23</i>	c.3685A>T	p.Ile1229Phe	Missense
10:90915813	G/A	<i>ANKRD1</i>	c.719C>T	p.Ala240Val	Missense

10:97057258	G/A	<i>SLIT1</i>	c.1109C>T	p.Thr370Ile	Missense
11:1188914	G/A	<i>MUC5AC</i>	c.10769G>A	p.Arg3590His	Missense
11:55344004	A/C	<i>OR4A16</i>	c.804A>C	p.Leu268Phe	Missense
11:65389453	G/A	<i>FRMD8</i>	c.178G>A	p.Ala60Thr	Missense
11:6567652	G/A	<i>DNHD1</i>	c.12143G>A	p.Arg4048Gln	Missense
11:66715280	A/T	<i>SPTBN2</i>	c.425T>A	p.Val142Glu	Missense
11:84534687	T/A	<i>DLG2</i>	c.402A>T	p.Leu134Phe	Missense
11:95979264	T/C	<i>MAML2</i>	c.3155A>G	p.Asn1052Ser	Missense
12:110614214	T/C	<i>TCTN1</i>	c.32T>C	p.Val11Ala	Missense
12:47796247	T/C	<i>HDAC7</i>	c.755A>G	p.Asn252Ser	Missense
12:49050509	G/A	<i>KMT2D</i>	c.3079C>T	p.Leu1027Phe	Missense
12:50352111	G/T	<i>FAM186A</i>	c.4721C>A	p.Ala1574Asp	Missense
12:50352111	G/T	<i>FAM186A</i>	c.4721C>A	p.Ala1574Asp	Missense
12:50352857	G/C	<i>FAM186A</i>	c.3975C>G	p.Ile1325Met	Missense
12:63802407	T/A	<i>RXYLT1</i>	c.743+2T>A		LoF
13:102875878	C/T	<i>ERCC5</i>	c.3536C>T	p.Ala1179Val	Missense
13:19835686	G/A	<i>ZMYM5</i>	c.1042C>T	p.Arg348Cys	Missense
13:95763714	G/A	<i>DNAJC3</i>	c.920G>A	p.Arg307His	Missense
14:104948630	G/A	<i>AHNAK2</i>	c.6821C>T	p.Ala2274Val	Missense
14:104948633	G/C	<i>AHNAK2</i>	c.6818C>G	p.Thr2273Arg	Missense
14:104948637	C/T	<i>AHNAK2</i>	c.6814G>A	p.Val2272Met	Missense
14:23990277	C/T	<i>DHRS4L2</i>	c.224C>T	p.Thr75Met	Missense
14:53093367	T/C	<i>DDHD1</i>	c.1111A>G	p.Thr371Ala	Missense
14:57208791	T/C	<i>EXOC5</i>	c.1945A>G	p.Met649Val	Missense
14:78967390	A/T	<i>NRXN3</i>	c.2960A>T	p.Asp987Val	Missense
14:81144181	G/C	<i>TSHR</i>	c.2123G>C	p.Gly708Ala	Missense
15:40200274	A/T	<i>BUB1B</i>	c.1432A>T	p.Thr478Ser	Missense
15:58821727	T/C	<i>MINDY2</i>	c.1133T>C	p.Ile378Thr	Missense
15:78180855	G/A	<i>ACSBG1</i>	c.1153C>T	p.Arg385Cys	Missense
15:88856906	A/G	<i>ACAN</i>	c.4321A>G	p.Thr1441Ala	Missense
15:89582731	C/G	<i>TICRR</i>	c.700C>G	p.Leu234Val	Missense
16:1775841	G/A	<i>EME2</i>	c.824G>A	p.Arg275His	Missense
16:2255717	T/C	<i>RNPS1</i>	c.686A>G	p.Asp229Gly	Missense
16:28538847	C/A	<i>NUPR1</i>	c.61G>T	p.Asp21Tyr	Missense
16:48138240	T/G	<i>ABCC12</i>	c.967A>C	p.Asn323His	Missense
16:5056123	C/G	<i>C16orf89</i>	c.693G>C	p.Met231Ile	Missense
16:53156715	A/G	<i>CHD9</i>	c.626A>G	p.Asn209Ser	Missense
16:67645262	G/A	<i>CARMIL2</i>	c.16G>A	p.Asp6Asn	Missense
16:9763618	C/T	<i>GRIN2A</i>	c.3926G>A	p.Arg1309Gln	Missense
17:19019527	C/T	<i>SLC5A10</i>	c.1394C>T	p.Ser465Phe	Missense
17:3216519	G/A	<i>OR1A1</i>	c.899G>A	p.Arg300Gln	Missense

17:33291652	C/T	<i>ASIC2</i>	c.464G>A	p.Gly155Asp	Missense
17:4032234	C/T	<i>ZZEF1</i>	c.6784G>A	p.Val2262Ile	Missense
17:41756183	T/C	<i>JUP</i>	c.2078A>G	p.Tyr693Cys	Missense
17:41821726	C/A	<i>FKBP10</i>	c.1472C>A	p.Thr491Lys	Missense
17:41912433	C/T	<i>ACLY</i>	c.269G>A	p.Gly90Glu	Missense
17:4884399	G/T	<i>MINK1</i>	c.343G>T	p.Asp115Tyr	Missense
17:4887701	C/T	<i>MINK1</i>	c.1141C>T	p.Arg381Ter	LoF
17:68921472	C/T	<i>ABCA8</i>	c.1522G>A	p.Glu508Lys	Missense
17:7284563	G/A	<i>SLC2A4</i>	c.806G>A	p.Arg269His	Missense
17:75809893	G/A	<i>UNK</i>	c.238G>A	p.Gly80Ser	Missense
17:9802513	A/G	<i>GSG1L2</i>	c.755T>C	p.Phe252Ser	Missense
18:35677701	G/A	<i>GALNT1</i>	c.425G>A	p.Arg142His	Missense
18:57701307	G/A	<i>ATP8B1</i>	c.400C>T	p.Pro134Ser	Missense
18:62211239	G/A	<i>RELCH</i>	c.613G>A	p.Ala205Thr	Missense
18:62570232	G/T	<i>ZCCHC2</i>	c.1975+1G>T		LoF
18:63793232	C/A	<i>SERPINB7</i>	c.291C>A	p.Ser97Arg	Missense
19:10403376	A/G	<i>CDC37</i>	c.102+2T>C		LoF
19:10514953	T/C	<i>S1PR5</i>	c.59A>G	p.Asn20Ser	Missense
19:12792168	G/A	<i>JUNB</i>	c.397G>A	p.Glu133Lys	Missense
19:13983583	C/T	<i>RFX1</i>	c.332G>A	p.Arg111Gln	Missense
19:20807211	C/A	<i>ZNF66</i>	c.1611C>A	p.His537Gln	Missense
19:20807211	C/A	<i>ZNF66</i>	c.1611C>A	p.His537Gln	Missense
19:20807213	A/T	<i>ZNF66</i>	c.1613A>T	p.Lys538Met	Missense
19:20807213	A/T	<i>ZNF66</i>	c.1613A>T	p.Lys538Met	Missense
19:35785048	C/T	<i>ARHGAP33</i>	c.1663C>T	p.Arg555Trp	Missense
19:41197899	G/A	<i>CYP2S1</i>	c.464G>A	p.Cys155Tyr	Missense
19:54575487	A/C	<i>LILRA2</i>	c.887A>C	p.Tyr296Ser	Missense
19:54773524	A/G	<i>KIR2DL1</i>	c.262A>G	p.Ser88Gly	Missense
19:54775225	A/G	<i>KIR2DL1</i>	c.431A>G	p.Asn144Ser	Missense
19:57874619	C/G	<i>ZNF814</i>	c.771G>C	p.Leu257Phe	Missense
19:58516973	G/A	<i>ZBTB45</i>	c.701C>T	p.Pro234Leu	Missense
19:8499546	C/A	<i>PRAM1</i>	c.262G>T	p.Val88Phe	Missense
19:8499546	C/A	<i>PRAM1</i>	c.262G>T	p.Val88Phe	Missense
19:8499546	C/A	<i>PRAM1</i>	c.262G>T	p.Val88Phe	Missense
19:8951340	G/C	<i>MUC16</i>	c.25430C>G	p.Ala8477Gly	Missense
20:46013314	C/A	<i>MMP9</i>	c.1390C>A	p.Pro464Thr	Missense
20:58854572	C/A	<i>GNAS</i>	c.1307C>A	p.Ala436Asp	Missense
21:44943819	G/A	<i>FAM207A</i>	c.265G>A	p.Val89Ile	Missense
22:29489649	T/A	<i>NEFH</i>	c.2009T>A	p.Val670Glu	Missense
22:38645588	C/T	<i>FAM227A</i>	c.200G>A	p.Arg67His	Missense
22:45328021	G/C	<i>FAM118A</i>	c.480G>C	p.Gln160His	Missense

Supplementary Table 1: List of *de novo* mutations (DNMs) identified in nsCL/P African case-parent trios through analysis of the Whole-genome sequence.



Supplementary Figure 1: Predicted effects of the DNMs on protein structures and functions. **A:** Deleterious p.Ser37Leu DNM in *DHRS3* found in the catalytic domain. **B:** Damaging p.Ser563Phe DNM in *TULP4* disrupts the secondary structure of the polypeptide chain. **C:** Deleterious p.Ser362Leu DNM in *SHH* disrupts the secondary structure of the protein. **D:** Deleterious p.Ile589Met DNM in *TP63* found in the sterile alpha motif (SAM) domain. This mutation cause a disruption in the protein interaction of this domain. **E:** p.Thr491Lys

DNM in *FKBP10* which cause a disruption in the structure of the protein. **F:** p.Thr1441Ala DNM in *ACAN* which likely affect the protein structure and function. **G:** Damaging p.Asp1102Tyr DNM in *RECQL4* which affect the charge thus affecting the interactive function of the protein. **H:** Deleterious p.Leu1027Phe DNM in *KMT2D* affects the structure and interaction with other proteins. **I:** Deleterious p.Gly164Arg DNM in *DLX6* affects the protein interaction function of the Homeobox-like domain. **J:** Damaging p.Pro290His DNM in the *EPHB2* alter the special conformation of the protein and interaction. **K:** Damaging p.Cys520Tyr DNM in the *SEMA4D* found in the highly conserved PSI domain. The wildtype amino acid residue is highly conserved at this location and mutation could cause a disruption in the binding function of the PSI domain. **L:** p.Ile82Val DNM in *SEMA3C* is found within the protein-binding domain thus it may abolish the function.

A	E10.5 Frontonasal	E11.0 Frontonasal	E11.5 Frontonasal	E10.0 Mandible	E10.5 Mandible	E10.5 Mandible (lateral)	E10.5 Mandible (medial)	E11.0 Mandible	E11.5a Mandible	E11.5b Mandible	E11.5 Mandible (medial)	E10.5 Maxilla	E11.0 Maxilla	E11.5 Maxilla	E13.5a Palate	E13.5b Palate	E14.5a Palate	E14.5b Palate	E14.5c Palate	P0 Palate
<i>Act16a</i>	2059.0	2286.8	1976.1	3464.7	1918.2	2578.5	3039.4	2330.2	3288.8	1768.0	2621.8	1820.3	2212.0	2328.0	2096.7	1941.4	1281.1	1581.7	1419.8	956.3
<i>Ankrd1</i>	49.2	38.9	36.1	38.5	50.9	32.4	32.3	34.9	41.5	40.3	48.3	42.6	42.1	35.6	52.3	37.7	43.5	39.6	40.4	488.6
<i>Bivm</i>	590.2	771.6	567.6	873.5	535.1	915.8	762.4	695.2	1064.1	540.8	607.2	513.5	702.2	686.5	946.2	944.2	456.0	611.5	757.9	501.8
<i>Bub1b</i>	2332.1	2807.7	2402.0	3662.5	2129.0	2684.9	2569.4	2656.8	1878.6	2085.3	2361.7	2191.4	2583.7	2589.7	1133.4	1007.8	1176.3	1175.6	1426.6	552.4
<i>Cdc37</i>	4071.1	4213.5	3833.5	5563.0	3921.9	4100.8	3897.7	4387.9	2701.7	3694.0	3921.6	3717.3	4796.3	4432.8	2305.8	1609.8	3131.6	3572.0	3776.8	1873.4
<i>Cdh23</i>	89.7	74.9	77.8	63.6	75.9	92.0	66.0	81.3	66.6	74.8	80.0	80.4	71.7	74.0	56.2	61.1	59.9	54.8	56.3	69.2
<i>Cep63</i>	457.0	576.5	464.1	742.9	394.4	446.5	467.1	467.6	748.0	387.4	436.7	430.6	538.6	503.8	588.5	690.6	437.0	458.1	437.3	546.6
<i>Coe7</i>	410.0	394.4	293.3	744.9	382.9	507.7	540.9	397.9	676.7	328.5	692.9	340.5	407.9	332.4	520.6	444.3	252.3	315.3	372.5	431.0
<i>Dhhf1</i>	103.3	144.4	125.2	91.8	145.8	95.4	80.2	109.4	75.2	122.8	119.7	132.4	111.1	116.3	70.4	98.5	125.4	201.2	88.0	117.1
<i>Dnah5</i>	69.0	51.6	55.5	42.8	62.8	42.3	41.5	56.7	46.9	64.1	37.2	60.2	67.1	93.3	36.8	37.0	44.7	35.5	35.0	30.8
<i>Dnajc3</i>	381.5	434.7	403.5	767.6	365.7	863.4	908.2	489.1	1258.5	369.0	778.0	394.5	435.7	388.8	1641.7	1400.1	1387.2	1278.3	1198.2	1789.9
<i>Dhhf1</i>	93.0	83.1	82.3	68.0	86.8	66.1	71.2	91.8	70.7	88.9	69.4	98.0	82.4	77.6	82.9	69.1	93.2	94.0	85.9	61.7
<i>Dock7</i>	1043.0	1237.2	1319.7	1533.6	1058.0	1880.8	2277.4	1334.0	2055.9	1381.5	2210.4	1033.2	1115.4	1381.2	1599.8	2199.2	2154.8	2180.2	2247.0	989.9
<i>Ercc5</i>	249.8	350.1	327.4	452.8	236.6	374.8	405.5	339.1	544.3	301.7	403.9	229.7	391.8	444.8	891.3	909.3	455.9	544.4	438.4	301.3
<i>Ercc5</i>	933.0	1096.2	1108.5	1401.7	839.2	1126.6	1349.5	1066.3	1839.1	1001.2	1278.5	862.4	1049.3	1233.7	1818.5	1355.8	1444.1	1130.0	1436.2	
<i>Fcn2 (Fcnb)</i>	66.8	60.8	58.5	60.7	66.3	76.2	51.3	65.9	54.6	63.1	52.0	64.6	58.2	58.8	60.4	57.1	56.7	48.9	57.4	174.5
<i>Gnas</i>	6157.7	8365.7	9888.6	11273.9	6492.0	10789.8	13403.9	10819.1	10843.6	9792.3	13202.7	6098.8	7397.4	8948.2	11017.9	10341.4	13372.4	13094.1	11680.8	11379.1
<i>Junb</i>	49.9	43.7	41.7	84.8	39.5	77.4	72.3	47.1	56.4	39.9	75.0	40.3	45.2	44.5	61.3	58.6	59.7	72.9	87.0	141.7
<i>Jup</i>	583.5	472.8	639.2	363.9	573.1	269.8	284.2	487.3	265.8	543.4	273.4	568.1	536.9	546.8	330.2	280.0	363.5	527.2	586.5	536.0
<i>Map3k4</i>	284.2	460.5	399.5	719.0	237.3	1384.5	1264.9	479.8	1428.2	333.3	1268.9	309.8	447.1	455.0	1405.1	1428.4	891.5	1047.3	1288.7	1006.9
<i>Mkrm2</i>	571.9	680.0	651.9	759.1	525.0	737.7	722.8	654.9	842.0	821.2	815.5	514.6	666.9	718.4	892.6	686.5	875.5	632.2	764.3	712.4
<i>Mmp9</i>	77.5	73.0	79.3	56.9	86.2	62.6	71.6	76.0	88.4	89.8	78.6	91.5	77.5	73.3	407.7	207.0	438.7	320.4	251.6	325.1
<i>Muc4</i>	39.1	31.7	58.4	21.7	44.9	18.1	20.3	25.2	22.9	46.6	27.1	48.2	32.0	47.6	25.1	25.5	65.6	141.0	26.7	23.8
<i>Nefn</i>	45.0	31.7	30.5	18.2	41.9	17.9	17.1	26.0	16.6	35.3	18.5	42.0	33.7	26.6	15.7	16.7	22.6	62.0	136.3	
<i>Neurog3</i>	61.7	57.6	51.6	35.6	80.6	32.2	27.8	54.7	34.1	55.6	33.2	74.1	58.8	41.6	27.1	31.1	33.3	24.8	30.7	29.0
<i>Nipa3</i>	125.5	141.1	145.8	154.5	98.1	163.3	182.5	122.6	152.1	119.3	144.5	115.9	118.6	125.3	188.6	140.7	154.4	152.1	200.5	322.6
<i>Ptpz1</i>	84.7	93.8	108.7	166.7	94.6	156.3	284.4	112.4	263.7	110.0	64.5	83.4	81.1	106.0	655.9	690.9	728.8	685.4	890.3	301.3
<i>Serpinb7</i>	25.1	29.3	23.1	19.4	30.3	16.8	17.6	22.6	16.5	24.2	17.1	27.0	25.5	23.6	53.8	19.4	42.8	54.7	90.2	32.6
<i>Slc20a1</i>	963.4	1214.2	1102.1	1547.6	821.2	1481.7	1795.4	1202.1	1109.5	1032.6	1373.6	963.7	1192.8	1207.6	883.1	780.6	1115.8	1260.7	891.9	1088.1
<i>Slit1</i>	142.5	156.6	167.0	218.9	130.7	232.7	286.0	157.0	113.8	164.6	247.1	137.4	146.0	150.7	182.4	177.3	508.2	307.7	362.1	168.8
<i>Tctn1</i>	105.4	159.0	159.6	245.4	93.5	397.8	314.9	147.2	459.3	127.2	341.3	103.4	125.4	154.4	581.2	559.8	387.2	443.9	343.8	425.9
<i>Zcchc2</i>																				

B	E10.5 Mandibular Columnar Epithelium	E10.5 Maxillary Columnar Epithelium
<i>Act16a</i>	2204.5	2204.1
<i>Ankrd1</i>	37.8	36.4
<i>Bivm</i>	140.4	29.4
<i>Bub1b</i>	219.6	186.2
<i>Cdc37</i>	2574.8	2210.9
<i>Cdh23</i>	50.8	55.2
<i>Cep63</i>	240.4	321.5
<i>Coe7</i>	1301.6	1162.9
<i>Dhhf1</i>	45.3	41.1
<i>Dnah5</i>	39.7	45.6
<i>Dnajc3</i>	382.3	150.8
<i>Dock7</i>	72.6	73.1
<i>Ercc5</i>	166.5	137.3
<i>Fcn2 (Fcnb)</i>	83.3	86.0
<i>Gnas</i>	518.0	588.7
<i>Junb</i>	115.7	192.2
<i>Jup</i>	174.7	197.2
<i>Map3k4</i>	79.6	89.3
<i>Mkrm2</i>	442.2	547.8
<i>Mmp9</i>	62.6	74.4
<i>Muc4</i>	58.2	63.7
<i>Nefn</i>	61.3	77.4
<i>Neurog3</i>	32.8	45.6
<i>Nipa3</i>	39.0	47.0
<i>Ptpz1</i>	34.5	29.9
<i>Serpinb7</i>	15.7	15.8
<i>Slc20a1</i>	107.2	112.8
<i>Slit1</i>	57.3	75.6
<i>Tctn1</i>	107.9	111.5
<i>Zcchc2</i>	30.1	37.0

C	E10.5 Lateral Nasal Eminence	E10.5 Medial Nasal Prominence	E10.5 Mandibular Arch	E10.5 Mandibular Arch Epidermal Ectoderm	E10.5 Maxillary Arch	E10.5 Maxillary Arch Epidermal Ectoderm
<i>Act16a</i>	923.3	302.9	215.7	306.1	365.5	119.9
<i>Ankrd1</i>	473.4	638.4	566.9	254.2	368.3	317.0
<i>Bivm</i>	173.5	157.4	168.0	122.0	196.7	183.2
<i>Bub1b</i>	43.4	37.3	32.4	39.7	37.5	51.8
<i>Cdc37</i>	23.1	23.8	20.6	27.2	21.0	31.1
<i>Cdh23</i>	21.0	19.9	20.7	22.7	20.0	23.2
<i>Cep63</i>	20.5	18.3	19.9	19.5	22.1	21.2
<i>Coe7</i>	38.6	37.5	39.1	38.5	36.4	41.5
<i>Dhhf1</i>	605.3	679.4	760.1	592.3	752.2	695.2
<i>Dnah5</i>	840.0	1070.8	680.5	956.7	666.7	891.9
<i>Dnajc3</i>	3131.0	3131.4	3178.5	3966.9	1833.8	3860.8
<i>Dock7</i>	363.2	29.3	98.2	32.3	28.6	29.7
<i>Ercc5</i>	202.1	281.8	297.3	171.8	214.1	167.2
<i>Ercc5</i>	178.8	156.0	161.5	158.4	198.9	168.3
<i>Fcn2 (Fcnb)</i>	81.0	70.5	72.4	58.9	82.0	82.5
<i>Gnas</i>	25.5	25.9	22.4	25.8	25.4	27.7
<i>Gagyl2</i>	40.7	33.6	34.6	39.9	39.5	37.2
<i>Junb</i>	78.9	60.6	73.3	66.1	89.6	89.3
<i>Jup</i>	90.6	90.5	91.3	72.9	103.0	106.5
<i>Map3k4</i>	57.0	59.2	52.6	88.8	67.2	59.5
<i>Mkrm2</i>	93.6	65.3	71.1	70.1	118.1	78.7
<i>Mmp9</i>	19.0	16.2	16.4	18.5	16.8	20.9
<i>Muc4</i>	90.6	92.6	91.4	78.3	95.0	99.9
<i>Nefn</i>	45.9	42.4	43.2	40.6	52.7	48.0
<i>Neurog3</i>	24.9	24.5	21.6	25.0	19.6	31.7
<i>Nipa3</i>	24.7	21.4	20.9	26.6	21.9	25.2
<i>Ptpz1</i>	143.3	457.1	193.6	230.0	118.4	572.5
<i>Serpinb7</i>	40.8	39.0	39.4	38.0	48.1	45.3
<i>Slc20a1</i>	126.5	92.9	102.4	99.0	119.3	142.1
<i>Slit1</i>	42.6	39.3	39.3	50.9	43.7	51.4
<i>Tctn1</i>	23.5	21.3	23.4	20.6	21.8	34.3
<i>Zcchc2</i>	123.1	140.7	200.0	145.5	142.6	85.9

Supplementary Figure 2: SysFACE-based expression analysis of candidate genes in mouse facial

generated on the Affymetrix Mouse Genome 430 2.0 Array platform, **(B)** FaceBase microarray data generated on the Affymetrix Mouse Gene 1.0 ST Array platform, and **(C)** GSE55965 microarray data generated on the Affymetrix Mouse Gene 1.0 ST Array platform. Heat-map denotes row-wise comparative expression of individual genes in different tissues at Embryonic (E) and/or postnatal (P) stages. Intensity of the color in the heat-map is representative of candidate gene expression and the average fluorescence signal intensity is shown.