# Population-Specific Insights: The Genetic Basis of Orofacial Clefts in Ghanaian Multiplex Families

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## INTRODUCTION

### Background

- Orofacial clefts (OFCs) are the most prevalent congenital defects, affecting 1 in every 700 live births[1].
- OFCs occur when the facial structures fail to fuse properly, resulting in either cleft palate, cleft lip, or both[2]
- The aetiology of OFCs is complex involving genetic and environmental risk factors[3]

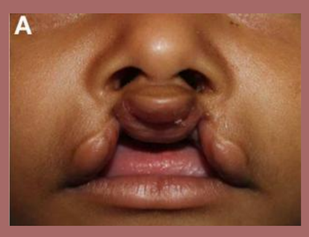


Figure 1: Cleft lip

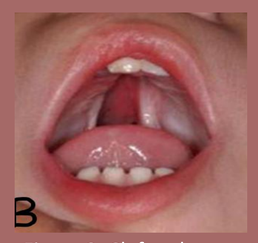


Figure 2: Cleft palate

### Main Aim

- Decipher genetic variants that may predispose multiplex families from Ghana to OFCs.

### Specific Aims

- To identify genetic variants underlying the aetiology of the OFCs in multiplex families, employing WES.
- To identify biological pathways implicated the pathogenesis of OFCs in these families, employing bioinformatics tools.
- To determine the inheritance pattern for the variants in these families.

## SUBJECTS AND METHODS

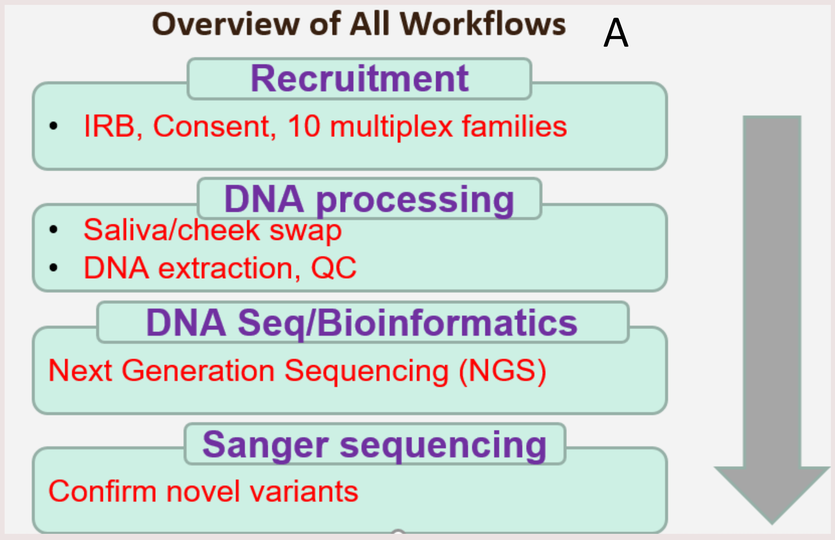


Figure 3: Project workflow

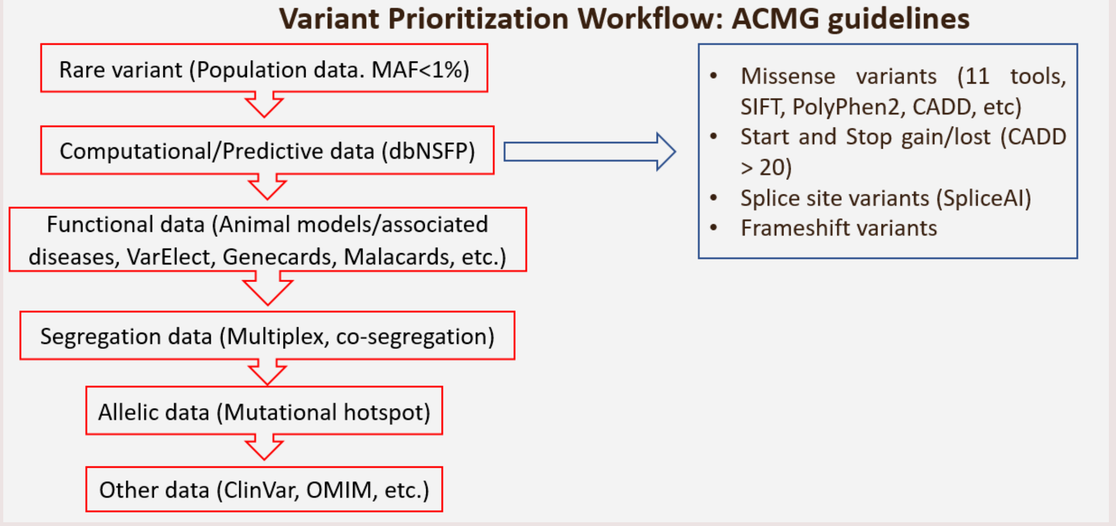


Figure 4: Variant prioritization workflow

## RESULTS AND DISCUSSION

**Probable Causative Variants Associated with Orofacial Cleft in Multiplex Families**

| Family_ID | Genomic_Coordinate | Symbol | Ref | Alt | Genotype | HGVSc | HGVSp | No_Predicted Pathogenic |
|---|---|---|---|---|---|---|---|---|
| GH20130786 | chr12:103638076 (novel) | *STAB2* | C | A | C/A | c.770C>A | p.Pro257Gln | 6 |
| GH20130793 | chr20:46725796 (rs1341502906) | *SLC2A10* | GCC | G | GCC/G | c.761_762del | p.Ala254ValfsTer107 | N/A |
| GH20130849 | chr19:38405419 (rs75686841) | *FAM98C* | T | C | C/C | c.631T>C | p.Trp211Arg | 7 |
| GH20134954 | chr1:209788626 (rs28942095) | *IRF6* | G | A | G/A | c.1198C>T | p.Arg400Trp | 11 |
| GH20134957 | chr12:39331769 (novel) | *KIF21A* | A | G | A/G | c.3074T>C | p.Val1025Ala | 8 |
| | chr12:39332713 (rs749918204) | | G | A | G/A | c.2734C>T | p.Arg912Ter | 8 |
| | chr3:184581042 (rs1309605764) | *EPHB3* | T | A | T/A | c.2609T>A | p.Leu870His | 11 |
| GH20160117 | chr1:24347483 (rs946439477) | *GRHL3* | G | A | G/A | c.1559G>A | p.Arg520Gln | 10 |
| GH20160155 | chr11:57795646 (rs201815246) | *CTNND1* | A | C | A/C | c.337A>C | p.Thr113Pro | 6 |
| GH20160161 | chr5:11346402 (rs201675268) | *ZFYVE21* | C | T | C/T | c.415C>T | p.Arg139Cys | 6 |
| GH20160211 | chr6:32195679 (rs562060812) | *NOTCH4* | G | A | G/A | c.5770C>T | p.Arg1924Trp | 6 |
| | chr6:32203795 (rs141267746) | | A | G | A/G | c.3206T>C | p.Leu1069Pro | 6 |
| GH20160239 | chr19:8136023 (rs1413219584) | *FBN3* | C | T | C/T | c.1529G>A | p.Gly510Asp | 8 |
| | chr19:8136276 (rs147206351) | | T | C | T/C | c.1379A>G | p.His460Arg | 8 |

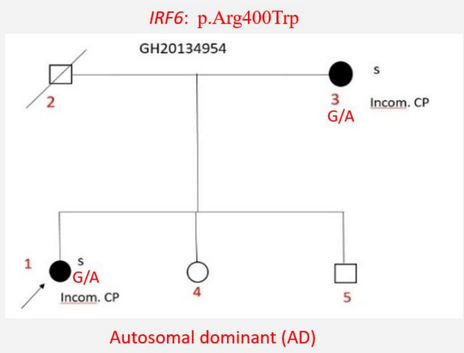


Figure 5: Pedigree of family GH20134954


| ID | Source | Term ID | Term Name | $P_{adj}$ (query_1) |
|---|---|---|---|---|
| 1 | GO:MF | GO:0050839 | cell adhesion molecule binding | $7.402\times10^{-4}$ |
| 2 | GO:MF | GO:0140999 | histone H3K4 trimethyltransferase activity | $4.082\times10^{-2}$ |
| 3 | GO:MF | GO:0005509 | calcium ion binding | $4.346\times10^{-2}$ |
| 4 | GO:BP | GO:0044331 | cell-cell adhesion mediated by cadherin | $9.743\times10^{-8}$ |
| 5 | GO:BP | GO:0034329 | cell junction assembly | $1.371\times10^{-5}$ |
| 6 | GO:BP | GO:0009653 | anatomical structure morphogenesis | $2.058\times10^{-4}$ |
| 7 | GO:BP | GO:0048333 | mesodermal cell differentiation | $2.318\times10^{-2}$ |
| 8 | GO:BP | GO:0007229 | integrin-mediated signaling pathway | $3.725\times10^{-2}$ |
| 9 | GO:CC | GO:0016342 | catenin complex | $2.292\times10^{-5}$ |
| 10 | GO:CC | GO:0005912 | adherens junction | $5.451\times10^{-5}$ |
| 11 | KEGG | KEGG:00310 | lysine degradation | $2.570\times10^{-2}$ |
| 12 | WP | WP:WP2064 | Neural crest differentiation | $4.598\times10^{-4}$ |
| 13 | REAC | REAC:R-HSA-42... | Cell-cell junction organization | $1.093\times10^{-2}$ |
| 14 | HP | HP:0100267 | Lip pit | $1.452\times10^{-2}$ |
| 15 | HP | HP:0000202 | Orofacial cleft | $2.654\times10^{-2}$ |

Figure 6: Enriched pathways

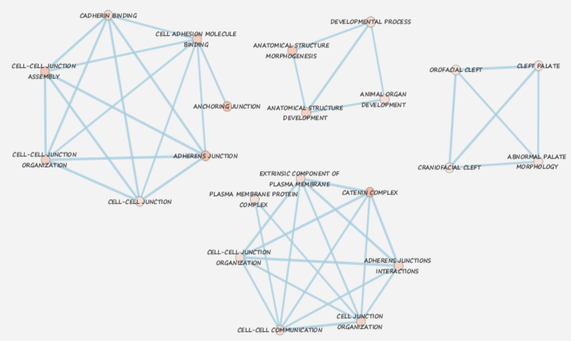


Figure 7: Pathway interaction network

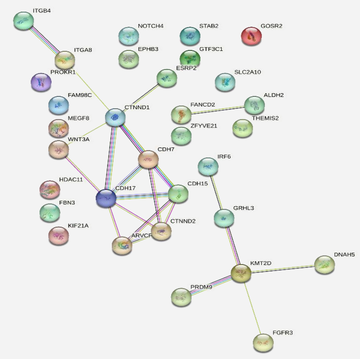


Figure 8: Protein-protein interaction network

**Hub Genes**

| Rank | Name | Node Score |
|---|---|---|
| 1 | *CDH17* | 20 |
| 2 | *CDH15* | 18 |
| 3 | *CDH7* | 12 |
| 3 | *CTNND2* | 12 |
| 5 | *CTNND1* | 10 |
| 6 | *ARVCF* | 6 |
| 7 | *KMT2D* | 4 |
| 8 | *GRHL3* | 2 |
| 8 | *ITGA8* | 2 |
| 8 | *WNT3A* | 2 |

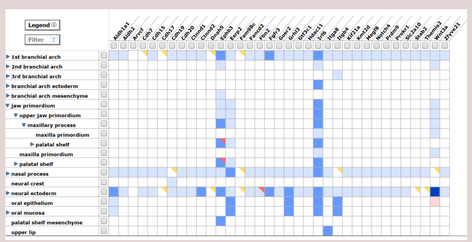


Figure 8: Anatomical expression matrix for candidate genes

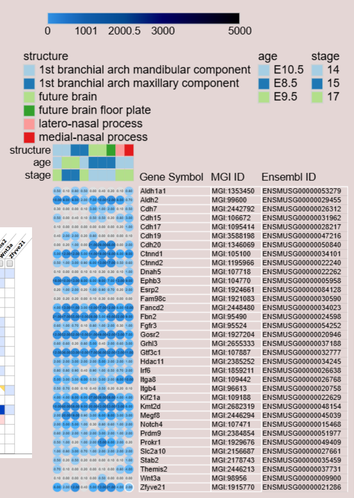


Figure 9: Expression heatmap for candidate genes

## CONCLUSION AND RECOMMENDATIONS

- In essence, we identified novel genetic and phenotypic insights into orofacial clefts (OFCs) in Ghanaian multiplex families.
- Enriched pathways and hub genes emphasise the role of these genes in OFCs development.
- Eighty percent of families exhibited autosomal dominant inheritance with incomplete penetrance in some cases, while 20% followed an autosomal recessive mode.
- Functional genomics studies are needed to validate novel variants.

## REFERENCES

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