Clinical versus automated assessments of morphological variants in twins with and without neurodevelopmental disorders

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Abstract

Physical examinations are recommended as part of a comprehensive evaluation for individuals with neurodevelopmental disorders (NDDs), such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder. These examinations should include assessment for morphological variants. Previous studies have shown an increase in morphological variants in individuals with NDDs, particularly ASD, and that these variants may be present in greater amounts in individuals with genetic alterations. Unfortunately, assessment for morphological variants can be subjective and time-consuming, and require a high degree of clinical expertise. Therefore, objective, automated methods of morphological assessment are desirable. This study compared the use of Face2Gene, an automated tool to explore facial morphological variants, to clinical consensus assessment, using a cohort of \( N = 290 \) twins enriched for NDDs (\( n = 135 \) with NDD diagnoses). Agreement between automated and clinical assessments were satisfactory to complete (78.3–100%). In our twin sample, individuals with NDDs did not have greater numbers of facial morphological variants when compared to those with typical development, nor when controlling for shared genetic and environmental factors within twin pairs. Common facial morphological variants in those with and without NDDs were similar and included thick upper lip vermilion, abnormality of the nasal tip, long face, and upslanted palpebral fissure. We conclude that although facial morphological variants can be assessed reliably in NDDs with automated tools like Face2Gene, clinical utility is limited when just exploring the
1 | BACKGROUND

During embryogenesis, the brain and skin are derived from the same neuroectodermal layer; therefore, morphological variants (abnormal physical features), especially in the facial region, may indicate altered brain development (Jones, 2013). Molecular signals are critical in the growth and development of the face and brain and are guided by genes. Therefore, altered signaling as a result of genetic variants could simultaneously affect development of both the face and brain (Marcucio, Hallgrimsson, & Young, 2015). Morphological variants are found in individuals with a variety of genetic syndromes and disorders and have been used to aid the diagnostic process. For example, there are some characteristic facial features that are present in nearly all individuals with Down syndrome and help guide health care providers in diagnosis like epicanthal folds, upslanted palpebral fissures, and brachycephaly (Ostermaier, 2019; Starbuck, Reeves, & Richtsmeier, 2011). Morphological variants are defined to include both major abnormalities and minor variants (Merks, van Karnebeek, Caron, & Hennekam, 2003; Ozgen et al., 2011). Minor variants include common features present in greater than 4% of the population and minor anomalies (often referred to as minor physical anomalies) present in 4% or less of the population (Merks et al., 2003; Miles & Hillman, 2000). Our past research on minor physical anomalies in twins has shown a high degree of correlation in the type and amounts within monozygotic (MZ) twins and lower in dizygotic (DZ) twins, indicating a high genetic influence on their development (Myers et al., 2017).

Neurodevelopmental disorders (NDDs) encompass a range of behaviorally defined conditions that usually emerge early in development and result in impairments in cognitive, social, academic, or occupational functioning (American Psychiatric Association, 2013; Bölte et al., 2019). According to the Diagnostic and Statistical Manual of Mental Disorders fifth Edition, NDDs include intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), attention–deficit/hyperactivity disorder (ADHD), specific learning disorders, and motor disorders (American Psychiatric Association, 2013). These disorders are believed to be highly heritable with a substantial amount of comorbidity among the diagnoses (Brikell, Kuja-Halkola, & Larsson, 2015; Colvert et al., 2015; Sandin et al., 2014; Thapar, Cooper, & Rutter, 2017). Genetic variants, along with altered brain development, have been found in individuals with NDDs (Dougherty, Evans, Myers, Moore, & Michael, 2016; Faraone & Larsson, 2018; Ha, Sohn, Kim, Sim, & Cheon, 2015; Rommelse, Buitelaar, & Hartman, 2017; Tamminies et al., 2015). As a result, morphological variants could suggest the possibility of an underlying genetic abnormality that affected early embryogenesis and led to both the presence of morphological variants and abnormal brain development, resulting in NDDs like ASD and ADHD (e.g., Jones, 2013; Minahim & Rohde, 2015; Ozgen et al., 2011; Ozgen, Helleman, de Jonge, Beemer, & van Engeland, 2013; Ozgen, Hop, Hox, Beemer, & van Engeland, 2010).

Best practice guidelines indicate children undergoing assessment for NDDs like ASD and ADHD should receive physical examinations and for ASD in particular, an examination to identify morphological variants (Johnson et al., 2007; National Institute for Health and Care Excellence, 2018; Subcommittee on Attention-Deficit/Hyperactivity Disorder Steering Committee on Quality Improvement Management et al., 2011). Despite efforts to identify NDDs earlier with behavioral screening measures, studies continue to demonstrate children often receive delayed diagnoses (Fridman, Banaschewski, Sikirica, Quintero, & Chen, 2017; Miodovnik, Harstad, Sideridis, & Huntington, 2015; Zuckerman, Lindly, & Sinche, 2015). Subsequently, researchers have explored different types and amounts of morphological variants as a tool for possibly detecting NDDs earlier, particularly for ASD and ADHD (e.g., Angkustsiri et al., 2011; Miles et al., 2008; Minahim & Rohde, 2015; Ozgen et al., 2010; Ozgen et al., 2011; Ozgen et al., 2013).

Historically, studies have relied on the use of in-person, head-to-toe, clinical morphological assessments. Although these assessments are considered the gold standard, they are time-consuming, costly, often subject to examiner bias, and are typically performed by dysmorphologists or clinical geneticists who have a high level of training and clinical experience. Automated morphological assessments have become available in recent years and may promote resource savings, along with the ability to accurately and objectively assess morphological features. Research regarding the use of these types of technologies in the assessment of NDDs and other disabilities are emerging (Aldridge et al., 2011; Gurovich et al., 2017; Gurovich et al., 2019; Lumaka et al., 2017; Obafemi-Ajayi et al., 2015). One of the early studies on the use of automated assessments in NDDs was published by Aldridge et al. (2011) and involved the use of a digital system (i.e., 3dMD Cranial System) to acquire three-dimensional (3D) facial images and measurements of the faces from boys diagnosed with ASD and typically developing controls. Aldridge et al. found differences in the facial features of the boys diagnosed with ASD compared with controls and identified subgroups of boys with ASD who showed distinct clinical and behavioral characteristics based on facial measurements. Aldridge et al. concluded that the use of facial dysmorphology as a marker for early identification and subgrouping of ASD was promising. A later study by Obafemi-Ajayi et al. (2015) used similar methods to Aldridge et al. and also found facial features could be used...
to separate boys with ASD into meaningful subgroups with differing clinical and behavioral profiles.

More recent articles have been published on the use of the automated facial dysmorphology analysis, such as Face2Gene (FDNA, Boston, MA), a proprietary product, and the technology behind it that has recently been described as DeepGestalt (Gurovich et al., 2017; Gurovich et al., 2019). The DeepGestalt algorithm in Face2Gene analyzes two-dimensional (2D) photos to detect morphological patterns and relationships of these patterns to genetic syndromes (Gripp, Baker, Telegrafi, & Monaghan, 2016; Gurovich et al., 2017; Gurovich et al., 2019). To use Face2Gene, a user submits a photo through the Face2Gene web platform that is available free-of-charge to medical professionals and researchers. The system uses an algorithm that analyzes the images to first detect the face and then 130 facial points that are fed into a deep convolutional neural network resulting in a probabilistic list of syndrome and gene matches. In order to visualize this process, a heat map is provided overlaying the individual's facial image, demonstrating areas in red that are most similar to those of others with the listed potential genetic syndromes (Basel-Vanagaite et al., 2016; Gurovich et al., 2017; Lumaka et al., 2017).

Recent studies have demonstrated Face2Gene to be as good as or superior to common clinical assessments performed by trained health care providers in identifying a variety of genetic conditions (e.g., mutations in the BAF gene in Gripp et al., 2016; Cornelia de Lange in Basel-Vanagaite et al., 2016; Emanuel and Pallister-Killian Syndromes in Liehr et al. (2018); inborn errors of metabolism in Pantel et al., 2018; Down syndrome in Vorrvavanpreecha, Lertboonnum, Rodjanadit, Sriplienchan, & Rojnueangnit, 2018). Face2Gene is resource saving as does not require sophisticated equipment that is generally needed to take 3D images, as used in the study by Aldridge et al. (2011) and Obafemi-Ajayi et al. (2015). Instead, frontal facial photos taken by conventional cameras or cellular phones can be used (Basel-Vanagaite et al., 2016; Gurovich et al., 2017). Face2Gene can be used by medical professionals and researchers who have limited access to trained dysmorphologists (Hadj-Rabia et al., 2017) or in settings with limited socioeconomic resources (Lumaka et al., 2017).

The use of automated technologies to perform morphological assessments to identify children at risk for NDDs may be a potentially cost-effective tool for clinical providers to help support early detection and diagnosis of NDDs. However, further research is needed to explore how well these technologies perform, especially when compared with what is generally considered the gold standard: in-person clinical assessments by trained providers like dysmorphologists and clinical geneticists. Therefore, this study aimed to (a) examine the agreement between the facial morphological variants identified through Face2Gene compared with in-person clinical assessments performed on the same participants by clinical geneticists; (b) report on facial morphological variants identified through Face2Gene on a large sample of twins enriched for NDDs; and (c) examine the ability of Face2Gene to identify distinct facial phenotypes for those diagnosed with NDDs. We hypothesized that (a) a convergence of automated and clinical consensus morphology assessment would exist; (b) an excess of morphological variants would be identified in individuals with NDDs compared to those with typical development using automated assessments; and (c) faces of individuals with NDDs would be distinguishable from those with typical development.

2 | MATERIALS

2.1 | Sample

Participants in this study were recruited from August 2011 to May 2017 as part of the Roots of Autism and ADHD Twin Study in Sweden. The purpose of this twin study is to explore the genetic and environmental causes of NDDs through the collection of a variety of biological and behavioral data from twin pairs with diagnoses of NDDs (Bölte et al., 2014). This study reports on head-to-toe clinical assessments performed on 106 individual twin participants and automated assessments with Face2Gene performed on facial photos of 290 individual twin participants.

2.2 | Clinical morphological assessments and facial photos

The study analyzed data from clinical morphological assessments and medical facial photos from participants in the Roots of Autism and ADHD Twin Study in Sweden, described in more detail in Bölte et al. (2014) and Myers et al. (2017). In brief, the clinical assessment consisted of in-person, head-to-toe examinations on participants using a comprehensive checklist covering a range of morphological variants. Further details regarding the development and content of the checklist are available in Myers et al. (2017) and the Supplemental Table S1. The exams took up to 1 hr to complete per twin pair and were performed either by one, or more often, two experienced clinical geneticists. Participants were examined for 217 variants and an additional eight variants on a genital exam for males only. Participants received a score of “1” for each variant present. Facial photos (2D) were taken of participants in RATSS at the Karolinska Hospital Medical Photography Lab by professional medical photographers, along with photos of the participants’ hands, feet, and habitus. The photos were securely transferred to Face2Gene and then de-identified data is extracted from the photos to determine the presence of any facial morphological variants using Human Phenotype Ontology (Köhler et al., 2019). A total of 56 unique facial morphological variants were identified in the photos of participants using Face2Gene.

3 | METHODS

3.1 | Editorial policies and ethical considerations

The study was approved by the regional and national ethical boards in Sweden and informed consent was obtained from participants and
their parents for participation in the study and for the analysis of their facial images.

3.2 | Diagnostic and behavioral assessments

The participants in RATSS receive detailed diagnostic behavioral assessments through a consensus process involving experienced clinicians and is described elsewhere (Bölte et al., 2014; Myers et al., 2017). Twin pairs are classified as concordant or discordant for ASD, ADHD, NDDs, and typical development and based on the presence of NDD diagnoses. Saliva was collected in the study for determination of zygosity. The severity of autistic traits was measured using the total raw score on the Social Responsiveness Scale-2 (Constantino & Gruber, 2012), with increasing scores corresponding with the presence of more severe traits. The severity of ADHD was quantified using the “Attention Problems” scale on the Child Behavior Checklist (Achenbach & Rescorla, 2000) for participants 18 years of age and younger and the Adult Behavior Checklist (Achenbach & Rescorla, 2003) for participants older than 18 years, with increasing scores indicating greater severity of ADHD. The severity of general problem behaviors in NDDs was quantified using the “Total Problems” score from either the Child Behavior Checklist or Adult Behavior Checklist, with increasing scores indicating greater behavioral and emotional problems.

3.3 | Clinical and automated assessment of morphological variants for interrater agreement

Using the original head-to-toe checklist designed for the Roots of Autism and ADHD Twin Study in Sweden (Supplemental Table S1), a new checklist containing only variants found in the facial region was derived for this study to determine agreement between variants identified through clinical assessment with variants identified through Face2Gene (Supplemental Table S1). The items in this new checklist were translated from Swedish to English and aligned with appropriate Human Phenotype Ontology terms. A total of 36 items were mutually assessed by both clinical assessment and Face2Gene on 106 individuals and used to calculate percentage agreement between the morphology judgments with R version 3.3.2 and the IRR package. Agreement, versus other forms of reliability like Cohen’s Kappa, was calculated due to rare nature of morphological variants (McHugh, 2012; Viera & Garrett, 2005) identified by either clinical assessment or Face2Gene. Overall agreement and the number of times a facial morphological variant was identified by each rater is reported in Table 2.

3.4 | Assessment of morphological variants in full sample and statistical analysis

Facial photos from a larger sample consisting of 290 twin participants in the Roots of Autism and ADHD Twin Study in Sweden were then analyzed with Face2Gene. The amount of facial morphological variants present in individual participants was counted to create a total facial morphological variant score. SPSS version 25 and R version 3.3.2 were used to conduct descriptive and associational analyses, respectively. Associational analyses in the twin sample were conducted using linear (for continuous outcomes) and logistic (for dichotomous outcomes) regression models, fitted by generalized estimating equations (Zetterqvist, Vansteelandt, Pawitan, & Sjölander, 2016). These models, described in further detail in Myers et al. (2017) and Myers, Van’t Westeinde, Kuja-Halkola, Tammimies, and Bölte (2018), were used to assess the relationship both between- and within-pairs using the facial morphological variant score and (a) any NDD diagnosis (including ASD and ADHD), (b) ASD diagnosis, and (c) ADHD diagnosis. Within-pair analyses were conducted using conditional linear and logistic regressions. Results are described using odds ratios (OR) or beta (β) estimates with 95% Confidence Intervals (CI). Since data could not be assumed independent between twins from the same pair, we used the generalized estimating equations model to assess differences in specific morphological variants between those with typical development and those with any NDD diagnosis (Table 3). For the associational analyses, two trios of triplets were reduced to a MZ twin pair with discordant NDD and a DZ twin pair with concordant NDD. Three families who participated in the study had two sets of twin pairs in each family. Because these multiple twin pairs within families share similar genetic backgrounds that could affect analyses within the conditional regression model, the twin pair in each family with qualitatively more NDD diagnoses was included in the analyses.

A lower intelligence quotient (IQ) has been previously associated with the presence of increased minor physical anomalies and broadly recommended to control for in statistical analyses (Myers et al., 2017; Özgen et al., 2010). IQ was inversely associated with the number of facial morphological variants in the within-pair model only (β = -1.538, 95% CI = 2.961–1.115, p = .034); therefore, we controlled for IQ in our analyses. Participant sex was not significantly related to the number of facial morphological variants (OR = .870, 95% CI = .751–1.007, p = .063).

To assess the performance of the Face2Gene software in identifying diagnoses based on facial features, receiver operating characteristic curve analysis was performed. The analyses were conducted using the Face2Gene Research application (FDNA Inc.) to evaluate the separation area in the facial photographs between participants with typical development and participants with (a) ASD diagnoses, (b) ADHD diagnoses, or (c) any NDD diagnoses (including ASD and ADHD). Area under the curve values and p-values are reported for these analyses. The p-value refers to testing whether the area under the curve is statistically significantly different from 0.5. Due to the high similarity in the type and amount of minor physical anomalies, we previously reported within MZ twin pairs (Myers et al., 2017), data points could not be assumed independent, which was needed for the receiver operating characteristic curve analyses. Thus, we selected one individual per MZ pair for analyses. For this, data from the more severely affected twin participant in either concordant ASD or ADHD MZ twin pairs, or the more severely affected twin participant in MZ
pairs concordant for NDDs other than ASD or ADHD, were used to calculate the receiver operating characteristic curve statistic. Severity was determined using Social Responsive Scale-2 scores for twin pairs with concordant ASD and the "Attention Problems" scale scores on the Adult Behavior Checklist/Child Behavior Checklist for twin pairs with concordant ADHD. Since no measure of severity in other NDDs was available, we used the "Total Problems" on the scale on the Adult Behavior Checklist/Child Behavior Checklist as a general measure of behavioral and emotional symptoms for twin pairs with concordant NDDs other than ASD or ADHD.

4 | RESULTS

4.1 | Participants

The sample consisted of 290 individual twin participants, which included 81 MZ twin pairs, 59 DZ twin pairs, and two trios of triplets. For some twin pairs, only one individual twin participant was examined and/or photographed, so the sample also included one individual twin participant from a MZ pair and three individual twin participants from DZ pairs. One twin pair had pending zygosity. The majority of participants were of European descent. The sample ranged in age from 8 to 31 years, with the average age at 16.2 years (SD = 5.3). The sample included 127 females and 163 males. Participants had a variety of NDD diagnoses, including 73 with ASD, 82 with ADHD, 19 with ID, 43 with other NDDs, and 135 with any diagnosis of a NDD (numbers not corrected for comorbid presentations). The number of participants with typical development was 155. Sixty-eight individual twin participants had other psychiatric disorders (e.g., depression, anxiety, eating disorders, obsessive–compulsive disorder). Table 1 breaks down the sample by diagnosis of NDD versus typical development and includes descriptions of these subsample by zygosity, age, facial morphological variant scores, and scores on measures of IQ, Social Responsiveness Scale-2, Child Behavior Checklist, and Adult Behavior Checklist scores. The percentage of individual twin participants with comorbid disorders is included in Table 1.

4.2 | Interrater agreement and facial morphological variants identified

Percentage agreement between facial morphological variants identified through clinical assessment versus those identified through Face2Gene was satisfactory to complete and ranged from 78.3 to 100% (Table 2). It is important to note these values are primarily based on
agreement between nonfindings between Raters 1 and 2 due to the low base rates of the identified morphological variants. The item with the lowest level of agreement was upslanted palpebral fissures (78.3%) and those with the complete agreement (100%) included medial flaring of the eyebrow, telecanthus, tented upper lip vermilion, and tented philtrum. Table 2 includes the number of times each facial morphological variant was identified by either Rater 1 and/or Rater 2.

A total of 56 facial morphological variants were identified in participants using Face2Gene. Typically developing individuals had a median of 2 facial morphological variants, with a range of 0–13. The top facial morphological variants identified in those with typical development included thick upper lip vermilion (22.6% of sample), abnormality of the nasal tip (20.6%), long face (20.6%), upslanted palpebral fissure (20.0%), and broad chin (12.9%).

### TABLE 2

| Facial morphological variants (including common variants and minor physical anomalies) | N    | Agreement between automated and clinical assessment (%) | Frequency of facial morphological variants found by Rater 1 and/or Rater 2 |
|--------------------------------------------------------------------------------------|------|----------------------------------------------------------|--------------------------------------------------------------------------|
| Narrow foreheada                                                                     | 105  | 94.3                                                    | 6                                                                        |
| High anterior hairlinea                                                              | 106  | 95.3                                                    | 5                                                                        |
| Sparse scalp haira                                                                   | 106  | 99.1                                                    | 1                                                                        |
| Highly arched eyebrowa                                                               | 106  | 96.2                                                    | 8                                                                        |
| Sparse eyebrowa                                                                      | 106  | 96.2                                                    | 4                                                                        |
| Medial flaring of the eyebrowa                                                       | 106  | 99.1                                                    | 1                                                                        |
| Synophrys                                                                            | 103  | 97.1                                                    | 3                                                                        |
| Triangular facea                                                                     | 101  | 94.1                                                    | 8                                                                        |
| Proptosis                                                                            | 106  | 100                                                     | 0                                                                        |
| Hypertelorism                                                                        | 106  | 95.3                                                    | 7                                                                        |
| Hypotelorism                                                                         | 104  | 94.2                                                    | 8                                                                        |
| Blepharophimosis                                                                     | 106  | 95.3                                                    | 5                                                                        |
| Downslanted palpebral fissuresa                                                      | 106  | 94.3                                                    | 6                                                                        |
| Uplanted palpebral fissuresa                                                          | 106  | 78.3                                                    | 27                                                                       |
| Epicanthal                                                                            | 105  | 93.3                                                    | 7                                                                        |
| Telecanthus                                                                          | 106  | 100                                                     | 0                                                                        |
| Ptosis                                                                               | 106  | 89.6                                                    | 11                                                                       |
| Tented upper lip vermiliona                                                          | 106  | 99.1                                                    | 1                                                                        |
| Tented philtrum                                                                      | 106  | 99.1                                                    | 0                                                                        |
| Thick upper lip vermilion                                                            | 106  | 84.9                                                    | 16                                                                       |
| Thick lower lip vermilion                                                            | 106  | 96.2                                                    | 4                                                                        |
| Thin upper lip vermilion                                                             | 106  | 87.7                                                    | 15                                                                       |
| Abnormality of the chin                                                              | 104  | 89.4                                                    | 11                                                                       |
| Long philtrum                                                                        | 105  | 95.3                                                    | 5                                                                        |
| Short philtrum                                                                       | 103  | 87.4                                                    | 13                                                                       |
| Smooth philtrum                                                                      | 106  | 97.2                                                    | 3                                                                        |
| Deep philtrum                                                                        | 106  | 99.1                                                    | 1                                                                        |
| Low-set ears                                                                         | 106  | 90.6                                                    | 10                                                                       |
| Overfolded helix                                                                     | 106  | 96.2                                                    | 4                                                                        |
| Short nose                                                                           | 106  | 98.1                                                    | 2                                                                        |
| Abnormality of the nasal tip                                                         | 103  | 86.4                                                    | 15                                                                       |
| Prominent nasal bridge                                                               | 106  | 91.5                                                    | 11                                                                       |
| Wide nasal bridge                                                                    | 106  | 99.1                                                    | 1                                                                        |
| Broad nasal tip                                                                      | 105  | 88.6                                                    | 12                                                                       |
| Underdeveloped nasal alae                                                            | 104  | 92.3                                                    | 8                                                                        |
| Anteverted nares                                                                     | 105  | 96.2                                                    | 5                                                                        |

*MPAs, minor physical anomalies.
| Facial morphological variant | TD (n = 155) n (%) | ASD (n = 73) % (n) | ADHD (n = 82) % (n) | NDD (n = 135) % (n) |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| Thick upper lip vermilion   | 35 (22.6)         | 14 (19.2)         | 18 (21.2)         | 29 (21.5)         |
| Abnormality of nasal tip    | 32 (20.6)         | 14 (19.2)         | 13 (15.9)         | 23 (17.0)         |
| Long face                   | 32 (20.6)         | 10 (13.7)         | 13 (15.9)         | 23 (17.0)         |
| Upslanted palpebral fissure| 31 (20.0)         | 10 (13.7)         | 16 (19.5)         | 23 (17.0)         |
| Broad chin                  | 20 (12.9)         | 7 (9.6)           | 6 (7.3)           | 10 (7.4)          |
| Highly arched eyebrow      | 14 (9.0)          | 4 (5.5)           | 4 (4.9)           | 6 (4.4)           |
| Thick lower lip vermilion   | 11 (7.1)          | 4 (5.5)           | 2 (2.4)           | 6 (4.4)           |
| Abnormality of the chin     | 11 (7.1)          | 3 (4.1)           | 2 (2.4)           | 4 (3.0)           |
| Long philtrum              | 10 (6.5)          | 3 (4.1)           | 4 (4.9)           | 6 (4.4)           |
| Broad philtrum              | 8 (5.2)           | 3 (4.1)           | 3 (3.7)           | 6 (4.4)           |
| Downslanted palpebral fissures | 7 (4.5)   | 5 (6.8)           | 4 (4.9)           | 7 (5.2)           |
| Low-set ears                | 7 (4.5)           | 2 (2.7)           | 3 (3.7)           | 6 (4.4)           |
| Broad eyebrow               | 6 (3.9)           | 2 (2.7)           | 6 (7.3)           | 10 (7.4)          |
| Downturned corners of mouth| 5 (3.2)           | 7 (9.6)           | 5 (6.1)           | 7 (5.2)           |
| Sparse eyebrow              | 5 (3.2)           | 4 (5.5)           | 3 (3.7)           | 6 (4.4)           |
| Prominent nasal bridge      | 5 (3.2)           | 4 (5.5)           | 3 (3.7)           | 5 (3.7)           |
| Chin with horizontal crease | 5 (3.2)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Underdeveloped nasal alae  | 5 (3.2)           | 1 (1.4)           | 0 (0)             | 1 (0.7)           |
| Triangular face             | 4 (2.6)           | 1 (1.4)           | 1 (1.2)           | 3 (2.2)           |
| Broad nasal tip             | 4 (2.6)           | 1 (1.4)           | 3 (3.7)           | 3 (2.2)           |
| Pointed chin                | 4 (2.6)           | 0 (0)             | 1 (1.2)           | 1 (0.7)           |
| Ptosis                      | 3 (1.9)           | 1 (1.4)           | 4 (4.9)           | 5 (3.7)           |
| Absent cupid's bow          | 3 (1.9)           | 4 (5.5)           | 1 (1.2)           | 5 (3.7)           |
| Hypotelorism                | 3 (1.9)           | 3 (4.1)           | 2 (2.4)           | 3 (2.2)           |
| Short philtrum              | 3 (1.9)           | 1 (1.4)           | 2 (2.4)           | 2 (1.5)           |
| Infra-orbital fold          | 3 (1.9)           | 1 (1.4)           | 0 (0)             | 2 (1.5)           |
| Smooth philtrum             | 3 (1.9)           | 0 (0)             | 1 (1.2)           | 1 (0.7)           |
| Malar flattening            | 2 (1.3)           | 2 (2.7)           | 0 (0)             | 2 (1.5)           |
| Exaggerated cupid's bow     | 2 (1.3)           | 0 (0)             | 3 (3.7)           | 3 (2.2)           |
| Tented upper lip vermilion  | 2 (1.3)           | 1 (1.4)           | 1 (1.2)           | 1 (0.7)           |
| Narrow forehead             | 2 (1.3)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Sparse scalp hair           | 2 (1.3)           | 3 (4.1)           | 1 (1.2)           | 3 (2.2)           |
| Anteverted nares            | 2 (1.3)           | 1 (1.4)           | 2 (2.4)           | 3 (2.2)           |
| Bony paranasal bossing      | 2 (1.3)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Epicanthus                  | 1 (0.1)           | 0 (0)             | 3 (3.7)           | 4 (3.0)           |
| Chin dimple                 | 1 (0.1)           | 2 (2.7)           | 2 (2.4)           | 2 (1.5)           |
| Proptosis                   | 1 (0.1)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Thick eyebrow               | 1 (0.1)           | 0 (0)             | 1 (1.2)           | 1 (0.7)           |
| Ectropion                   | 1 (0.1)           | 0 (0)             | 1 (1.2)           | 1 (0.7)           |
| Short nose                  | 1 (0.1)           | 0 (0)             | 0 (0)             | 1 (0.7)           |
| Everted lower lip vermilion | 1 (0.1)           | 1 (1.4)           | 0 (0)             | 1 (0.7)           |
| Hypertelorism               | 1 (0.1)           | 1 (1.4)           | 3 (3.7)           | 3 (2.2)           |
| Synophrys                   | 1 (0.1)           | 1 (1.4)           | 0 (0)             | 1 (0.7)           |
| Thin upper lip vermilion    | 1 (0.1)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Overfolded helix            | 1 (0.1)           | 0 (0)             | 0 (0)             | 0 (0)             |
| Prominent helix             | 1 (0.1)           | 0 (0)             | 0 (0)             | 0 (0)             |
Facial morphological variants by NDDs

Individuals with a diagnosis of any NDD had a median of 1 facial morphological variant, with a range of 0–8 (Table 1). There was no significant difference in the number of facial morphological variants in those with NDDs versus those with typical development ($p = .280$). The most common facial morphological variants were thick upper lip vermilion (21.5% of sample), abnormality of the nasal tip (17%), long face (17%), and upslanted palpebral fissure (17%) (Table 3). No significant association existed between a diagnosis of any NDD and the number of facial morphological variants (OR = .937, 95% CI = .822–1.068, $p = .330$). The OR here represents the change in odds of the presence of a diagnosis based per additional facial morphological variant. There were no statistically significant associations identified between a diagnosis of any NDD and facial morphological variants in the within-pairs model or when looking at MZ or DZ only twins, nor when we controlled for IQ (Table 4).

Facial morphological variants by ASD

Individuals with a diagnosis of ASD had a median of 1 facial morphological variant, with a range of 0–8 (Table 1). The most common facial morphological variants were thick upper lip vermilion (21.5% of sample), abnormality of the nasal tip (19.5%), upslanted palpebral fissure (15.9%), and long face (15.9%) (Table 3). No significant association existed between a diagnosis of ASD and the number of facial morphological variants (OR = .951, 95% CI = .819–1.103, $p = .505$). There were no significant associations identified between a diagnosis of ASD and facial morphological variants in the within-pairs model or when looking at MZ or DZ only twins, nor when we controlled for IQ (Table 4).

Facial morphological variants by ADHD

Individuals with a diagnosis of ADHD had a median of 1 facial morphological variant, with a range of 0–8 (Table 1). The most common facial morphological variants were thick upper lip vermilion (21.2% of sample), upslanted palpebral fissure (19.5%), abnormality of the nasal tip (15.9%), and long face (15.9%) (Table 3). No significant association existed between a diagnosis of ADHD and the number of facial morphological variants (OR = .936, 95% CI = .792–1.106, $p = .438$). There were no significant associations identified between a diagnosis of ADHD and facial morphological variants in the within-pairs model or when looking at MZ or DZ only twins, nor when we controlled for IQ (Table 4).

Receiver operating characteristic curve analysis in NDDs

Receiver operating characteristic curve analysis was conducted to assess the performance of the Face2Gene software in discriminating the facial images of individuals with typical development ($n = 121$) to those with a diagnosis of any NDD ($n = 113$). The area under the curve was .521 (95% CI = .462–.580, $p = .371$), representing poor accuracy in distinguishing participants with NDD from TD. Additional receiver operating characteristic curve analyses were performed comparing those with diagnoses of ASD ($n = 60$) and ADHD ($n = 67$), respectively, to those with typical development ($n = 121$). The area under the curve was .485 (95% CI = .387–.583, $p = .589$) for ASD versus typical development and .577 (95% CI = .459–.695, $p = .205$) for ADHD versus typical development, representing poor accuracy in distinguishing those with diagnoses of ASD or ADHD from those with typical development. The gestalt images produced by Face2Gene which include computer-generated faces that demonstrate the

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**Table 3 (Continued)**

| Facial morphological variant | TD ($n = 155$) n (%) | ASD ($n = 73$) % (n) | ADHD ($n = 82$) % (n) | NDD ($n = 135$) % (n) |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Wide nasal bridge          | 1 (0.1)             | 0 (0)               | 0 (0)               | 0 (0)               |
| Strabismus                 | 1 (0.1)             | 0 (0)               | 0 (0)               | 0 (0)               |
| Telecanthus                | 1 (0.1)             | 0 (0)               | 0 (0)               | 0 (0)               |
| Blepharophimosis           | 1 (0.1)             | 0 (0)               | 0 (0)               | 0 (0)               |
| Medial flaring of the eyebrow | 1 (0.1)         | 0 (0)               | 0 (0)               | 0 (0)               |
| Tented philtrum           | 1 (0.1)             | 0 (0)               | 0 (0)               | 0 (0)               |
| Deep philtrum              | 0 (0)               | 0 (0)               | 1 (1.2)             | 1 (0.7)             |
| High anterior hairline     | 0 (0)               | 0 (0)               | 1 (1.2)             | 1 (0.7)             |
| Depressed nasal bridge     | 0 (0)               | 0 (0)               | 1 (1.2)             | 1 (0.7)             |
| Facial asymmetry           | 0 (0)               | 0 (0)               | 1 (1.2)             | 1 (0.7)             |

**Abbreviations:** ADHD, Attention-Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; NDD, Neurodevelopmental Disorder; TD, Typical Development.

*Minor physical anomaly.

Using the GEE model to compare those with typical development to those with a diagnosis of an NDD, significant differences ($p < .001$) exist for noted morphological variants. Due to the comorbidity of NDD diagnoses and some participants having more than one NDD diagnosis, comparisons between groups of NDDs were not performed.
## Table 4: Between- and within-pair associations: number of facial morphological variants and NDD diagnoses

| Dimensional variables | Between-pair estimate | Within-pair estimate | MZ only within-pair estimate | DZ only within-pair estimate |
|-----------------------|-----------------------|----------------------|-----------------------------|-----------------------------|
|                       | $\hat{\beta}$ | 95% CI ($\hat{\beta}$) | $p$ | $\hat{\beta}$ | 95% CI ($\hat{\beta}$) | $p$ | $\hat{\beta}$ | 95% CI ($\hat{\beta}$) | $p$ | $\hat{\beta}$ | 95% CI ($\hat{\beta}$) | $p$ |
| IQ and facial variant  | No adjustments          | $-0.41$ | $-1.64$ to $0.82$ | $0.515$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
|                       | Adjusted for IQ         | $-1.790$ | $-4.082$ to $0.51$ | $0.126$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
| SRS and facial variant | No adjustments          | $-1.317$ | $-3.975$ to $1.180$ | $0.288$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
|                       | Adjusted for IQ         | $-1.790$ | $-4.082$ to $0.51$ | $0.126$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
| CBCL/ABCL and facial variant | No adjustments          | $-1.561$ | $-3.661$ to $0.538$ | $0.145$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
|                       | Adjusted for IQ         | $-1.790$ | $-4.082$ to $0.51$ | $0.126$ | $-1.538$ | $-2.961$ to $-0.115$ | $0.034$ | $-1.382$ | $-3.534$ to $0.770$ | $0.208$ | $-1.662$ | $-3.596$ to $0.271$ | $0.092$ |
| Categorical diagnoses | Any NDD and facial variant | No adjustments | $-0.06$ | $-0.196$ to $0.066$ | $0.330$ | $-0.088$ | $-0.373$ to $0.197$ | $0.545$ | $0.135$ | $-0.342$ to $0.612$ | $0.579$ | $-0.209$ | $-0.563$ to $0.145$ | $0.247$ |
|                       | Adjusted for IQ         | $-0.098$ | $-0.228$ to $0.031$ | $0.138$ | $-0.290$ | $-0.666$ to $0.085$ | $0.129$ | $-0.097$ | $-0.909$ to $0.714$ | $0.814$ | $-0.444$ | $-0.907$ to $0.018$ | $0.060$ |
|                       | Any NDD and facial variant | No adjustments | $-0.51$ | $-0.200$ to $0.098$ | $0.505$ | $0.013$ | $-0.307$ to $0.332$ | $0.937$ | $0.272$ | $-0.251$ to $0.794$ | $0.308$ | $-0.159$ | $-0.553$ to $0.234$ | $0.428$ |
|                       | Adjusted for ADHD       | $-0.036$ | $-0.188$ to $0.116$ | $0.642$ | $-0.026$ | $-0.361$ to $0.309$ | $0.879$ | $0.096$ | $-0.510$ to $0.701$ | $0.756$ | $-0.142$ | $-0.521$ to $0.238$ | $0.465$ |
|                       | Adjusted for NDDs       | $-1.653$ | $-1.86$ to $1.124$ | $0.693$ | $-0.009$ | $-0.357$ to $0.340$ | $0.961$ | $0.219$ | $-0.458$ to $0.894$ | $0.526$ | $-0.149$ | $-0.519$ to $0.221$ | $0.430$ |
|                       | Adjusted for IQ         | $-0.089$ | $-0.254$ to $0.076$ | $0.288$ | $-0.075$ | $-0.390$ to $0.241$ | $0.642$ | $-0.063$ | $-0.415$ to $0.850$ | $0.500$ | $-0.306$ | $-0.809$ to $0.197$ | $0.233$ |
|                       | Any NDD and facial variant | No adjustments | $-0.066$ | $-0.233$ to $0.101$ | $0.438$ | $0.108$ | $-0.303$ to $0.520$ | $0.606$ | $0.145$ | $-0.550$ to $0.838$ | $0.683$ | $0.092$ | $-0.411$ to $0.596$ | $0.718$ |
|                       | Adjusted for ADHD       | $-0.058$ | $-0.230$ to $0.114$ | $0.510$ | $-0.054$ | $-0.487$ to $0.378$ | $0.805$ | $-1.295$ | $-3.150$ to $0.561$ | $0.172$ | $0.034$ | $-0.474$ to $0.542$ | $0.896$ |
|                       | Adjusted for NDDs       | $-0.041$ | $-0.206$ to $0.124$ | $0.625$ | $0.015$ | $-0.435$ to $0.465$ | $0.947$ | $-1.046$ | $-2.786$ to $0.695$ | $0.239$ | $0.070$ | $-0.449$ to $0.589$ | $0.792$ |
|                       | Adjusted for IQ         | $-0.083$ | $-0.248$ to $0.082$ | $0.323$ | $0.015$ | $-0.432$ to $0.463$ | $0.946$ | $0.156$ | $-0.738$ to $1.053$ | $0.730$ | $-0.003$ | $-0.561$ to $0.554$ | $0.990$ |

**NOTE:** The significance for bold values in table 4 is $p < .05$.

Abbreviations: ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; Facial Variant, Facial Morphological Variant score; IQ, intelligence quotient; NDD, neurodevelopmental disorder; OR, odds ratio.
features that are present in participants with typical development and each NDD diagnosis are found in Figure 1.

5 | DISCUSSION

This study compared the identification of facial morphological variants through in-person clinical assessment with those identified through an automated system, Face2Gene. The results of the study demonstrate a high level of agreement between the two types of assessments. The Face2Gene system was able to identify some commonly occurring facial morphological variants (i.e., thick upper lip vermilion, abnormality of the nasal tip, long face, and upslanted palpebral fissure) that were present in individuals with both typical development and those with NDDs. However, despite the presence of several facial morphological variants, the overall amount in participants was not related to diagnoses of NDDs. Using conditional regression analyses, the study did find an association between lower IQ and increasing facial morphological variants within twin pairs. The within-pairs model accounts for shared genetic and environmental factors within twins and significance indicates possible nonshared environmental influences on the variable of interest (i.e., IQ). Finally, receiver operating characteristic curve analyses comparing typically developing individuals with NDDs were not able to distinguish between the photos of participants based on facial features alone.

Previous studies exploring morphological variants in individuals with NDDs have primarily focused on in-person clinical assessments that spanned the entire body from head to toe (Accardo, Tomazic, Morrow, Haake, & Whitman, 1991; Angkustsiri et al., 2011; Manouilenko, Eriksson, Humble, & Bejerot, 2014; Minahim & Rohde, 2015; Myers et al., 2017; Ozgen et al., 2011; Ozgen et al., 2013; Tamimies et al., 2015; Tripi et al., 2008). However, it has been said that "the face predicts the brain" (Demyer, Zeman, & Palmer, 1964) and both the face and brain are developing simultaneously in utero (Marcucio et al., 2015). Therefore, researchers and clinicians alike have explored facial features to identify individuals with disorders, such as ASD and ADHD, who may also have altered brain development and functioning.

Although it may make sense from a biological standpoint to focus on just the face in the physical examination of individuals with NDDs due to its similarly timed development of the face alongside the brain, a complex interplay between environments and genetics is believed to be involved in the development of specific NDDs like ASD (Bölte, Girdler, & Marschik, 2018; Lai, Lombardo, & Baron-Cohen, 2014; Sahin & Sur, 2015) and ADHD (Faraone & Larsson, 2018; Thapar & Cooper, 2016). As a result, the presentation of these disorders in individuals can be highly variable. Therefore, limiting the clinical assessment of an individual with an NDD to the facial region only may fail to detect features on other areas of the body that were affected during early development and are related to genetic and/or environmental factors. In a previous study by our research group (Myers et al., 2017), we found individuals with NDDs had increased amounts of morphological variants outside of the facial region like hypermobility, being overweight, arachnodactyly or long toes, or pes planus. Therefore, it appears that focusing on just the facial region and using the number of morphological variants in this area of the body alone may be associated with a significant loss of information regarding the presence of morphological variants in NDDs. Indeed, our study, which is the first known to explore distinct facial morphological variants that can be identified through both clinical and automated assessment, failed to demonstrate a relationship between the presence of facial morphological variants and those with diagnoses of NDDs in a large sample of twins.

Although past studies on morphological variants have suggested certain variants and measurements to be present in greater amounts in individuals NDDs compared with controls (e.g., Aldridge et al., 2011; Ozgen et al., 2013; Tripi et al., 2008), the findings across studies are variable and no consistent set of variants or measurements have been identified that can be used for early screening of NDDs. Instead, some researchers have focused more broadly on what they have
termed dysmorphism, or the presence of abnormal physical traits identified through clinical assessment. In fact, Miles and Hillman (2000) published a study purporting the “Value of a Clinical Morphology Examination” in the assessment of individuals with ASD specifically to identify dysmorphism in the form abnormal physical traits. Miles and Hillman’s study results indicated that the clinical morphology exam was valuable in identifying children with increased morphological variants that correlated with the presence of genetic syndromes and abnormal brain MRI findings. Later, Miles et al. (2005) classified 260 children with ASD who were dysmorphic (had six or more morphological variants) and had microcephaly as having “complex autism,” while those who were not dysmorphic (had less than three morphological variants) as having “essential autism.” Miles et al. (2005) found that children with “complex autism” were more likely to have lower IQs, more seizures, and abnormal electroencephalograms and magnetic resonance imaging exams compared with those with “essential autism.” Through genetic testing, all the individuals in the study by Miles et al. who had an identifiable genetic syndrome were correctly placed in the “complex” group. Similarly, Tamimies et al. (2015) found a relationship between increased morphological variants in individuals with genetic and brain abnormalities, who also had a diagnosis of ASD.

Despite best practice guidelines for physical examinations during the diagnostic process for NDDs (Johnson et al., 2007; National Institute for Health and Care Excellence, 2018; Subcommittee on Attention-Deficit/Hyperactivity Disorder Steering Committee on Quality Improvement Management et al., 2011), these examinations can be time-consuming, costly, and subjective and it is unknown how many children and young adults actually receive these examinations. Health care providers performing assessments for morphological variants in particular need to be highly trained and may require years of experience seeing patients with dysmorphic features before they are able to detect these often subtle variants. Therefore, the potential for automated assessments (such as Face2Gene) that may help improve accuracy and reduce the time and costs associated with in-person clinical assessments is promising. However, further research is needed, especially with automated systems that explore morphological variants in the entire body, since our study showed that focusing only on the assessment of facial morphological variants was not able to distinguish participants with NDDs from those with typical development.

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CONFLICT OF INTERESTS

All authors declare no direct conflict of interest related to this article. S.B. discloses that he has in the last 5 years acted as an author, consultant, or lecturer for Shire, Medice, Roche, Eli Lilly, Prima Psychiatry, GLGroup, System Analytic, Ability Partner, Kompetento, Expo Medica, and Prophase. S.B. receives royalties for textbooks and diagnostic tools from Huber/Hogrefe, Kohlhammer, and UTB.

AUTHOR CONTRIBUTIONS

L.M. analyzed the data, drafted the manuscript, and made the final edits to the revised manuscript. B.A. and A.N. conducted the clinical assessments for the study and provided a critical review of the manuscript. K.L. provided content related to the diagnostic process used in the RATSS study and provided a critical review of the manuscript. R.H.K. developed the statistical models used for analysis in the study and provided a critical review of the statistical procedures and the overall manuscript. K.T. provided support with the design of the study and provided a critical review of the manuscript. S.B. designed the overall RATSS study and assisted with design of this study, along with drafting and revision of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed in this study are not publicly available due Swedish privacy laws but are available from the senior author on reasonable request.
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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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