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The society for craniofacial genetics and developmental biology 46th annual meeting

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Abstract

The Society for Craniofacial Genetics and Developmental Biology (SCGDB) held its 46th Annual Meeting at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio on October 10th–12th, 2023. On the first day of the meeting, Drs. Sally Moody and Justin Cotney were each honored with the SCGDB Distinguished Scientist Awards for their exceptional contributions to the field of craniofacial biology. The following two days of the meeting featured five sessions that highlighted new discoveries in signaling and genomic mechanisms regulating craniofacial development, human genetics, translational and regenerative approaches, and clinical management of craniofacial differences. Interactive workshops on spatial transcriptomics and scientific communication, as well as a poster session facilitated meaningful interactions among the 122 attendees representing diverse career stages and research backgrounds in developmental biology and genetics, strengthened the SCGDB community.

KEYWORDS

cleft lip, cleft palate, craniofacial, craniofacial development, craniosynostosis, genetics, neural crest cells, TMJ

The 46th Annual Meeting of the Society for Craniofacial Genetics and Developmental Biology was held at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio on October 10th–12th, 2023. The meeting commenced at the Cincinnati Art Museum, where the SCGDB Distinguished Scientists Awards were presented to the 2023 honorees followed by an evening reception. The following two days of the meeting, which included workshops, four scientific sessions, a poster session, and a special clinical session on craniofacial

differences, were convened in the Sabin Auditorium at Cincinnati Children's Hospital Medical Center. Below is a summary of the topics discussed, as well as the awards given.

1 | SCGDB DISTINGUISHED SCIENTIST IN CRANIOFACIAL RESEARCH AWARDS

Chair: Dr. Amy Merrill, SCGDB President (University of Southern California)

The SCGDB presents two annual awards to members that have made exceptional contributions to craniofacial research: the David Bixler Distinguished Scientist Award, and the Marylou Buyse Distinguished Scientist Award. In the first session of the meeting, the awards were conferred to the 2023 honorees.

Dr. Sally Moody, Professor and Chair of Anatomy and Cell Biology at the George Washington University, was the recipient of the **2023 SCGDB David Bixler Distinguished Scientist Award**. This award, named after the first President of the SCGDB, is the Society's highest scientific honor and was created to recognize distinguished leadership and exceptional contributions to craniofacial research by a senior investigator. Dr. Moody earned a bachelor's degree in Biological Sciences from Goucher College, a master's degree in Anatomy from the University of Maryland School of Dentistry, and a Ph.D. in Neurosciences at the University of Florida. During her postdoctoral fellowship at the University of Utah, Dr. Moody investigated mechanisms that pattern axon outgrowth using clonal analysis in *Xenopus*. In 1983, Dr. Moody joined the Department of Anatomy and Cell Biology at the University of Virginia School of Medicine as an Assistant Professor. It was during this time that she published her most highly cited works on blastomere fate mapping. Following promotion Associate Professor, she joined the faculty in the Department of Anatomy and Cell Biology at the George Washington University in 1992, where she was promoted to Professor and has served as Chair since 2016. Her work has defined gene regulatory networks in neural plate development and specification of placode-derived sensory structures. Throughout her career, Dr. Moody has been well-funded through national and international agencies and has published more than 100 scientific articles. She was the editor-in-chief of *genesis*, *The Journal of Genetics and Development* and co-editor of the Evolutionary Cell Biology book series. Dr. Moody served as the SCGDB's Vice President (2016–2018), President (2018–2020), and immediate past President (2020–2022). She guided the SCGDB through challenges of the COVID-19 pandemic, holding the 43rd annual meeting virtually in 2020.

Dr. Moody presented the work that led to her lab's discovery of SIX1 as a key transcriptional regulator that specifies cranial placode-derived sensory structures during vertebrate development. When Dr. Moody first began her independent research program, she was using *Xenopus* to clone and identify genes involved in retina fate determination. Following identification of the eye specification transcription factors Sine oculis (So) and Eyes absent (Eya) in *Drosophila*, Dr. Moody cloned the *Xenopus* gene homologue for *So*, called *Six1*, and along with her graduate student Petra Pandur, examined its expression through development. Fascinated by the pattern of *Six1* expression in the pre-placodal ectoderm (PPE) and the neurogenic placodes which give rise to the sensory organs in the vertebrate head, Dr. Moody shifted to determine both how Six1 is regulated and how it functions in development of the cranial placodes. Dr. Moody and her graduate student at the time Samantha Brugmann showed that Six1 and Eya1 function within a gene regulatory network that promotes placodal fate and inhibits neural crest cell (NCC) and epidermal fate within the neurogenic ectoderm. Around the same time, genetic variants in SIX1 and EYA1 were linked to branchiootic syndrome (BOS) and branchio-oto-renal syndrome (BOR), which present with branchial fistulas and cysts, outer ear differences, and well as hearing loss. Dr. Moody's research has thus focused on three main questions: (1) Are there other Six1 co-factors like Eya1 involved in PPE development? (2) What are the Six1 target genes during PPE development? (3) Do human SIX1 variants in BOS/BOR syndrome differentially impact development?

To identify Six1 co-factors, Dr. Moody and collaborators Francesca Pignoni and Dominique Alfandari used a combination of yeast two-hybrid and immunoprecipitation mass spectrometry screens to identify a large number of putative interacting proteins. They found that Pa2G4 and Mcrs1 bind to Six1, decrease Six1–Eya1 interactions, and block transcriptional activation of Six1–Eya1 targets. Targeted loss of *Pa2G4* and *Mcrs1* expands expression of genes associated with neural plate, and decreased expression of genes associated with the NCC and cranial placodes. Similarly, Andre Tavares, a former postdoctoral fellow of the Moody lab, showed that the Six1-interacting protein Sobp acts as a transcriptional co-repressor by interfering with Six1 and Eya1 interactions and is required to establish the ectodermal domains at neural plate stages and for normal otic vesicle development in Xenopus. Finally, work by Karyn Jourdeuil in the Moody lab found that Zmym4, while not a bona fide Six1 co-factor, is necessary for normal NCC and cranial placode gene expression, as well as craniofacial cartilage development.

To next identify Six1 transcriptional targets Aparna Baxi, a graduate student in the Moody lab, in collaboration with Peter Nemes used proteomics to identify 6000 proteins expressed in the Xenopus otic vesicle over multiple developmental stages using quantitative mass spectrometry. They identified Tgfbi as a putative Six1 target gene and went on to show that Tgfbi, a member of Fascilin family of secreted ECM proteins involved in integrin signaling, is transcriptionally regulated by Six1 in the otic vesicle of mice and required for otic vesicle development in Xenopus.

Dr. Moody concluded her presentation by describing her lab's investigation into the extent to which BOS/BOR-associated *SIX1* variants result in different developmental outcomes. By selectively injecting *Six1* mRNA harboring one of four selected BOS variants into blastomeres that give rise to NCC and PPE precursors of Xenopus embryos, Ankita Shah in the Moody lab showed that these BOS/BOR variants have different, and highly variable disruptions in gene expression associated with the neural border zone, NCC, and PPE gene expression, as well as in otic vesicle morphology. They are currently re-testing these variants in a newly generated *Six1* null Xenopus line.

Dr. Moody's talk highlighted her significant contributions to the fields of neural, retinal and placodal fields over her 40-year career as an independent scientist. As Dr. Moody has recently retired, her talk as a Bixler Award recipient served as a well-deserved sendoff. The Society deeply appreciates her dedication to craniofacial research and wishes her all the best in her retirement.

Dr. Justin Cotney, Associate Professor of Genetics and Genome Sciences at the University of Connecticut Health Center was the recipient of the **2023 Marylou Buyse Distinguished Scientist Award**. This award which honors the memory of the Society's first female President Dr. Marylou Buyse, a prominent clinical geneticist, recognizes a mid-career scientist who has made important contributions to the craniofacial sciences. Dr. Cotney received his bachelor's degree from Birmingham-Southern College and Ph.D. from Emory University under the guidance of Dr. Gerald Shadel. In 2009, he joined the lab of Dr. James Noonan as a post-doctoral fellow in the Department of Genetics at the Yale University School of Medicine. There he employed functional genomic approaches to understand mechanisms of gene regulation during limb and brain development. In 2015, Dr. Cotney launched his research program at the University of Connecticut and was promoted to Associate Professor with tenure in 2021. His laboratory has revealed new insights into the role and evolution of enhancers in controlling craniofacial, heart, limb, and brain development. He has made strong contributions to understating genetic variants associated with normal facial variation in humans and risk for congenital craniofacial anomalies. In addition to his research, Dr. Cotney is the director of the Genetics and Developmental Biology Graduate Program.

Dr. Cotney described approaches his lab is taking to identify and validate risk loci for craniofacial differences in the human genome. Non-syndromic orofacial clefting is one of the most common craniofacial differences and yet nearly half of cases that are likely to have a genetic component remain unexplained. While genome-wide gene association studies (GWAS) have identified dozens of risk loci, very few fall within coding regions, making it difficult to identify the causal variant and the associated gene(s) that are impacted. Dr. Cotney's lab is integrating multiple genomic modalities to identify variants in regulatory regions that cause non-syndromic developmental differences called enhanceropathies.

To understand the impact of noncoding variants, his group identified regulatory sequences important for forming the human face by profiling histone modifications with ChIP-seq in human embryonic craniofacial tissues over multiple timepoints obtained from Human Developmental Biology Resource. This analysis identified over 100K enhancer segments across the genome that are active in the face and have predicted associations with genes involved in craniofacial differences. Interestingly, 7000 of the enhancers identified are uniquely specific to craniofacial tissues. Enhancers active early in craniofacial development are associated with craniofacial differences, while those enhancers that are active in later stages of development are associated with orofacial variation in human populations.

Dr. Cotney next described how his group generated an extensive set of transcriptomic data from human embryonic craniofacial tissues and then leveraged publicly available gene expression profiles including those from mouse development and human adult tissues (GTEx) to identify genes that have biased expression in craniofacial tissues. This analysis identified a cohesive set of over 50 genes that include genes with known association to craniofacial differences and also novel genes. By then employing their craniofacial epigenomic annotations along with this expression analyses, they have been able to predict enhancer-gene pairs.

With this information, his lab has now started to interpret which noncoding GWAS variants identified in non-syndromic cleft lip and palate are disease-causing. For orofacial clefting, enhancers active early harbor major risk for orofacial clefts compared to late acting enhancers, such as those in *IRF6* locus. This approach may work for a number of diseases, with enhancers active at different stages of development likely dictating differences in disease susceptibility. The Cotney lab is also identifying individual cell types involved using single cell (sc) multiomic analyses to simultaneously profile gene expression and chromatin accessibility in mouse and human craniofacial cell types over multiple embryonic stages. He showed that integration of sc-multiomic datasets can predict GWAS targets: a noncoding GWAS variant located within a periderm-enriched enhancer at the *ABCA4* locus, which is not expressed in craniofacial tissue, is instead associated with *ARHGAP29* that has periderm expression and links to cleft palate.

Dr. Cotney concluded his presentation with a description of how his lab is using sc-multiomic data that combines gene expression and chromatin accessibility to identify new genes involved in craniofacial disease. He showed that by using a functional genomics approach, his lab has identified 539 genes, many of which are known to be involved in aspects of facial development. By taking variants in these genes found in human cohorts, they have identified 50 genes that show systematic enrichment and potential involvement in orofacial clefts.

2 | PROFESSIONAL DEVELOPMENT WORKSHOPS

Chair: Dr. Jean-Pierre Saint-Jeannet (New York University)

Dr. Matthew Warman (Harvard Medical School) presented a workshop on spatial transcriptomics. Dr. Warman started his presentation by contrasting bulk versus single-cell transcriptomics, highlighting some of their limitations. Importantly, neither of these approaches considers where the cells are positioned in the tissue of interest. Spatial transcriptomics provides that information by analyzing the totality of the RNAs from individual cells and mapping them back to their original position in the tissue. The starting material is typically a section of tissue collected on a glass slide. RNAs are then assigned an address or barcode based on their position on the section. Barcoded transcripts are then collected, sequenced, and mapped with their relative abundance to the original section based on their specific RNA addresses. Dr. Warman described four commercially available spatial transcriptomic platforms, Visium (10X Genomics), GeoMx (Nanostring Technologies), Curio Seeker (Curio BioScience), and Stereo-seq

(STOmics), discussing the basic principle of each platform, their benefits and limitations considering cost, the need for proprietary equipment or reagents, and applicability across species. Finally, Dr. Warman briefly introduced Light-seq, developed by Dr. Peng Yin (Harvard University), as a less expensive alternative to these commercial platforms. The workshop provided a wealth of information on the most recent advances in spatial transcriptomics that will benefit the entire craniofacial community.

Dr. Jason Organ (Indiana University School of Medicine) presented a workshop on scientific communication entitled "Communicating with Public Audiences Requires Different Approaches." Dr. Organ, an Associate Professor of Anatomy, Cell Biology and Physiology, and the Editor-in-Chief of Anatomical Sciences Education, reminded the audience that when we communicate with non-scientists, it is important to adjust and adapt our message, with the main reason being that there is a difference between where scientists and the general public get their information. In science communication, the information deficit model theorizes that if someone fails to act in a manner consistent with scientific evidence, they must not have enough information—this is an incorrect assumption. Evidence suggests that beliefs are shaped by the social groups that people considered themselves to be a part of. Therefore, reframing a message to attend to an audience's identity and needs is the single most powerful way to communicate information. Through insightful examples and lively interactive demonstrations among attendees, Dr. Organ illustrated the importance of dynamically adapting the message to the audience, and highlighted some of the basic principles for successful communication: (i) reframe your message to meet your audience's need and what they care about; (ii) know your audience, their interests, education level and experience with the topic; and (iii) draw on your audience's experiences to make your message more meaningful—follow the follower.

3 | SCIENTIFIC SESSION I: SIGNALING IN CRANIOFACIAL DEVELOPMENT

Chair: Dr. Katherine Fantauzzo (University of Colorado Anschutz Medical Campus)

The first scientific session of the meeting focused on signaling in craniofacial development. **Dr. Lisa Taneyhill** (University of Maryland, College Park), the invited plenary speaker for the session, discussed how NCC and neurogenic placode precursor cells generate the trigeminal ganglion. The trigeminal ganglion evolves into a network with three primary branches that innervate the eye and nose (ophthalmic nerve), upper jaw (maxillary nerve), and lower jaw (mandibular nerve). These nerves sense pain, touch and temperature in the face and head. Formation of the trigeminal ganglion begins with reciprocal interactions between undifferentiated NCCs and placode cell-derived neurons. The NCCs eventually differentiate into both neurons and supporting glia cells. The Taneyhill lab has a long-standing interest in identifying the molecular signals that regulate assembly, differentiation, and function of the trigeminal ganglion, and further, how cranial nerves control craniofacial morphogenesis and patterning. In the first vignette, the role of Elongator complex protein 1 (Elp1) was explored in NCC-derived trigeminal ganglion neurons in mice. Elp1 is the scaffolding subunit of the elongator complex, which functions in transcriptional elongation. However, this protein also has demonstrated roles outside of the nucleus, some of which are relevant to neuron development. Splice site mutations in *ELP1* cause familial dysautonomia in humans, which is characterized by smaller trigeminal nerves, decreased ability to sense facial pain and temperature, and neurogenic swallowing difficulties. In mice, *Elp1* is expressed in all trigeminal sensory neurons, irrespective of cellular origin. Upon conditional ablation of *Elp1* in the mouse NCC lineage, trigeminal nerve complexity is reduced, and innervation deficits are observed by embryonic day (E) 12.5. Further, these knockout embryos have decreased expression of TrkA, a marker of NCC-derived neurons associated with sensation of pain and temperature. These defects stem from premature apoptosis of TrkA-expressing neurons. In the second half of the talk, the role of N-cadherin was examined in placodal neurons in the trigeminal ganglion of chick. Previous work in the Taneyhill laboratory demonstrated that undifferentiated NCCs and placodal neurons express Cadherin-7 and N-cadherin, respectively, which can interact in *trans* to promote condensation of these two precursor populations. Later, NCCs that have differentiated into neurons also express N-cadherin. A morpholino was used to knock down N-cadherin in trigeminal placode cells, leading to later defects in axon outgrowth from placode- and NCC-derived neurons. These defects include decreased axon bundle width and innervation area. Through sequential labeling of NCCs and placode cells via electroporation, it was confirmed that knock down of N-cadherin in placode cells impair axon outgrowth of NCC-derived neurons. A model was put forward in which early placodal axons grow out first and use cell adhesion molecules such as N-cadherin to permit interactions with NCC-derived axons.

Next, **Dr. Jennifer Fish** (University of Massachusetts Lowell) presented work on the role of Fgf8 in jaw development. FGF8 is expressed in the oral ectoderm, lateral clefts, and pharyngeal pouches. The Fish laboratory has employed hypomorphic and null mouse models of *Fgf8* to explore how dosage of this signaling protein affects craniofacial development. While heterozygous embryos are phenotypically normal, embryos homozygous for the hypomorphic allele have a milder phenotype with greater variation (within and between individuals) than those homozygous for the null allele. This finding argues that in hypomorphic embryos, relatively small molecular variation can have a large phenotypic effect. Severe defects in these *Fgf8*-mutant embryos include discontinuous Meckel's cartilage and fusion between the upper and lower jaws. Directional asymmetry is often observed, with the left side more severely affected than the right. Exploring these defects at earlier timepoints, E10.5 embryos were found to have defective epithelial clefts, and continuous first and second pharyngeal arches. One day earlier, pharyngeal pouches of mutant embryos have altered morphology with less depth and a failure in outpocketing. *Fgf8*-mutant embryos were shown to lack expression of the endoderm marker *Sox2* and fail to downregulate E-cadherin expression in the caudal proximal region of the cleft that contacts the

outpocketing pouch. A hypothesis was proposed in which interactions between this region of the cleft and the endoderm of the pouch are responsible for pouch outgrowth. Finally, at E8.5, migrating precursors in the first arch, which may be second heart field precursors, exhibit a clear difference in left versus right side distribution. These cells may contribute to the early development of the cleft and pouch, thereby allowing the right side of the face to be more buffered against losses in *Fgf8*.

Dr. Jennyfer Mitchell (University of Colorado Anschutz Medical Campus), a postdoctoral fellow in the Nichols Lab, then presented her work on the function of Alx transcription factors in development of the frontonasal skeleton of zebrafish. While the Hox and Dlx codes explain anterior–posterior and dorsal–ventral patterning, respectively, in the pharyngeal arches across varying species, no such code has been established for the frontonasal region. scRNA-seq analysis of zebrafish NCCs by the Nichols laboratory previously isolated a frontonasal population with expression of multiple members of the Alx family of transcription factors. In situ hybridization analyses demonstrated that *alx3* is the most broadly expressed, followed by *alx4a* and *alx1*, suggestive of a nested code. Zebrafish homozygous for a null allele of *alx3* exhibits a subtle phenotype with disrupted cell morphology at the medial portion of the ethmoid plate. Additional deletion of *alx4* results in a more severe phenotype with loss of the medial ethmoid plate and ectopic cartilage in the dorsal region of the head. Lineage tracing revealed that cells between the nasal placode and the eye with the highest *alx3* expression remain undifferentiated above the ethmoid plate in wild-type fish, but give rise to ectopic cartilage in *alx3; alx4* double mutant embryos. Further scRNA-seq analysis showed a loss of cells from the frontonasal population and a reciprocal gain in the anterior pharyngeal arch population in double mutant embryos, indicative of an identity transformation. Finally, *alx1*;*alx3*;*alx4* triple mutant zebrafish exhibit the most severe phenotype with no medial structures of the face and ectopic bone lining the palatoquadrate cartilage. In situ hybridization analysis confirmed ectopic expression of the pharyngeal arch marker *dlx2* in double and triple mutant embryos. A model was put forward supporting the ancestral pharyngeal "arch zero hypothesis" for the frontonasal cell population.

Evan Brooks (Cincinnati Children's Hospital Medical Center), a graduate student in Samantha Brugmann's lab, concluded the session by presenting his work on ciliary protein C2cd3 in patterning mandibular musculoskeletal tissues. Primary cilia are microtubule-based organelles that extend out of the cell surface. The membrane of these structures is populated with receptors for various signaling pathways such as SHH, FGF and BMP, among others. The *talpid*^{2} chick model has a hypomorphic mutation in *C2CD3*, which encodes for a protein that localizes to basal bodies of primary cilia. Mutant embryos exhibit a loss of ciliogenesis, as well as upper beak and palatal clefting, micrognathia, hypoglossia, and polydactyly. *C2CD3* variants in human patients result in a ciliopathy called orofaciodigital syndrome XIV. The Meckel's cartilage of *talpid*^{2} embryos was previously found to display ectopic bilateral cartilaginous processes that extend off the distal portion of Meckel's cartilage. The intermandibular tendons and muscles, which normally run adjacent to the Meckel's cartilages, instead insert directly into the Meckel's chondrodysplasias in *talpid*^{2} mutants. SHH, FGF8, and BMP4 are expressed in the epithelia of the first pharyngeal arch and signal to the underlying mesenchyme to direct the differentiation of NCCs into musculoskeletal tissues. In the *talpid*^{2} mandibular prominence, he found that the expression domains for *FGF8* is shifted, while that for *BMP4* is increased and *SHH* is decreased. CellChat analysis of scRNA-seq data confirmed an ectopic *BMP4* signaling domain that is able to signal to NCC-derived mesenchymal and epithelial populations. *C2cd3* was then conditionally ablated in the mouse ectoderm and/or NCC lineage. While approximately 70%–75% of single tissue knockout embryos exhibit the Meckel's chondrodysplasia phenotype, this phenotype is fully penetrant and commonly bilateral when *C2cd3* is ablated in both tissues, demonstrating a requirement for this protein in the mesenchyme and epithelia for proper Meckel's cartilage development. A working model was presented in which ectopic BMP4 signaling directs NCCs to make extra cartilage.

4 | SCIENTIFIC SESSION II: GENOMICS OF CRANIOFACIAL DEVELOPMENT

Chair: Dr. Matthew Harris, SCGDB Vice President (Harvard Medical School; Boston Children's Hospital)

The Genomics of Craniofacial Development session was led off by **Dr. Robert Cornell** (University of Washington), the invited plenary speaker for the session. Cleft lip and/or cleft palate is relatively common, with an incidence of 1 in 700 live births in the U.S. Dr. Cornell discussed how his lab is revealing the hidden variability and expressivity of cleft lip and/or palate in children through discovery of the transcriptional regulatory networks. The premise of his lab's work is that changes in regulatory connections between genes with known associations with clefting will be key regulators of disease expressivity and heritability. Dr. Cornell focused on an experimentally accessible model for clefting: the regulation of enveloping layer (EVL) periderm formation in zebrafish. Zebrafish have been used as a powerful experimental model to assay the impact of genetic variants on gene activity in clefting. Dr. Cornell described his hypothesis that genes associated with clefting risk will encode highly connected members of a transcriptional regulatory network for EVL differentiation in zebrafish. His lab has focused on genes encoding transcription factors to construct a 'clefting' transcriptional regulatory network. Combined scRNA-seq and scATAC-seq of early periderm have revealed 394 cell expression profiles of EVL cells with chromatin availability and expression correlations. To test this network analysis, they used *irf6*, *grhl3*, and *tfap2a* mutant zebrafish to identify direct targets associated with periderm development as a proxy for clefting. Morpholino knockdown of candidates *tead3b* and *klf6a*, along with known regulators such as grainyhead-like (*grhl*) genes, do not show similar phenotype as seen following *irf6* knockdown. Experimentally, this could be due to often incomplete reduction with knockdown approaches. However, in combination with *grhl3*, both *tead3b* and *klf6a* show synergy, causing a synthetic genetic effect on rupturing. Thus, these findings detail discovery of new modifiers of clefting mechanisms. Finally, Dr. Cornell

examined whether the constructed EVL network had predictive value to human clefting regulators, finding that transcription factors associated with clefting in humans that also caused cleft lip and palate in mice were more likely to be central, for example, have a high linking/edge score in the network, than genes not associated with clefting. Thus, through use of this experimental model in the zebrafish, the group has delineated at least part of the scaffold of early regulation of clefting through analysis of network properties of shared transcriptional regulators.

Next, the session moved towards natural evolutionary case studies for genomic discovery of craniofacial form. **Dr. Kara Powder** (Clemson University) described her work detailing the genetic regulation of craniofacial development through understanding adaptation across African cichlid species in their evolution into new environments. Lake Malawi cichlids over the last 2 million years have showed a large range in forms and function of the skull that expose similar axes as we observe in human populations, including syndromic disorders. One source of variation arises from fixation of standing ancestral genetic variation that is selected once different lineages populate new environments. Using broad genomic comparisons across Lake Malawi cichlids, Dr. Powder's group has identified a panel of variant SNPs that varied by habitat among 111 different species. Of these changes, only a small percentage are found within coding sequences, presumably instead lying within regulatory domains. They intersected datasets on 82 species from museum specimens to detail morphological variation by geometric morphogenesis and performed a GWAS on a species level. Their results show linkage to a select number of SNPs with significant association. An interesting candidate, *sim2*, is a target of DLX transcription factors in mice, having distinct roles in craniofacial development conserved in both mice and zebrafish. The other three candidates, *znrf1* (a ubiquitin ligase), *opcml* (a gene associated with cell migration), and *heatr5a* (encoding an undefined gene product) are not yet associated with craniofacial development, thus pointing to the potential of such evolutionary models in gene discovery. Ongoing work in her lab is testing the function of these genes, as well as the impact of the particular genetic variants.

Dr. Lorena Maili (Stowers Institute for Medical Research), a postdoctoral fellow in Paul Trainor's laboratory, presented her work on ribosome biogenesis in craniofacial development and disease. Her work centers on Treacher Collins syndrome and Acrofacial Dysostosis—Cincinnati type, both linked to genes active in the complex regulating transcription of ribosomal RNAs. Deletion of these regulators, such as RNA polymerase I subunit a (*Polr1a*) specifically in NCCs in the mouse has been shown to cause deficient ribosomal function and decreased NCC survival in a p53-dependent manner. The resulting decrease in ribosome levels results in hypoplasia of the pharyngeal arches. However, due to embryonic lethality, the role these factors play in NCC differentiation could not be assessed. To overcome this difficulty, Dr. Maili temporally deleted *Polra1a*. Deletion of *Polr1a* at E9.5 induces a wide-range of defects similar to those observed when *Polra1a* is deleted in NCCs. However, inactivation at E10.5 leads to more specific effects on palatogenesis, and jaw development. By E11.5, the importance of *Polr1a* in regulating craniofacial growth is greatly reduced. To explore the molecular and cellular consequences of *Polr1a* loss at E10.5, scRNA-seq was undertaken at E12.5, and a decrease in the number of mesenchymal cells are thought underlie the skeletal dysmorphologies observed.

The last talk of the genomic section was presented by **Timothy Nguyen** (University of Iowa), a graduate student from the Van Otterloo laboratory. Timothy discussed his work on the role of the TFAP2 paralogues in midface development. NCCs provide the working material for midface variation, fine tuning their response to region-specific signals. The ability of NCCs to integrate signals is controlled through activation of positional-specific transcriptional programs, which for the midface remain poorly understood. The TFAP2 paralogs are key transcriptional regulators in NCCs. Of these, the TFAP2a and TFAP2b paralogs regulate craniofacial development and are associated with human syndromes that present with craniofacial differences. The shared expression domains, and binding affinities of these TFAP2a/b suggest overlapping roles and potential redundancy between the genes in midface development. In mice, conditional deletion of *Tfap2a* or *Tfap2b* in post-migratory NCCs using *Sox10-Cre* does not lead to significant phenotypes; however, combined deletion of *Tfap2a* and *Tfap2b* in post-migratory NCC induces midfacial clefting reminiscent of frontonasal dysplasia. To test the prediction that TFAP2 regulates post-migratory NCC programs or positional patterning of the midface, Timothy performed scRNA-seq in NCCs derived from *Tfap2a/b* mutant allelic series at E11.5. He demonsrtated that loss of *Tfap2a/b* leads to changes in the midface gene regulatory network including downregulation of frontonasal dysplasia-related *Alx* genes. Using ChIP-seq he found that TFAP2 occupies regulatory elements of the *Alx* genes, including *Alx3*, suggesting direct regulation. Using ATAC-seq he showed evidence that TFAP2 regulates chromatin accessibility at ALX regulatory elements in NCC of the mid-face. Finally, he showed that homozygous loss of *Alx3* in mice with NCC-specific deletion of *Tfap2a* exhibit a midfacial cleft unlike the individual mutants, supporting the idea that these TFAP2 paralogs act together in midface patterning.

5 | SCIENTIFIC SESSION III: HUMAN GENETICS OF CRANIOFACIAL DEVELOPMENT

Chair: Dr. Juhee Jeong, SCGDB Treasurer (New York University)

The third scientific session opened with a presentation from plenary speaker **Dr. Timothy Cox** (University of Missouri, Kansas City). Dr. Cox discussed challenges of elucidating the genetics of common craniofacial anomalies such as cleft lip and palate (CL/P), and presented new insights from his group's studies of human patients. Dr. Cox and colleagues examined 85 multi-affected families with non-syndromic CL/P through whole exome sequencing (WES) and whole genome sequencing (WGS), uncovering novel genetic causes of CL/P. The first part of the presentation focused on coding sequence variants. Some CL/P patients have missense mutations in *CDH1*, encoding E-cadherin, which destabilizes E-cadherin and weakens

epithelial adhesion. Similarly, missense mutations in *CTNND1*, encoding p120-catenin, disrupts its interaction with E-cadherin and increases E-cadherin endocytosis. Targeted re-sequencing of other CL/P patients and mouse model studies further confirm the importance of cell adhesion genes in CL/P. Dr. Cox also highlighted AMOTL1 (Angiomotin-like protein 1)-Associated Syndrome, which includes CL/P, large ears, and cardiac defects. Pathogenic variants in *AMOTL1* are located in a few highly conserved amino acids, with the Cox team showing that these residues are crucial to regulation of YAP (Yes-associated transcriptional regulator) by AMOTL1. Next, Dr. Cox presented examples of variants in non-coding regions associated with CL/P. One family with nonsyndromic CL/P, identified by Dr. Pedro Sanchez-Lara (Cedars-Sinai Medical Center), has a synonymous variant in *IRF6*. In silico analysis followed by in vitro validation showed that this mutation disrupts splicing. Another family with BOR syndrome has a potential pathogenic variant in an intron of *EYA1*. Further inspection found that the variant is in Alu repetitive elements, which disrupts splicing, a phenomenon known as Alu 'exonization' that is not detected in current bioinformatic pipelines. Lastly, Dr. Cox discussed allelic conditions, where variants of the same gene result in very different phenotypes depending on specific variants. *ACTN1* (non-muscle alpha-actinin) variants are known to cause thrombocytopenia, but a few novel variants of *ACTN1* were found in patients with craniofrontonasal dysplasia without thrombocytopenia. In an in vitro assay, only the variants associated with craniofrontonasal dysplasia disrupt the intracellular localization of ACTN1. Similarly, it is well-known that *TWIST1* variants underly Saethre-Chotzen syndrome with mild craniosynostosis, but new variants of *TWIST1* were found in patients with far more severe phenotypes than Saethre-Chotzen syndrome. To summarize, Dr. Cox's presentation highlighted the importance of detailed phenotyping, examining a large number of patients, consideration of non-coding variants and allelic conditions, and attention to population-level variants when scanning genomic data for causative variants.

The second speaker of the session was **Dr. Soma Dash** (University at Albany), who discussed the role of Med23 in craniofacial and vascular development. The project stemmed from a forward genetic screen in mice for craniofacial defects previously performed while in Paul Trainor's lab. The "snouty" mutant line was selected for follow-up studies due to the smaller frontonasal region, and it was shown to have a point mutation in *Med23*, encoding a subunit of the mediator complex. The core mediator complex forms a molecular bridge in the global transcriptional machinery and therefore is required for transcription of most protein coding genes by RNA-Pol II. *snouty* embryos exhibit defects in both NCCs and the vasculature. To focus on the vascular phenotype, Dr. Dash generated endothelial cell-specific *Med23* mutants. These mutants show widespread vascular defects as early as E10.5, and the number of endothelial cells in the mandible is significantly reduced at E14.5. Furthermore, craniofacial bone is smaller at E16.5, indicating that the vasculature plays a role in craniofacial osteogenesis. To determine how loss of Med23 in the vasculature affect osteogenesis, spatial transcriptomics was performed on sections of the lower jaw from control and endothelial cell-specific *Med23* mutants. This result reveal that, in *Med23* mutants, osteochondroprogenitors close to the vasculature have upregulated expression of osteoblast markers. Thus, the working hypothesis is that the loss of *Med23* in the vasculature leads to precocious differentiation of osteochondroprogenitors, which in turn leads to depletion of cell population to make bone. The Dash lab is currently investigating this idea.

Next, **Dr. Sarah Curtis** (Emory University) a postdoc from Elizabeth Leslie's lab then presentented her work on genetic variants in craniofacial enhancers in orofacial clefts (OFCs). Non-coding genetic variants are associated with many human diseases, but how they cause defects are not always clear even though many are thought to alter gene expression. To study non-coding variants for OFCs, Dr. Curtis mined WGS data from the Gabriella Miller Kids First research consortium to select >70,000 de novo mutations (DNMs) from OFC trios, intersecting the list with >300,000 potential craniofacial enhancers from public datasets and collaborators (Axel Visel and Justin Cotney). A computational method was developed to test whether OFC DNMs are significantly enriched in craniofacial enhancers, considering average mutation rates of enhancers. The analysis showed that DNMs are indeed enriched in seven craniofacial enhancers. Furthermore, 62 out of 63 DNMs in these enhancers are predicted to be in transcription factor binding sites, with some of the DNMs destroying binding sites for known transcriptional regulators of craniofacial development such as TWIST1, SOX9, and TFAP2A. Dr. Curtis then focused on one enhancer most significantly associated OFC DNMs, which has 20 DNMs. This enhancer is in a topologically associated domain with *PTK2*, encoding a tyrosine kinase important for cell adhesion and migration. *PTK2* is highly expressed throughout craniofacial development, and although global knockout in mice resulted in embryonic lethality, NCC-specific knockout causes cleft palate. In conclusion, this study developed a method to test for a burden of non-coding DNMs, and identified enhancers significantly associated with DNMs of OFCs.

The last speaker of the session was **Jang Kim** (University of Oklahoma Health Sciences Center), a graduate student in Lorin Olson's lab, who presented work on calvaria agenesis in a mouse model of Penttinen Syndrome. This syndrome is caused by point mutations in the kinase domain of PDGFRB (platelet derived growth factor receptor beta), which leads to leaky kinase activity. Phenotypes include premature aging, distinctive underdevelopment of facial features and thin calvaria with delayed closure of the anterior and posterior fontanelles. To study the underlying mechanism, a gain-of-function mouse model was generated in which Cre-mediated recombination led to expression of PDGFRB carrying the pathogenic variant V665A. In these mutants, PDGFRB signaling is constitutively active and the phosphorylated version of the downstream effector STAT1 is increased. The mutants expressing $PDGFRB^{V665A}$ in the whole body show hypoplastic dermis and lack of ossification in the top part of the head at P0. Examination of head sections at E13.5 and E14.5 revealed that STAT1 is increased in the meningeal layer of the mutant cranial mesenchyme, but not in the calvarial bone rudiments in the supra-orbital ridge. Furthermore, the pia mater of the meninges are expanded in the mutants.

Because STAT1 was greatly increased in *PDGFRB*^{V665A} mutants, Jang then tested whether reducing STAT1 dosage could alleviate the defects in the *PDGFRB*^{V665A} mutants. Indeed, homozygous knockout of STAT1 almost completely rescues the calvaria agenesis phenotype of *PDGFRB*^{V665A} mutants. Together, this work provides key insights into the role of STAT1 in the pathogenesis of *PDGFRB* mutations.

6 | SCIENTIFIC SESSION IV: TRANSLATIONAL AND REGENERATIVE APPROACHES IN CRANIOFACIAL BIOLOGY

Chair: Dr. Lindsey Barske (Cincinnati Children's Hospital Medical Center)

The fourth scientific session discussed translational and regenerative approaches in craniofacial biology. **Dr. Mildred Embree** (Columbia University) was the invited plenary speaker and presented her group's work on chondrocyte cell identity. A crucial component of the skeletal system is the complex of synovial joints that confer mobility. Osteoarthritis causes progressive joint degeneration and pain. A physiologic healing response is challenging as articular cartilage at the joints is avascular and has limited capacity for repair. Pharmaceutical complements are not yet available, and this constitutes an unmet clinical need. Chondrocytes are particularly crucial for joint homeostasis but maintain minimal turnover of the extracellular matrix. A large focus of the Embree lab is on the temporomandibular joint (TMJ) as a model for understanding chondrocyte biology and testing possible therapeutic applications. Areas of active investigation include the identification of the niche regulating chondrocyte stability and the cell of origin of TMJ chondrocytes. Previous work in the Embree lab has joined other groups in showing that high WNT signaling in chondrocytes induces osteoarthritic phenotypes, including loss of superficial zone cells and expression of osteoblast markers. This is seen in mouse models with null alleles of *Sclerostin* (a WNT inhibitor) and *Prg4*. An injury model in mini-pigs and cells harvested from humans undergoing joint replacement surgery confirm dysregulated WNT signaling with bulk RNA-Seq and marker analyses in pathological chondrocytes. Studies with LGR5 suggest it may regulate WNT signaling in this tissue through secretion of WNT inhibitors. In an attempt to mimic this inhibitory niche, the StemJel product was created by combining sclerostin protein with high molecular weight hyaluronic acid to promote sustained release of sclerostin. This was successful in vitro to suppress active β-catenin and rescue chondrocyte phenotypes based on marker analysis. StemJel was tested in an in vivo rabbit model of TMJ osteoarthritis and restored mechanical properties of the joint and reduced an osteoarthritis severity score. This approach has been extended to the knee where damage is more age-dependent and the lab is assessing the role of canonical WNT in cell senescence during knee joint osteoarthritis. StemJel application was successful in reducing osteoarthritis and performance in a rat knee injury model as well. This product is now being prepared for FDA approval. Having demonstrated that WNT signaling is a crucial component of joint health and a therapeutic point of intervention, the lab turned to try to identify the chondrocyte progenitor cell. scRNA-seq of the TMJ at E16.5 in the mouse indicated candidate populations expressing *Thy1* and *Gli1*. Expression analysis of these genes was consistent with this hypothesis and current studies are examining the lineage and consequence of loss of function for these genes in TMJ chondrocyte development.

Dr. Jianfu Chen (University of Southern California) continued on the topic of TMJ osteoarthritis with a talk focused on mapping the two-dimensional and three-dimensional spatial organization of the TMJ, and observing the dynamic changes in TMJ osteoarthritis and associated pain to identify therapeutic targets. The mouse TMJ osteoarthritis model is a whole animal treated with an intra-articular injection of complete Freund's Adjuvant. Treatment was shown to lead to joint remodeling with loss of bone and cartilage remodeling with increased macrophages in the synovial tissue area. Two measures of pain confirmed the validity of this model: a von Frey assay and bite force measurement. The lab used the TUBB3 marker and *Thy1-eGFP* transgenic mouse line to highlight the increased innervation seen around the TMJ in this model. They then used scRNA-seq to identify other cellular changes and observed increases in a number of cell types, including endothelial cells, macrophages and fibroblast-like synovial cells. *Pdgfra* expression was used to confirm the expansion of fibroblasts in the synovial tissue, as well as *Prg4* and *Thy1* to highlight lining and sub-lining fibroblasts, respectively. The macrophage increase was marked by expression of *Cx3cr1*, with these cells acting as a barrier and sitting next to the fibroblasts lining the synovial joint. Motivated by previous work in a craniosynostosis model highlighting important functions of the lymphatic system, the group closely examined these cells. *Lyv1* and *Vegfr3* showed an increase and dynamic remodeling of lymphatic vessels in the injured tissues. High resolution iDISCO imaging with the *Cx3cr1-EGFP* transgenic mouse line and Vegfr3 antibody showed the relative organization of these cells in exquisite detail. Ongoing work is focused on further mapping the changing cell types and dynamic locations in this powerful TMJ osteoarthritis model.

Next, **Dr. Michi Kanai** (University of Colorado Anschutz Medical Campus), a postdoctoral fellow in the Clouthier lab, presented his work on the role of Gq/11 family of Gα subunits during lower jaw development. Animal jaws grow from pharyngeal arches, which are patterned quite early in craniofacial development (by E9.5 in the mouse). There is a conserved patterning mechanism through a series of transcription factors that include Nrfs in the maxillary domain and Dlxs in the mandibular domain. Mandibular identity is established by Endothelin receptor type A (EDNRA) and its ligand, Endothelin-1 (EDN1). EDNRA is a G-protein coupled receptor whose signaling is mediated by heterotrimeric G proteins. Activated EDNRA acts as a guanine exchange factor and stimulates Gα protein dissociation to activate downstream signaling. EDNRA activation in NCCs regulates mandibular patterning, with loss of *Edn1* or *Ednra* leading to a homeotic transformation of the lower jaw into an upper jaw-like structure. Similar phenotypes are seen in humans with pathogenic variants in these genes. Dr. Kanai described loss-of-function and gain-of-function experiments to elucidate basic signaling mechanisms downstream of EDNRA. Gq/11 conditional ablation in mice has been shown to disrupt patterning of the proximal mandible, unlike the phenotype observed *Ednra*$^{-/-}$ mouse embryos, in which the entire mandible is

affected. Dr. Kanai showed that zebrafish lacking *gnaq*, *gna11a*, and *gna11b* mimic the *Ednra* null mouse, with the entire mandible affected. Further, these studies illustrated that the main G protein involved in this process is G11. These experiments were complemented by a transgenic rescue, in which a constitutively active Gq point mutant under the control of a minimal heat shock promoter was used to make a stable transgenic zebrafish line. Heat shock at 16 h post-fertilization was sufficient to rescue lower jaw development in the *gnaq*, *gna11a*, *gna11b* triple knockout fish. Gq/11 wild-type embryos with the Gq11 overexpression were also observed to have a homeotic transformation of the upper jaw, reflected in morphological analysis and ectopic dorsal expression of mandibular (ventral) patterning genes in wild-type embryos. Thus, Gq/11 is a key molecule in determining jaw patterning. Further elucidation of downstream effectors in this pathway may be particularly valuable as candidate genes in human genetic studies.

The session concluded with a talk from **Katherine Inskeep** (Nationwide Children's Hospital), a student in the Stottmann lab, discussing the role of sphinogmylein phosphodiesterase 4, neutral membrane (SMPD4) in brain and primary cilia development. *SMPD4* variants were recently shown to be a cause of a human syndromic condition with facial dysmorphisms, microcephaly and cerebellar hypoplasia. The talk focused on a new mouse model and human induced pluripotent stem cell (hiPSC) models to study the cause of the *SMPD4* loss of function phenotypes. SMPD4 catalyzes the production of ceramide which is enriched in the cilia and is required for proper cilia function. A null mouse model showed perinatal demise and overall smaller animals with specific reductions in the cerebellum relative to body size. Immunohistochemistry showed that the number of Purkinje cells in the *Smpd4*-null mice was reduced, which is consistent with cerebellar hypoplasia. Despite very intriguing expression of *Smpd4* in the developing forebrain, no molecular explanation for reduced brain size has been found. A parallel approach was taken with hiPSCs, as several critical aspects of brain development differ between mouse and human. Control cells, a line engineered to have a deletion in *SMPD4* and a line derived from an *SMPD4* patient were used and grown into neural rosettes as a two-dimensional model of neural development. Neural rosettes with perturbed *SMPD4* were smaller with reduced proliferation and increased cell death. Primary cilia in the null and patient cells were present in similar number to control cells but were significantly shorter. This length deficit was rescued with exogenous supplementation in vitro of ceramide. RNA-seq analysis of these cells showed signs of WNT signaling dysregulation in the absence of *Smpd4*, which is consistent with disruption in primary cilia. These studies demonstrate a requirement for *SMDP4* in multiple neural tissues with the intriguing possibility of a human specific function.

7 | SPECIAL SESSION: CLINICAL MANAGEMENT OF CRANIOFACIAL DIFFERENCES

Chair: Dr. Elizabeth Leslie (Emory University)

The final session of the meeting focused on discussing the clinical management of craniofacial differences from the perspective of a surgeon, a clinical geneticist, and parents of children with craniofacial differences.

Dr. Russell Reid, MD (University of Chicago) a Professor of Surgery who focuses on pediatric plastic and reconstructive surgery started the session. His clinical specialties include the repair of conditions which impact the face, jaw, palate, and skull. Dr. Reid shared his approach, experiences, and outcomes of operating on children with craniofacial differences. He emphasized the importance of communication, not only with the parents, but also with the patients.

Dr. Howard Saal, MD (Cincinnati Children's Hospital Medical Center) is clinical geneticist, board certified cytogeneticist, and dysmorphologist. His interests focus on the genetic causes of craniofacial disorders, especially cleft lip and cleft palate. Dr. Saal shared the journey of discovery for causal genetic variants for several patients with craniofacial differences. He highlighted the power and necessity of collaboration between clinicians and discovery-based researchers in finding the molecular mechanism for diseases that impact the craniofacial complex.

Brittney Underwood recounted her family's journey in obtaining a diagnosis of mandibulofacial dysostosis with microcephaly (MFDM) for her son. The process of diagnosis can take many years for individuals with rare disease due to limited clinical expertise and healthcare accessibility. Brittney emphasized how her advocacy for her son facilitated his diagnosis and connected them with a supportive community of MFDM families.

Carolina Sommer, who out of her own experience of raising a child with Pfeiffer Syndrome, started the nonprofit organization Born A Hero that is accelerating innovation and research to improve the quality of life for patients with fibroblast growth factor receptor (FGFR)-related syndromes. Carolina shared how her daughter is inspiring others through her rare disease experience and also making a difference in rare disease research.

8 | POSTER SESSIONS

Organizer: Matthew Harris, SCGDB Vice President (Harvard Medical School)

The second day of the meeting concluded with a two-hour poster session, in which faculty, post-docs and students presented their work.

AWARD WINNERS

Poster presentation awards sponsored by the American Association for Anatomy (AAA)

Winners of the poster presentation awards, sponsored by AAA were Drs. Elizabeth Shock (Northwestern University) (1st), Jingyue Xu (Cincinnati Children's Hospital Medical Center) (2nd), and Nirpesh Adhikari (Cincinnati Children's Hospital Medical Center) (3rd) in the post-doctoral fellow category, and David Paulding (Cincinnati Children's Hospital Medical Center) (1st), Emily Adelizzi (University of Iowa) (2nd), and Thomas Forman University of Colorado Anschutz Medical Campus (3rd) in the graduate student trainee category.

Platform presentation awards sponsored by American Association of Dental, Oral and Craniofacial Research (AADOCR)

Winners of the platform presentation awards sponsored by AADOCR, which recognized impactful studies in craniofacial research, were Dr. Kara Powder (Clemson University) in the early career investigator faculty category, Dr. Michi Kanai (University of Colorado Anschutz Medical Campus) in the post-doctoral fellow category, and Timothy Nguyen (University of Iowa) in the graduate student trainee category.

9 | SUMMARY

In summary, the 46th annual meeting of the Society for Craniofacial Genetics and Developmental Biology convened over 120 scientists from 21 states, representing over 40 different scientific institutions, to better our understanding and treatment of craniofacial development and disease. The meeting continues to be an exceptional forum for researchers regardless of career stage, gender, or background. We look forward to reconvening for the 47th annual meeting of the SCGDB in Kansas City, MO in 2024.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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