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Research Paper

Investigation of a dysmorphic facial phenotype in patients with Gaucher disease types 2 and 3

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ABSTRACT

Gaucher disease (GD) is a rare lysosomal storage disorder that is divided into three subtypes based on presentation of neurological manifestations. Distinguishing between the types has important implications for treatment and counseling. Yet, patients with neuronopathic forms of GD, types 2 and 3, often present at young ages and can have overlapping phenotypes. It has been shown that new technologies employing artificial intelligence and facial recognition software can assist with dysmorphology assessments. Though classically not associated nor previously described with a dysmorphic facial phenotype, this study investigated whether a facial recognition platform could distinguish between photos of patients with GD2 and GD3 and discriminate between them and photos of healthy controls. Each cohort included over 100 photos. A cross validation scheme including a series of binary comparisons between groups was used. Outputs included a composite photo of each cohort and either a receiver operating characteristic curve or a confusion matrix. Binary comparisons showed that the software could correctly group photos at least 89% of the time. Multiclass comparison between GD2, GD3, and healthy controls demonstrated a mean accuracy of 76.6%, compared to a 37.7% chance for random comparison. Both GD2 and GD3 have now been added to the facial recognition platform as established syndromes that can be identified by the algorithm. These results suggest that facial recognition and artificial intelligence, though no substitute for other diagnostic methods, may aid in the recognition of neuronopathic GD. The algorithm, in concert with other clinical features, also appears to distinguish between young patients with GD2 and GD3, suggesting that this tool can help facilitate earlier implementation of appropriate management.

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1. Introduction

Individuals and families impacted by rare diseases are all too familiar with the phrase "diagnostic odyssey", the time between initial symptom manifestation and a final diagnosis. During this period, patients are subjected to tests and assessments that often require visits to different medical facilities for evaluations conducted by multiple physicians over an average period of five years [1,2]. A lack of diagnosis following potentially invasive assessments can lead to feelings of frustration, uncertainty, and hopelessness [3,4]. Conversely, receiving a diagnosis can empower patients and their families, while also informing appropriate medical care and long-term support [5–7]. Therefore, minimizing the time between initial disease recognition and accurate diagnosis is a common goal held by patients and healthcare providers alike.

Gaucher disease (GD) is one such rare disease that may include a turbulent journey to diagnosis. GD is an autosomal recessively inherited disorder caused by biallelic pathogenic variants in *GBA1* which encodes for the lysosomal glycoside hydrolase, glucocerebrosidase (GCase, EC 3.2.1.45). Deficient or altered GCase results in a buildup of its substrates, glucosylceramide and other glycosphingolipids, in lysosomes of macrophages and other cells [8,9]. Disease manifestations include hepatosplenomegaly, thrombocytopenia, anemia, infiltrative lung disease, polyclonal and monoclonal gammopathy, avascular osteonecrosis, and osteopenia [10–13]. Specific neurological phenotypes encountered in neuronopathic forms of GD include slowed horizontal saccades, progressive myoclonic epilepsy, strabismus, failure-to-thrive, behavioral

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abnormalities, swallow dysfunction and developmental delay or progressive deterioration [10,12,14–18]. The three types of GD are categorized based on the presence and severity of neurological manifestations with Gaucher disease type 1 being the non-neuronopathic form (GD1, OMIM 230800). Gaucher disease type 2 is considered the acute neuronopathic form (GD2, OMIM 230900) and Gaucher type 3 the chronic neuronopathic form (GD3, OMIM 231000). All types of GD may present in childhood, but GD2 manifests exclusively prenatally, perinatally or during the first months of life, and GD3 predominately manifests in infancy or early childhood [19,20]. There is also a continuum of presentations between GD2 and GD3 [21]. Diagnosing GD can be achieved pre-clinically via newborn screening, carrier screening, and other prenatal testing methods. Once the diagnosis is considered upon symptom presentation, GD can be confirmed molecularly by sequencing *GBA1*, or by measuring GCase enzymatic activity. The type of GD diagnosed is based on phenotypic presentation. Despite these available diagnostic measures, patients with GD still often undergo a lengthy diagnostic odyssey, including invasive tissue biopsies, because of limited physician awareness, the presentation of nonspecific symptoms and the rarity of the disease.

Advancements in genomic and computational technologies have increased the number of diagnostic tools available to clinicians. Software including artificial intelligence (AI) run by deep convolutional neuronal, networks (DCNNs), have standardized the way that images can be analyzed. Dysmorphology, the study assessing variation of physical features, has long been an integral part of recognizing rare inherited diseases [22,23]. With the aid of novel facial recognition tools, dysmorphology may be evaluated by utilizing DCNNs to analyze patient photos [24]. One such tool, Face2Gene (FDNA Inc., USA), is powered by an algorithm called DeepGestalt that has been trained to recognize over 300 syndromes including Down, Angelman, Noonan, and Coffin-Lowry syndromes as well as certain inborn errors of metabolism [25–30]. Clinicians upload a frontal facial image of a patient for image analysis and a ranked list of 30 suggested syndromes is generated. Despite prior attempts to train the algorithm with diverse images of patients with GD, it was not a syndrome previously recognized by the algorithm. While this might suggest that there is no perceptible facial phenotype GD associated with patients with, these algorithm trainings were conducted using a small number of photos that included patients with all three GD types.

Distinguishing clinically between GD2 and GD3 may be challenging, especially in young patients. Yet, recommended treatment regimens and familial support for patients with GD2 are very different from patients with GD3, highlighting the importance of a swift differentiation between Gaucher types [31]. In recent years, both physicians who treat patients with GD and family members of patients with GD2 and GD3 have observed that some unrelated patients seem to share certain facial features [32]. In light of this anecdotal evidence, this study aims to explore whether facial recognition algorithms identify a facial phenotype unique to patients with GD2 or GD3, with the hope that this technology may help shorten the time to accurate diagnosis.

2. Methods

2.1. Photo collection

Publicly available images were collected and uploaded to the HIPAA compliant Face2Gene platform. Image sources included parents' blogs, obituaries, and the Children's Gaucher Research Fund newsletters, among others (Table 1). The diagnostic criteria used to discern GD2 from GD3 was as recently described [18].

To assess whether there was a shared facial phenotype among subjects with GD, we compared photos of subjects with neuronopathic GD to age, sex, and ethnicity-matched controls. Controls were facial photos of individuals who did not have GD, nor any other known genetic condition.

Table 1
Sources of collected photos of subjects with Gaucher disease.

Source Information	Unique GD2 Subjects Obtained from Source (n)	Unique GD3 Subjects Obtained from Source (n)
Paper published in an academic journal*	3	6
Parent or other family member's blog*	3	1
Facebook group	2	0
Obituary	3	0
Children's Gaucher Research Fund	20	6
Presentation	1	4
YouTube video	4	7
Patients seen by the investigators and photographed with informed consent	10	31
Gauchers Association UK pamphlet	3	8
Other media outlet*,#	1	1

* For the GD2 cohort, there was overlap in photo sources for some individuals among the categories marked by the asterisk.
# Other media outlets include a hospital website, parent support networks, and a GoFundMe campaign.

2.2. Cohort demographics

We collected 103 photos of 47 different patients with GD2 and 143 photos of 86 different patients with GD3. For GD2, the maximum number of photos per subject was 9, and the average number of photos per individual was 2.19. For GD3, these numbers were 17 and 1.66, respectively. The GD2 cohort had more female individuals and photos than males, while the GD3 cohort had more male individuals than females but fewer photos of males (Table 2). Both cohorts were majority Caucasian, and the GD3 cohort was more ethnically diverse than the GD2 cohort (Fig. 1). We also conducted a pilot evaluation using 133 photos of 48 individuals with GD1 (Supplementary Table 1).

2.3. Control cohort demographics

The control cohorts were age, sex, and ethnicity-matched based on four ethnic categories: Caucasian, Asian, Latin American, and African. Photos of individuals belonging to an ethnic group not represented in the list were assigned to one of the four categories (Table 3). Photos of subjects who identify as Asian – East, Asian – South, and Asian – Southeast were classified as "Asian". Photos of subjects who identify as African American were classified as "African", and photos of Latinx individuals were classified as "Latin American". Photos of subjects who identify as Asian – West/Middle Eastern were designated as "Caucasian" as prior internal studies showed no ethnic bias for the algorithm between these two ethnicities and, the number of Middle Eastern healthy controls in the Face2Gene database was limited.

2.4. Face2Gene analysis

Each photo was uploaded as an individual case in the Clinic application of Face2Gene. Demographic information including age, sex, and ethnicity for each individual was filled out accordingly to allow for matched control groups. Information about GD-related manifestations were also annotated, and the desired cohorts created.

Every individual photo undergoes analysis as described by Gurovich et al. [25]. Once the face and facial landmarks are detected, DCCNs normalize and crop the face into scaled regions converted to grayscale. The software then analyzes the regions and predicts the probability for each syndrome it has been trained to recognize, resulting in a ranked list of inherited conditions. The Gaucher photos generated lists of suggested syndromes other than GD, as DeepGestalt was not previously trained to recognize GD.

A minimum of two cohorts, each with at least ten photos, is required when analyzing groups of photos. The comparison and separation quality between all cohorts was evaluated by measuring the Area Under the

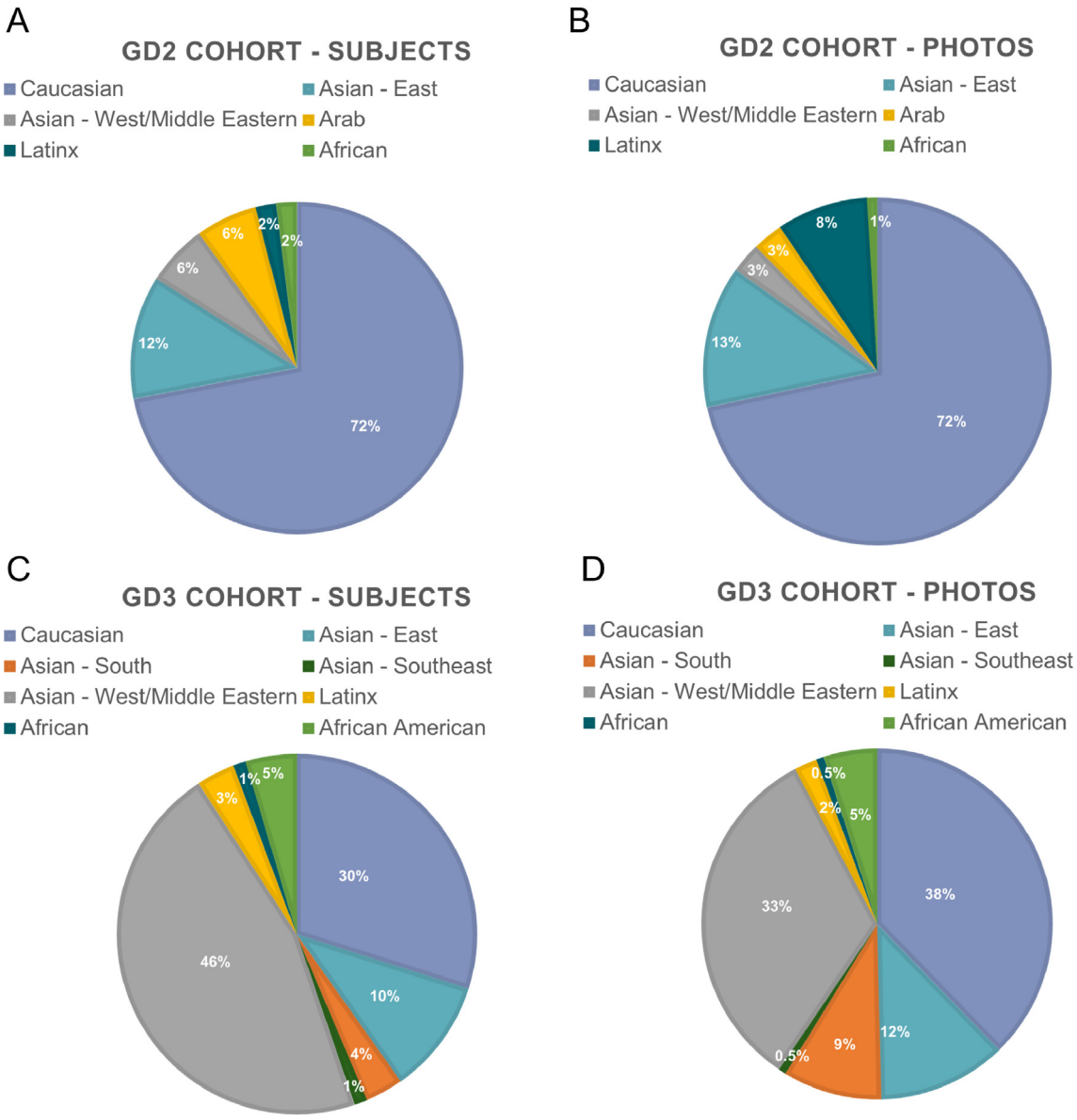

Fig. 1. Ethnic breakdowns of the GD2 and GD3 cohorts. A) Percentages of patients with GD2 who identify with a given ethnicity. B) Percentages represent the number of photos from patients belonging to a given ethnicity in the GD2 cohort. C) Percentages of patients with GD3 who identify with a given ethnicity. D) Percentages represent the number of photos belonging to a given ethnicity in the GD3 cohort.

Curve (AUC) of the Receiver Operating Characteristic (ROC) curve. To estimate the statistical power of DeepGestalt in distinguishing patients with GD2 from patients with GD3 and from unaffected controls, a cross validation scheme was used, including a series of binary comparisons between all groups. For these binary comparisons, the data was split randomly multiple times into training sets and test sets. Each set contained half of the cohort, and this random process was repeated 10 times. Outputs included a composite photo of each cohort, the distribution of clinical features based on the collected phenotypic data, and either a binary or multiclass comparison, depending on the number of cohorts analyzed within the project.

Table 2
Composition of GD2 and GD3 cohorts.

	GD2	GD3
Total number of patients	47	86
Total number of photos	103	143
Maximum number of photos (individuals with this number of photos)	9 ($n = 3$)	17 (n = 1)
Average number of photos per individual	2.19	1.66
Number of female subjects (%)	25 (53%)	41 (48%)
Number of female photos (%)	65 (63%)	81 (57%)
Number of male subjects (%)	22 (47%)	45 (52%)
Number of male photos (%)	38 (37%)	62 (43%)
Age range	4 days −10 years	1 month −30 years

Table 3
Ethnic breakdown of the control photos.

	Controls for GD2 Cohort	Controls for GD3 Cohort
Caucasian (%)	79 (77%)	100 (70%)
Asian (%)	14 (13%)	31 (22%)
Latin American (%)	9 (9%)	4 (3%)
African (%)	1 (1%)	8 (5%)

3. Results

3.1. Binary comparisons

Overall, binary comparisons assessed how well DeepGestalt was able to assign photos to the correct group. If there was no overlap between the true positive group and the true negative group, or the disease group and the healthy group, this would result in an AUC of 1. Therefore, an AUC of 1 means that there is likely a 100% chance that the algorithm will be able to distinguish between the disease and control groups. The most distinct separations in the binary comparisons analyzed were the GD2 cohort vs controls, the GD3 cohort vs controls, and the GD2 cohort vs the GD3 cohort (Fig. 2). The AUC was highest when comparing the GD2 versus the control cohort and lowest when comparing the GD3 versus the control cohort. All the AUC's were ≥0.89 and p-values <0.0001.

Other binary comparisons performed were between subsets of our GD2 and GD3 cohorts. To reflect the diversity of included patients with GD, we investigated the performance of DeepGestalt when analyzing patients of different ages and ethnicities. The effect of age was examined specifically in the GD3 cohort, as the GD2 cohort had a narrower range with only four individuals living more than three years (Fig. 3). The effect of patient ethnicity was examined in both the GD2 and GD3 cohorts, but could only be evaluated in the East Asian and Middle Eastern subsets since the minimum cohort size required was ten (Fig. 4).

3.2. Multiclass comparisons

It was also possible to assess the algorithm's ability to correctly assign photos to more than two groups. To test DeepGestalt's multiclass comparison performance with our GD cohorts we added one control cohort consisting of 143 photos, some of which were used in evaluating the original GD2 and GD3 cohorts. Overall, the mean accuracy was found to be 76.6%, which was much higher than the 37.7% random chance for comparison (Fig. 5). Looking at each of the three groups individually, the control group had the highest true positive rate (83%), followed by GD2 (80%), and GD3 (67%).

4. Discussion

To our knowledge, this is the first description of the use of DeepGestalt or any other facial recognition software with defined cohorts of patients with GD. We collected over 100 GD2 photos as well as over 100 GD3 photos. The GD2 cohort was more homogenous in

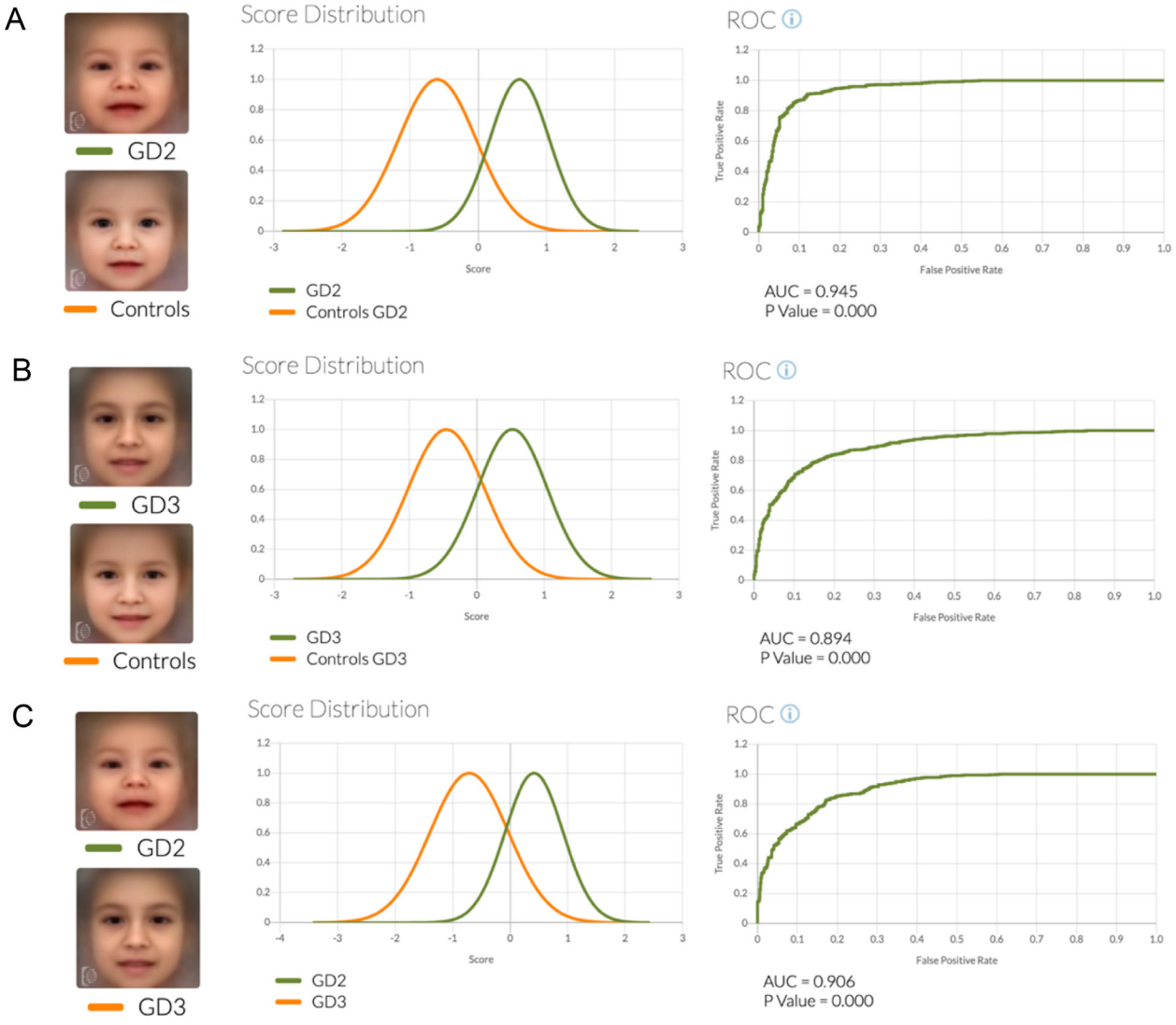

Fig. 2. Binary comparisons. (A) The GD2 cohort and its age, sex, and ethnicity-matched controls. (B) The GD3 cohort and its age, sex, and ethnicity-matched healthy controls. (C) The GD2 and GD3 cohorts.

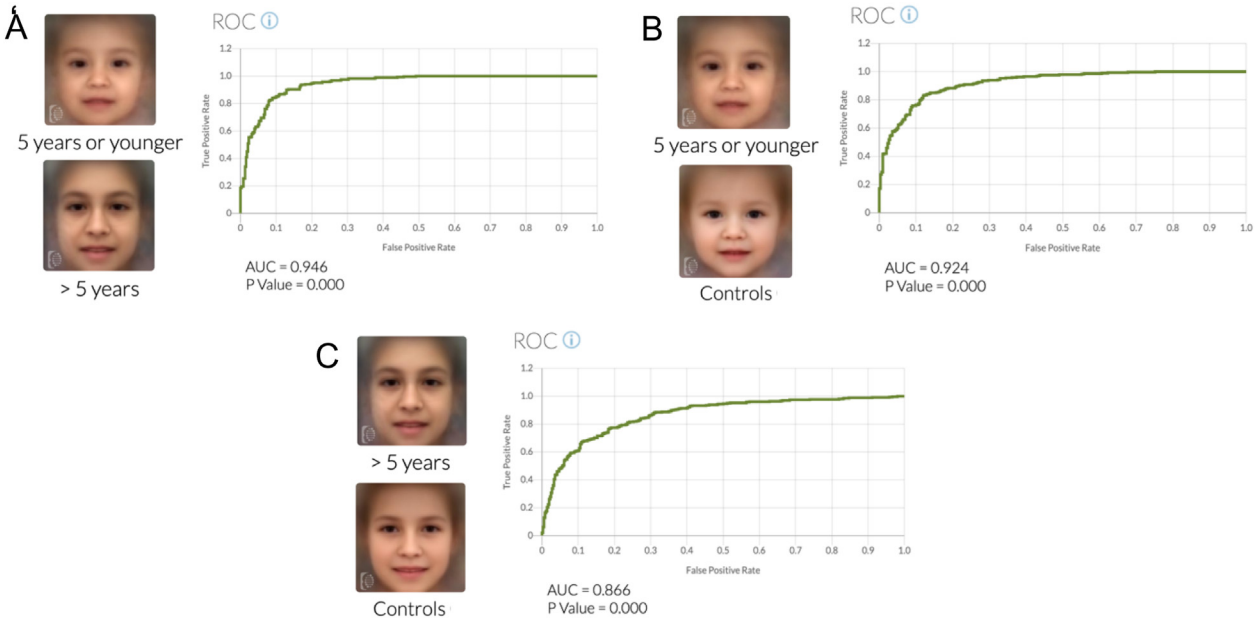

Fig. 3. Binary comparisons of subsets of the GD3 cohort categorized by age. (A) Binary comparison of photos of patients with GD3 ≤ age 5 years ($n = 59$) compared to those > age 5 ($n = 76$). (B) Binary comparison of the same photos of patients with GD3 ≤ age 5 compared to age, sex, and ethnicity-matched control photos. (C) Binary comparison of the same photos of patients with GD 3> age 5 compared to age, sex, and ethnicity-matched controls.

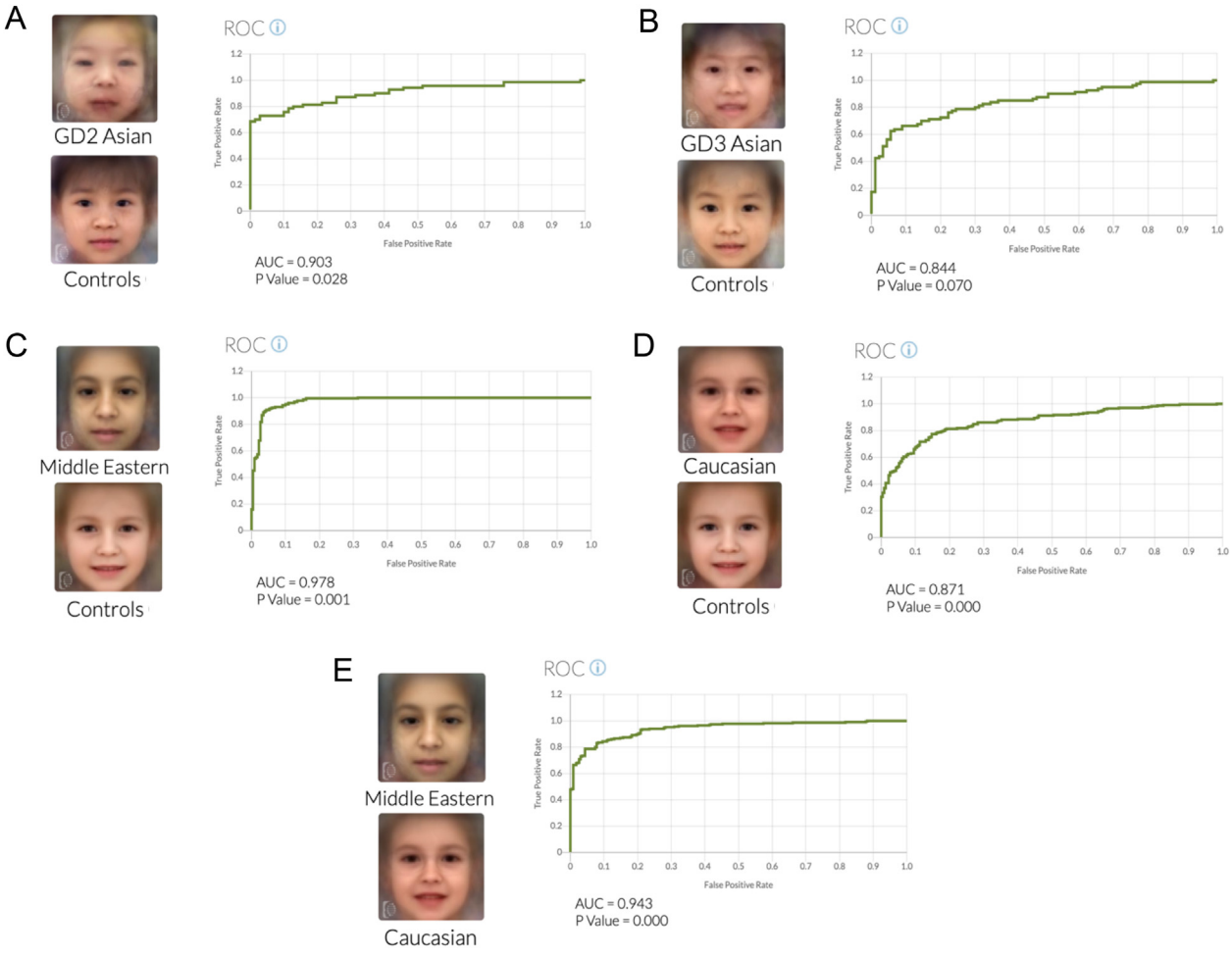

Fig. 4. Binary comparisons of subsets of each cohort categorized by ethnicity. (A) Binary comparison of East Asian GD2 photos ($n = 14$) compared to age, sex, and ethnicity-matched controls. (B) Binary comparison of East Asian GD3 photos ($n = 17$) compared to age, sex, and ethnicity-matched controls. (C) Binary comparison of Middle Eastern GD3 photos ($n = 46$) compared to age and sex matched Caucasian controls. (D) Binary comparison of Caucasian GD3 photos (n = 46) compared to age, sex, and ethnicity-matched controls. (E) Binary comparison of Middle Eastern GD3 photos (n = 46) compared to Caucasian GD3 photos (n = 46).

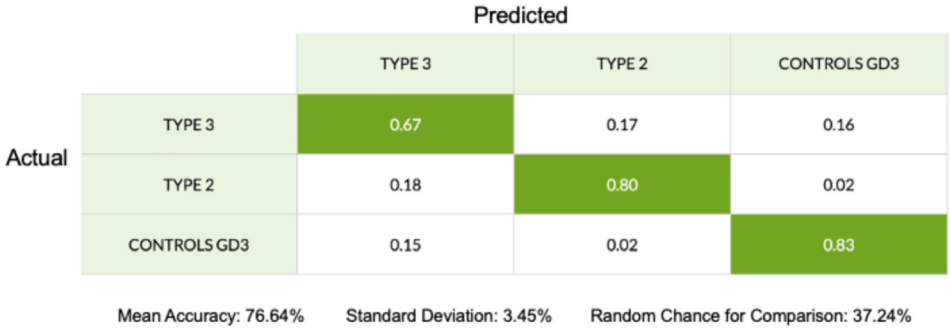

Fig. 5. A confusion matrix of our multiclass comparison of the GD3 ($n = 143$), GD2 ($n = 103$), and control cohort (n = 143). Diagonal green boxes are the true positive rates. White boxes are false positive and false negative rates. Mean accuracy, standard deviation, and random chance for comparison are listed below. The control photos collected for the GD3 group were used, as their age range spanned that of both the GD2 and GD3 cohort. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

terms of age and ethnicity compared to the GD3 cohort, which may explain the generally lower AUC values seen when comparing the GD3 cohort to healthy controls. The binary comparisons of our GD2 and GD3 cohorts compared to controls, as well as GD2 versus GD3 resulted in AUC values above 0.89. When we tested the algorithm in a multiclass setting for the two GD cohorts and a control cohort, its mean accuracy was 76.6% as compared to the random chance of 37.7%. Therefore, this study demonstrates the potential clinical utility of automated image recognition platforms in assisting with the diagnosis of GD2 or GD3; in fact, even with the limited number of photos submitted to Face2Gene, DeepGestalt was trained to recognize neuronopathic GD as a defined syndrome and both GD2 and GD3 will become available in Face2Gene Clinic as syndromes recognized by facial analysis.

This study included a pilot comparison of patients with GD1. However, patients with GD1 are extremely diverse with an age range from infancy to old age, and there is little clinical indication that such patients have a specific associated facial phenotype. Our pilot analysis of 133 photos of 48 individuals with GD1 ranging in age from 2 to 75 years demonstrated that unlike GD2 and GD3, GD1 did not pass the statistical threshold to allow it to be included as one of the syndromes identified by DeepGestalt. A larger collection of photos of infants and young children would be needed to conduct more definitive comparisons between GD1 and the neuronopathic forms of GD. Furthermore, additional photos of patients from underrepresented ethnic groups would be necessary to determine DeepGestalt's predictive power in these different groups. The present study did not include sufficient images of non-Caucasian patients for meaningful comparisons across ethnic groups. As the technology evolves and more photos are collected, the applications of this software may expand, ultimately helping to shorten the diagnostic odyssey for patients with GD and facilitating earlier appropriate management plans.

Declaration of Competing Interest

Emily Daykin, Magy Abdelwahab, Nehal Hassib, Raphael Schiffmann, Emory Ryan, and Ellen Sidransky each declare that they have no conflict of Interest. Nicole Fleischer is an employee of FDNA Inc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2021.09.008.

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