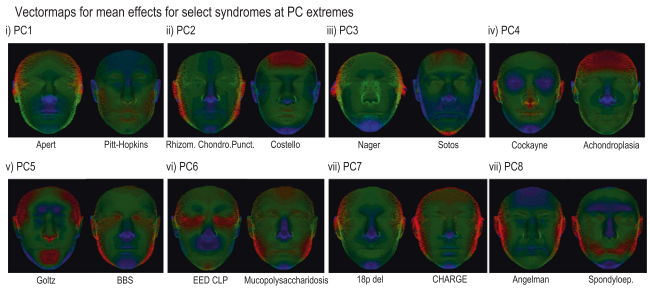
IN THIS ISSUE

3D facial imaging for genetic diagnosis

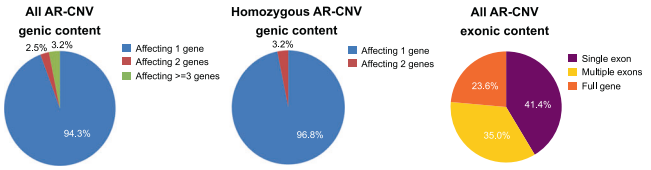
https://doi.org/10.1038/s41436-020-0845-y



More than 2000 inherited disorders in humans affect the oral cavity and the shape of the face. In a study reported in this issue, Hallgrímsson and colleagues investigated whether genetic syndromes can be diagnosed from 3D images of human faces. The researchers assembled a library of 3D facial images from nearly 7000 individuals with genetic syndromes who display facial dysmorphism and their unaffected relatives. They also included 3D facial images from more than 3000 unrelated, unaffected individuals. After standardizing facial shape by age and sex, the researchers then assessed variation in facial shape and classified faces using parametric and machine learning approaches. The researchers found that syndrome diagnosis accounted for nearly 19% of the total variation in facial shape. When the researchers used canonical variates analysis to discriminate syndromic faces from unaffected faces, the approach correctly classified 80% of subjects as unaffected or syndromic based on facial shape alone. Next, the team used high-dimensional regularized discriminant analysis (HDRDA) models to classify subjects to specific syndromes. Overall, the approach classified 72% of subjects to the correct syndrome and listed the correct diagnosis among the top ten ranked diagnoses for 87% of syndromic subjects. Phenotypic distinctiveness explained the greatest variation in classification accuracy, followed by phenotypic severity. The researchers were surprised to find that only 77% of apparently unaffected relatives of syndromic subjects were classified as unaffected. Instead, HDRDA often classified them with the same syndrome as their affected relative. The finding suggests that seemingly unaffected relatives may in fact be undiagnosed or incompletely penetrant syndromic cases. The authors conclude that quantitative 3D facial imaging analysis has the potential to advance diagnosis of genetic syndromes. —*V. L. Dengler, News Editor*

Copy-number variants contribute to autosomal recessive conditions

https://doi.org/10.1038/s41436-020-0864-8



Defects in both copies of an autosomal gene lead to autosomal recessive (AR) genetic conditions. Single-nucleotide variants (SNVs), small insertions/deletions (indels), and copy-number variants (CNVs) are largely responsible for AR disorders. Recent advances in molecular technologies have allowed a greater understanding of the role CNVs play in monogenic disorders. Here, Yuan and colleagues retrospectively examined the ways in which AR-CNVs contribute to AR conditions in a clinical cohort. The researchers analyzed more than 80,000 clinical samples submitted to Baylor Genetics for exome sequencing (ES) and chromosomal microarray analysis (CMA). The investigation identified 87 cases that involve AR-CNVs. In most of the cases (80%), CNVs affected both alleles. A CNV and an SNV/indel in *trans* affected the remaining 17 cases, indicating that analyses of both SNVs/indels and CNVs provide a more comprehensive assessment of a clinically affected individual. Most AR-CNV alleles (94%) affected one gene, while nearly half (41%) affected a single exon and more than one-third (35%) covered two or more exons of a gene. In total, AR-CNVs affected 57 AR loci. Recurring CNVs were identified: while AR-CNVs impacted nine loci in more than one case in the cohort, *TANGO2* was the most frequently affected gene, contributing to nine cases. The researchers also discovered that nearly 20% of cases had multiple molecular diagnoses. The team found that AR-CNVs affected haploinsufficient genes as well as AR disease genes, leading to genomic conditions and AR disorders. In addition, the researchers discovered that AR-CNVs led to haploinsufficiency of dosage-sensitive genes and unmasked recessive pathogenic variant alleles. The authors conclude that AR-CNVs contribute to multiple molecular diagnoses and suggest combined CMA and ES analyses for individuals with complex or atypical phenotypes. —*V. L. Dengler, News Editor*