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Identification of paternal uniparental disomy on chromosome 22 and a de novo deletion on chromosome 18 in individuals with orofacial clefts

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Abstract
Background: Orofacial clefts are the most common malformations of the head and neck region. Genetic and environmental factors have been implicated in the etiology of these traits.
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Methods: We recently conducted genotyping of individuals from the African population using the multiethnic genotyping array (MEGA) to identify common genetic variation associated with nonsyndromic orofacial clefts. The data cleaning of this dataset allowed for screening of annotated sex versus genetic sex, confirmation of identify by descent and identification of large chromosomal anomalies.

Results: We identified the first reported orofacial cleft case associated with paternal uniparental disomy (patUPD) on chromosome 22. We also identified a de novo deletion on chromosome 18. In addition to chromosomal anomalies, we identified cases with molecular karyotypes suggesting Klinefelter syndrome, Turner syndrome and Triple X syndrome.

Conclusion: Observations from our study support the need for genetic testing when clinically indicated in order to exclude chromosomal anomalies associated with clefting. The identification of these chromosomal anomalies and sex aneuploidies is important in genetic counseling for families that are at risk. Clinicians should share any identified genetic findings and place them in context for the families during routine clinical visits and evaluations.

KEYWORDS
cleft lip and palate, deletions, GWAS, uniparental disomy

1 | INTRODUCTION

Orofacial clefts can be classified as syndromic and nonsyndromic clefts. Syndromic clefts (SC) are clefts with other structural and cognitive phenotypes and they account for 30% of all clefts. There are over 500 Mendelian clefting syndromes currently indexed in OMIM (www.omim.org), with other causes secondary to environmental teratogens, chromosomal anomalies or sporadic events of unknown etiology.

Nonsyndromic clefts (NSC) are the most common forms of clefts accounting for 70% of all clefts (Marazita et al., 2002). NSC affect 1/700 live births worldwide and prevalence varies significantly due to ethnicity and geographical locations. The etiology of NSC is complex and many genes have been reported to be associated (Dixon, Marazita, Beaty, & Murray, 2011). In addition to genes, environmental factors such as smoking have been identified as teratogens that increase the risk for clefting (Little, Cardy, & Munger, 2004).

Chromosomal abnormalities have been reported in both isolated clefts and clefts with associated congenital anomalies. In fact, almost all clefts with associated congenital anomalies have chromosomal abnormalities (Maarse et al., 2012). The prevalence of clefts with associated anomalies and chromosomal abnormalities varies by cleft types and time of diagnosis (prenatal and postnatal). For instance, reported prenatal rates for cleft lip (CL) are 33.3%, cleft lip and palate (CLP) is 50–63.3 and CP is 100%. Postnatal rates for CL are 10.4–22.2%, CLP is 5–31%, and CP is 14%–18%. postnatally (Calzolari et al., 2007; Kallen, Harris, & Robert, 1996; Rittler et al., 2011; Tan et al., 2009; Walker, Ball, Babcook, & Feldkamp, 2001). Furthermore, reported prenatal rates for isolated clefts with chromosomal abnormalities are 5.3%–7.1% for CLP (Maarse et al., 2012; Nyberg, Sickler, Hegge, Kramer, & Kropp, 1995) and postnatal rates are 1.8% for CL, and 1% for CLP (Rittler et al., 2008; Rittler et al., 2011).

Paternal Uniparental Disomy (patUPD) is a situation whereby an individual has inherited a pair of homologous chromosomes from the father (Engel, 1980). patUPD can arise through multiple mechanisms: (a) Trisomy rescue (TR), when a trisomic zygote forms from a disomic sperm with two paternal chromosomes and a normal ovum, followed by subsequent loss of the maternal chromosome; (b) Gamete complementation (GC), where a disomic sperm fertilizes a nullisomic egg missing a chromosome, resulting in a normal chromosome count; (c) Monosomy rescue (MR), when a monosomic sperm fertilizes a nullisomic egg producing a monosomic zygote followed by duplication of the paternal chromosome, (d) Postfertilization mitotic nondisjunction (Mit), leading to mosaicism for trisomic and monosomic cell lines with subsequent duplication in the monosomic line (Liehr, 2014).

Although paternal and maternal uniparental disomy (UPD) in orofacial clefts are very rare, they have been reported on chromosomes 6, 7, 10, 12, 15, 16 and 21 (Hahnemann, Nir, Friberg, Engel, & Bugge, 2005; Kotzot,
2004; Kotzot, 2008; Leslie et al., 2015; Romanelli et al., 2011; Salahshourifar et al., 2010; Tsai, Gibby, Beischel, McGavran, & Johnson, 2004). However, none have been reported on chromosome 22.

To identify variation associated with presumed nonsyndromic clefts in a sub-Saharan African population, we genotyped samples from affected cases, case family members and unrelated controls. We hypothesized that chromosomal abnormalities are present in some individuals with nonsyndromic clefts and that these individuals will need to be excluded before genome-wide association studies for clefting are conducted. In our preliminary analyses and data quality control (QC) process, we identified individuals with chromosomal anomalies on several chromosomes including uniparental disomy on chromosome 22, large chromosomal deletions and duplications.

2 METHODS

2.1 Ethical approval and sample collection

Eligible subjects are individuals who have nonsyndromic OFC and were born to Ghanaian, Ethiopian, and Nigerian parents. The offspring of Caucasians and Asians were excluded. Eligible cases were identified following IRB approval through the free clefts surgical repair projects. Currently, the network for treatment of clefts in Africa is enhanced, due to the efforts of the Pan African Association for Cleft Lip and Palate (PAACLIP). This network is supported by cleft charities, and all members use a common, standardized protocol for phenotyping. In addition, the grant requires that surgeons at all centers perform standardized protocol for phenotyping. In our preliminary analyses and data quality control process, we identified individuals with chromosomal anomalies on several chromosomes including uniparental disomy on chromosome 22, large chromosomal deletions and duplications.

2.2 DNA extraction and preliminary quality control

Saliva samples were labeled at the Butali laboratory in Iowa and assigned a unique identification (UNID) number prior to DNA extraction. DNA extraction was done at the Butali lab using the Murray lab protocol (genetics@uiowa.edu). Each sample was quantified using Qubit (http://www.invitrogen.com/site/us/en/home/brands/Product-Brand/Qubit.html) and divided into a stock and several working aliquots. This set-up allowed us to verify sample identity using the stock if mislabeling or cross-contamination of the working aliquot was suspected during sample handling. As a preliminary quality check, gender reported in the Redcap database was confirmed using Taqman XY genotyping. A 25ul aliquot of consented samples with confirmed genetic sex and DNA concentration of ≥ 50ng/ul was sent for MEGA array genotyping at the Center for Inherited Disease Research (CIDR).

2.3 Genotyping

The expanded Illumina Multi-Ethnic Genotyping Array (MEGA) v2 15070954 A2 (genome build 37) that contains over 2 million Single Nucleotide Polymorphisms and over 60,000 rare variants selected from populations of African origin was used for genotyping. Genotyping was carried out on 3,347 samples which included 3,198 unique samples and 70 duplicates. HapMap controls (70 unique samples and 9 duplicates) were also genotyped as part of the quality control process.

2.4 Data cleaning

The goal of the data cleaning process was to identify a high-quality genotype dataset that can be used for detecting significant genotype associations with nonsyndromic clefts. This process included sex chromosome checks, a check for missing call rates, batch effects, identification of large chromosomal anomalies, confirmation of relatedness (i.e., identity by descent) and establishment of continental ancestry with respect to HapMap samples using methods described in Laurie et al. (2010) and implemented using R packages GWAS Tools (Gogarten et al., 2012), SNPRelate (Zheng et al., 2012) and GENESIS (Conomos & Thornton, 2016). Large chromosomal anomalies, such as aneuploidy, copy number variations and mosaic uniparental disomy, can be detected using “Log R Ratio” (LRR) and “B Allele Frequency” (BAF) (Conlin et al., 2010; Peiffer et al., 2006). LRR is a measure of relative signal intensity (log2
of the ratio of observed to expected intensity, where the expectation is based on other samples). BAF is an estimate of the frequency of the B allele of a given single nucleotide polymorphism (SNP) in the population of cells from which the DNA was extracted. In a normal cell, the B allele frequency at any locus is either 0 (AA), 0.5 (AB) or 1 (BB) and the expected LRR is 0. Both copy number changes and copy-neutral changes from biparental to uniparental disomy (UPD) result in changes in BAF, while copy number changes also affect LRR.

To identify aneuploid or mosaic samples systematically, we used the “Circular Binary Segmentation” (CBS) (Venkatraman & Olshen, 2007) and identification of runs of homozygosity. For anomalies that split the intermediate BAF band into two components, we used CBS on BAF values for SNPs not called as homozygotes. For heterozygous deletions (with loss of the intermediate BAF band), we identified runs of homozygosity accompanied by a decrease in LRR (Laurie et al., 2012). All sample-chromosome combinations with anomalies greater than 5 Mb or sample-chromosome combinations with the sum of the lengths of the anomalies greater than 10 Mb were verified by manual review of BAF and LRR plots.

### RESULTS

The clinical information of all individuals with sex aneuploidies, trisomies, chromosomal anomalies, large deletions and duplications are described in Tables 1–3, respectively.

| Table 1 | Individuals with sex aneuploidies |
|---------|----------------------------------|
| **Observed clinical sex** | **Sex annotation from genotype analysis** | **Cleft type** | **Cleft description** | **Additional clinical feature** |
| F | XXX/X | CLP | Unilateral – right |
| M | XXY | CL | Unilateral – left |
| F | XXX | Case mom |
| M | XXY | CPO | Submucous cleft palate |
| M | XXY | Control |
| F | XXX | CPO | Soft palate |

**Note.** CL, cleft lip; CLP, cleft lip and palate; CPO, cleft palate only; F, females; M, males; VPI, Velo-pharyngeal Insufficiency.

| Table 2 | Individuals with trisomy, age at recruitment and maternal age at child’s delivery |
|---------|----------------------------------|
| **Trisomy** | **Cleft type/Control** | **Proband sex** | **Age at recruitment** | **Mother age when proband was born** | **Father age when proband was born** | **Additional clinical feature** |
| Trisomy 13 | CLP | F | 3 weeks | 45 | 50 | Right unilateral microphthalmia. Hexadactyly of both hands (fingers). Hexadactyly of left foot (toes)a |
| Trisomy 13 | CLP | F | Unknown |
| Trisomy 13 | Unknown | F | Unknown |
| Trisomy 21 | CLP | M | 1 week | 30 | 36 |
| Trisomy 21 | CLP | M | 5 months | 32.5 | 46.5 |
| Trisomy 21 | Control | M | 10 years | 36 |
| Trisomy 21 | Control | M | 10 months | 43 |
| Trisomy 21 | Control | M | 7 months | 35 |
| Trisomy 21 | Control | M | 15 months | 40 |
| Trisomy 21 | Control | M | 14 months | 34 |
| Trisomy 21 | Control | F | 8 years | 30 | 42 |
| Trisomy 21 | Control | F | 13 years | 24 | 27 |
| Trisomy 21 | Control | M | 10 months | 35 | 40 |

**Note.** aThe additional clinical features indicate that this is a syndromic case which was confirmed during our study.
We identified three individuals with XXX, four individuals with XXY and one with mosaic XX/X (see Figure 1). They could be mosaics and not actually have the syndromic phenotypes generally associated with these sex chromosome anomalies. We also identified three individuals with Trisomy 13 (Patau syndrome), and 10 individuals with Trisomy 21. Representative BAF and LRR plots from this study for each of these aneuploidies are shown in Figure 2.

We also identified an apparent case of paternal uniparental disomy (patUPD) on chromosome 22. The UPD is apparent from the nearly complete homozygosity on chromosome 22 (Figure 3) for an affected offspring whose mother was also genotyped. The father was not genotyped.

The inference of paternal UPD origin was based on lack of identity by state (IBS0) estimates by chromosome for the mother–offspring pair, for which the expected value is zero. The IBS0 estimate for the mother–offspring pair in Figure 3 using chromosome 22 SNPs is much higher (0.34) than zero and much higher than the IBS0 on any other autosome (IBS0 range 0–0.002) in this pair, or any other parent–offspring pair in this study (IBS0 range 0.001 to 0.0001).

Furthermore, an affected individual with a de novo 23MB deletion on Chromosome 18 was also identified. BAF and LRR plots of this individual and its parents are shown in Figure 4. Other cases with large deletions that are 5 Mbs or more, as well as large duplications were identified in chromosome 10, 18, and 21. Each of these was in a mother–affected child pair where mother does not have the deletion. The absence of paternal samples means we could not determine if the deletion is de novo. About 30 individuals with large autosomal deletions and duplications were identified (data not provided).

### TABLE 3

| Chromosome | Sex | Case/Control | Cleft type  |
|------------|-----|--------------|-------------|
| 18         | F   | Case         | CLP         |
| 13         | F   | Case         | Unknown cleft type |
| 7          | M   | Case         | CLP         |
| 8          | M   | Case         | CLP         |
| 8          | M   | Case         | CL          |
| 5          | F   | Case         | CL          |
| 13         | F   | Case         | CLP         |
| 5          | F   | Case         | CLP         |
| 18         | M   | Case         | CPO         |
| 21         | M   | Case         | CLP         |
| 22         | M   | Case         | CPO         |
| 18         | M   | Case         | CLP         |
| 6          | F   | Case         | CL          |
| 9          | M   | Case         | CLP         |
| 15         | M   | Case         | CL          |
| 4          | F   | Case         | CPO         |
| 7          | M   | Case         | CL          |
| 5          | F   | Case         | CL          |
| 18         | F   | Case         | CPO         |
| 8 & 9      | M   | Case         | CLP         |
| 15         | F   | Case mom of CLP | CLP    |
| 3          | M   | Case         | CLP         |
| 10         | F   | Case         | CPO         |
| 5          | F   | Case mom of CLP | CLP    |
| 6          | F   | Case mom of CLP | CLP    |
| 18         | F   | Case         | CLP         |
| 18         | M   | Case         | CLP         |
| 8          | M   | Case         | CL          |
| 7          | M   | Case Control | CL          |

Note. CL, cleft lip; CLP, cleft lip and palate; CPO, cleft palate only; F, females; M, males.

FIGURE 1 The X and Y chromosome intensity plots showing the cluster of males (blue) and female genotypes (red). Individuals with sex chromosome aneuploidies are shown as indicated in the figure legend. Sample sizes are given in the axis labels.

We conducted genotyping of individuals from the African population using the multiethnic genotyping array (MEGA) v2 15070954 A2 to identify genetic variation associated with presumed nonsyndromic clefts. The data cleaning of this dataset allowed us to check the annotated versus
genetic sex, confirm identify by descent and identify large chromosomal anomalies. We identified an individual with UPD on chromosome 22 and the result of our analysis strongly indicates that the UPD observed is of paternal origin. Previous UPD associated with clefts has been reported in other chromosomes and are mainly due to maternal UPDs as a result of advanced maternal age during pregnancy leading to trisomy rescue and error (Romanelli et al., 2011). A recent study reported an association with maternal UPD (matUPD) on chromosome 21 with Bartsocas Papas Syndrome (Leslie et al., 2015). In the absence of any other obvious large genetic aberration, it is possible that the affected individual has a recessive form of clefting arising from a heterozygous father and unmasked by the patUPD on chromosome 22. Furthermore, we cannot rule out the possibility that the observed anomaly might be an incidental occurrence and other genomic events such as SNPs or small chromosomal anomalies may be causing the phenotype either in combination with this chromosomal anomaly or independently. In addition, this could well be a mosaic anomaly and, if so, it might not occur in the tissues that lead to cleft palate.

The de novo deletion in chr18 is particularly interesting. It is likely due to gametogenesis because both parents do not carry the deletion and we suspect it may account for clefting since the parents are clinically normal. The deleted region overlaps a 23MB region found deleted in individuals with a spectrum of developmental anomalies including clefts as reported in DatabasE of genomiC varIation and Phenotype in Humans using Ensembl Resources (DECIPHER (https://decipher.sanger.ac.uk/index)). The 23MB de novo deletion included the ZADH2 gene which has been reported in DECIPHER for most individuals with developmental disorders including clefts. Over 50% of individuals with large deletions including the child with a de novo deletion had CLP. Large deletions in individuals with CL/P have been previously reported (Maarse et al., 2012).

There are inconsistent reports of clefting in some individuals with sex aneuploidies (Perrotin et al., 2001). The individuals with these sex aneuploidies have the different
types of clefts that can be seen in nonsyndromic cleft cases. Most often, they appear as NSC and thus will require additional genetic diagnosis. Three of the children had trisomy 13 otherwise known as Patau syndrome. These infants do not usually survive beyond the first few days of life (Rasmussen, Nielsen, & Dahl, 1982). We followed up with their mothers and confirmed that the three infants died shortly after birth. This is consistent with the expectation
that about 90% of children with this syndrome do not survive beyond the first few days of life (Rasmussen et al., 1982). These children were recruited into this study at birth and may have been incorrectly enrolled as nonsyndromic clefts.

It is very important to carry out detailed clinical evaluation of children with apparent nonsyndromic clefts by individuals with the skill to investigate family history, environmental exposures and do a thorough clinical exam on child and parents. Genetic testing to exclude chromosomal anomalies may be indicated by the findings of these exams and also in cases of prenatal detection of clefting where phenotyping is more difficult. This study is limited by clinical examination information available at birth or within a few days after delivery. Therefore a detailed periodic exam is advised in order to identify associated anomalies that may become clinically obvious days after birth. This is because over 15% of clefts with associated anomalies are caused by chromosomal defects (Rasmussen et al., 1982) and genetic testing is advised in clefts with associated anomalies. Genetic testing may not be readily available in resource-limited setting but clinicians should share any identified genetic findings and place them in context for the families during routine clinical visits and evaluations.

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CONFLICTS OF INTEREST

None to declare.

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