Background

Molecular diagnosis in clinical genetics requires knowledge-driven variant interpretation and prioritization to correctly identify the pathogenic variant from the complex output of whole-genome and whole-exome sequencing. In addition, limitations exist for patients with craniofacial anomalies or defects accessing clinical genetics exist. The current bioinformatic tools and databases now available has created the potential for genomic sequencing and phenotype descriptors to provide clinical assessments to aid clinicians, geneticists, and families with their diagnoses.

In particular, the set of RASopathies are a collection of syndromes that encode genes in the RAS/MAPK pathway. These include Noonan, Costello, Cardiofaciocutaneous (CFC), and Neurofibromatosis Type 1 (NF1). Although this group’s mapping of the genotype to phenotype is complex, the biological pathway is well-studied and provides an excellent model for mapping other genotype-phenotype relationships. Specifically, our categorization of atypical faces is explored in detail, giving insight to the genetic underpinnings of the RAS/MAPK mechanisms as well as model an algorithm for other rare clinical diagnoses.

Materials & Methods

Facial signatures (z-scores at many points of the face) provide an age- and sex-normalized description of the unique characteristics of an individual and were computed for each face by using the subject in x (lateral), y (vertical), z (depth), and along the direction perpendicular to the surface at each point. Euclidean distance to centroids classifier was next used to determine which group’s mapping of the genotype to phenotype is complex, the biological pathway is well-studied and provides an excellent model for mapping other genotype-phenotype relationships.

Results

Objective categorization of participants

Mean facial signatures of subjects were assigned to each group on >90% of the time. This classification was repeated 10,000 times with a random and different 10-fold partitioning of the data.

Genotype-phenotype relationships

NOONAN

Among the 49 cases of Noonan, the most common genetic cause was PTPN11, showing a variable phenotype. Half presented with typical Noonan features, along with SHOC2 and SOS1 mutations. No evidence of PTPN11 were more likely to have typical Noonan features than other genetic causes. Interestingly, unrelated individuals with RAF1, BRAF, NOO127 mutations were misclassified as CFC >99% of the repetitions. NOO129 was classified as Costello, while NOO149 and CBL as unaffected.

CFC

Among the 14 cases of CFC, the common PTPN11 gene appears to not have a more typical Noonan face than unaffected individuals, while other Noonan-associated genes may present with facial features indicative of CFC, which contradicts several case reports findings. As we continue to build and refine algorithms for facial genotype-phenotype mapping, we can uncover more about the biology, morphology, development, and diagnoses of the craniofacial complex.

References

We represented 3D visualizations of characteristic phenotypes within Noonan, Costello, CFC, and NF1. Individuals diagnosed with Noonan syndrome were characterized appropriately at rates similar to those previously reported. Additionally, the common PTPN11 gene appears to not have a more typical Noonan face than unaffected individuals, while other Noonan-associated genes may present with facial features indicative of CFC, which contradicts several case report findings.

Conclusions

As we continue to build and refine algorithms for facial genotype-phenotype mapping, we can uncover more about the biology, morphology, development, and diagnoses of the craniofacial complex.

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