Cancer predisposition in children: genetics, phenotypes & screening
Hopman, Saskia

Citation for published version (APA):
3D Morphometry enhances facial analysis of individuals with a childhood cancer

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Submitted
Abstract

A group of patients who had cancer as a child were previously found to have distinct patterns of morphological abnormalities. In this study, we investigated the added value of 3D shape analysis to characterize their facial morphology. Primarily, we showed in an objective and quantitative manner that the overall facial dysmorphism of the individuals who had had a childhood cancer was significantly greater than that of the controls. We also demonstrated how the same approach can be used to detect a similar disparity for a more localized malar region comprising customized disconnected patches defined on both sides of the face. In addition, by comparing original face surfaces to their mirrored forms, we confirmed that the patient group had significantly greater facial asymmetry than the controls. Each of these results made use of surface shape differences not detectable by simple linear or angular characteristics as might be used in analyses based on measures captured manually or derived from landmarks annotating 2D photographic images.

We conclude that 3D morphometric analysis of a relatively small heterogeneous patient group can further delineate face shape differences from typically developing individuals that are too subtle or geometrically complex to identify or quantify objectively with conventional clinical and anthropometric approaches.
Introduction

Many genetic syndromes involve facial morphological characteristics, and the facial ‘Gestalt’ can be an important clue in the identification of genetic conditions. We also know that in tumor predisposition syndromes, the constitutional molecular defects that lead to oncogenesis may also play an important role in facial development. Traditionally, anthropometry has been an important tool in analyzing the phenotype of an individual. It has the disadvantage of inter-observer variability and requires prolonged co-operation of the subject as well as their presence for capturing additional measurements. This limits the use of anthropometry on children or individuals with an intellectual disability. Two-dimensional photography overcomes some of these limitations, but the quality and usability of a 2D picture is highly dependent on the experience of the photographer and cooperation, pose and lighting of the subject.

Three-dimensional (3D) photogrammetric images are independent of pose, and offer repeat measurement without the subject’s presence or prolonged cooperation. Typically, 3D face images are annotated with anatomical landmarks to produce linear and angular measurements. For facial analysis, dense surface modelling (DSM) techniques induce tens of thousands of densely corresponded points as quasi-landmarks from a small number of manually placed landmarks. Using DSMs, the average surface of a group of faces can be computed and quantitative shape comparisons of face surfaces can be performed between individuals or relative to ethnically, age- and sex-matched means. DSM based analysis has successfully delineated the facial phenotype of a variety of neurodevelopmental conditions.

In a previous study, we used ‘traditional’ anthropometry and morphological examination in a cohort of 1,073 individuals who had cancer as a child, and compared these to 1,007 healthy schoolchildren. We demonstrated significantly increased incidence of morphological abnormalities and high prevalence of syndromes. Furthermore, we described four new patterns of co-occurring morphological abnormalities as tumor predisposition syndromes. These were named after key abnormalities: “blepharophimosis (BP) pattern”, “epicanthal folds (EF) pattern”, “asymmetric lower limbs (LLA) pattern” and “Sydney creases (SC) pattern” (Table 1). The structural genomic variants identified in these patients were reported recently. The purpose of this study is to bear in mind the results of the traditional morphological examination and anthropometry and determine the added value of 3D facial morphometry. More specifically, we used 3D dense surface modelling techniques: to reconfirm the greater facial dysmorphism found previously in childhood cancer patients compared to controls; to show how to objectify shape characteristics of a geometrically complex facial region, e.g. the malar region, that previously could only be evaluated subjectively; and, to identify additional morphological signs, namely facial asymmetry, that were previously undetected.
Chapter 5

Subjects and methods

Because of recent findings of face-shape differences even in phylogenetically-related populations, we confined our analyses to subjects of self-reported Dutch descent. Forty-nine childhood cancer patients, previously designated as showing one of four patterns of morphological abnormalities were asked to participate and only one declined. The 3D photos of 7/48 patients were excluded for technical reasons or due to their non-Dutch descent. The characteristics of the patient subgroups are shown in Table 2.

Table 1: Summary of patterns of statistically significant co-occurring morphological abnormalities and number of patients in each pattern for 3D analyses. In the current study 41 patients were available for 3D facial analyses. The patients from the current cohort were selected from a large prospective cohort of childhood cancer patients and all showed one of the four patterns of statistically significant co-occurring morphological abnormalities. The table shows the criteria for each of the patterns and the number of patients included from each pattern, based on the morphological examination by Merks et al. (partly described in 10). This table is adapted from 11.

* = Modified according to Elements of Morphology nomenclature 19-26.

<table>
<thead>
<tr>
<th>Name pattern of co-occurring morphological abnormalities</th>
<th>Morphological abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLEPHAROPHIMOSIS PATTERN (n=10)</td>
<td>≥2 of the following:</td>
</tr>
<tr>
<td></td>
<td>Blepharophimosis</td>
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<tr>
<td></td>
<td>Patchy hypopigmentation</td>
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<tr>
<td></td>
<td>Café-au-lait spots</td>
</tr>
<tr>
<td></td>
<td>Increased angulation of the spine</td>
</tr>
<tr>
<td>ASYMMETRIC LOWER LIMBS PATTERN (n=17)</td>
<td>≥2 of the following:</td>
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<tr>
<td></td>
<td>Asymmetric lower limbs</td>
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<tr>
<td></td>
<td>Tall stature</td>
</tr>
<tr>
<td></td>
<td>Ptosis</td>
</tr>
<tr>
<td></td>
<td>Malar flattening*</td>
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<tr>
<td></td>
<td>Pectus carinatum or pectus excavatum</td>
</tr>
<tr>
<td>EPICANTHAL FOLDS PATTERN (n=8)</td>
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<tr>
<td></td>
<td>Epicanthus*</td>
</tr>
<tr>
<td></td>
<td>Flat wide nose, broad nasal tip, wide nasal ridge*</td>
</tr>
<tr>
<td></td>
<td>Thick vermillion of the upper and/or lower lip*</td>
</tr>
<tr>
<td></td>
<td>Protruding ears*</td>
</tr>
<tr>
<td></td>
<td>Café-au-lait spots</td>
</tr>
<tr>
<td></td>
<td>Hyperlaxity of joints</td>
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<tr>
<td>SYDNEY CREASE PATTERN (n=6)</td>
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<tr>
<td></td>
<td>Sydney crease</td>
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<td></td>
<td>Fullness of upper eyelid*</td>
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<tr>
<td></td>
<td>Microdontia</td>
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<tr>
<td></td>
<td>Clinodactyly digitus V</td>
</tr>
<tr>
<td></td>
<td>Hypermobility of small joints</td>
</tr>
</tbody>
</table>

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Subjects and methods

Patients and control subjects

Because of recent findings of face-shape differences even in phylogenetically-related populations, we confined our analyses to subjects of self-reported Dutch descent. Forty-nine childhood cancer patients, previously designated as showing one of four patterns of morphological abnormalities were asked to participate and only one declined. The 3D photos of 7/48 patients were excluded for technical reasons or due to their non-Dutch descent. The characteristics of the patient subgroups are shown in Table 2.
The control group consisted of 274 subjects of self-reported Dutch descent recruited from university scientific and hospital medical professionals (81/274, 30%) and unaffected parents and sibs of children with a molecularly proven genetic syndrome who visited out-patient departments or attended family support group meetings (193/274, 70%). The composition and average ages of patient and control groups are shown in Table 3.

**Image capture and preparation**

3D facial imaging was undertaken using commercial stereo-photogrammetric cameras able to capture more than 25,000 3D points on an adult face surface (Canfield Imaging Systems, New Jersey, USA; 3dMD, Atlanta, USA). Each face image was manually annotated using in-house software with 22 landmarks previously shown to be reliable and reproducible. The landmarks were used to induce a dense correspondence across all subjects of all 25,000+ surface points. A DSM of all faces in the dataset was generated as the set of principal component analysis (PCA) modes covering 99% of shape variation of face shape difference from the overall mean face. DSM construction involved methods developed in-house which are described elsewhere.

Subjective morphological signs that show differences in a specific direction were evaluated along an appropriate axis (lateral, vertical, anterior-posterior) and in a model confined to...
a region containing the sign under study. Separate DSMs of the reduced face without ears and the malar region (Figure 2A) were computed. Ears were omitted because of their frequent partial, or occasional complete, occlusion by hair.

Statistical analyses

For the continuous outcome variables with a normal distribution, student-t-tests were performed using a significance level of 0.05. For t-tests, only the controls in the patient defined age range of 10 to 40 years were included. Anthropometric calculations and t-tests were performed in Excel (Microsoft Office 2010) and StatPlus (AnalystSoft, version 5.7.5). In order to maximize the analysis of the relatively small number of female patients, male and female asymmetry measures were adjusted for sex and age based on the control population before combined analysis. Age adjustment was achieved using separate age-based linear regressions for male and female controls, and the formula:

\[ \text{adjusted} = \frac{\text{original} - m \times \text{age} - c}{\sqrt{1 + m^2}} \]

where \( y = m \times x + c \) is the equation of the regression line for original against age. Following age adjustment, z-scores were computed based on means and standard deviations for the appropriate age range and same sex controls.

Face signatures and colour-coded heat maps of average and individual faces

Each individual was matched with 50 age-contiguous same sex controls whose mean age most closely matched that of the individual. The displacements of the densely corresponded points on an individual’s face were normalized with respect to corresponding displacements on the faces of matched controls to produce a face signature. In order to match the age range of the patient group, only control subjects aged between 10 and 40 years were included in signature graph analysis (the full age range was employed when selecting age-sex matched controls).

Individual face signatures were heat mapped to visualize normalized shape differences from matched controls using a red-green-blue colour scale at min-0-max units of standard deviation for appropriate minima and maxima (-2SD and +2SD unless otherwise stated). Thus, for differences normal to the face surface, the red/green/blue spectrum corresponded to contraction/coincidence/expansion of the surface being compared. Analogous processes produce signatures for surface shape differences parallel to lateral, vertical, and depth (anterior-posterior) axes. The signature weight of an individual face or face patch (square root of the sum of the squared normalized differences orthogonal to the face surface for all relevant points) reflects the deviation of a subject from matched controls and was used as an estimate of dysmorphism.

A face signature graph is constructed using face signatures as vertices or nodes and a directed edge links each vertex to its most “similar” signature. An alternative, but topologically identical, “coloured” form of a face signature paints the vertices to reflect a diagnostic or
other subgroup labelling such as control-patient dichotomy or tumor disposition pattern. Finally, a “coloured” signature graph can be “collapsed” to a simplified form where vertices represent clusters of same-coloured connected vertices of the original. An entropy-like measure is used to summarize the associated clustering or dispersion of the members of each labelled subgroup. The lower the dispersion factor of a labelled subgroup, the stronger is the similarity of the facial dysmorphism of subcluster members compared to other subgroups. A maximum dispersion factor of 1.00 means that a subgroup’s members are perfectly dispersed into singleton subsets and so do not cluster at all because they lack homogeneity and differ from other labelled subgroups in their dysmorphism. All signature graphs were drawn using the open source software GraphViz (version 2.26, www.graphviz.org).

Facial asymmetry
As in previous studies of facial asymmetry, we constructed a DSM containing the original and reflected face surfaces of all study participants. We estimated individual facial asymmetry as the generalized Euclidean distance between the DSM representations of the original and mirrored face surfaces. This was adjusted to take age and sex into consideration since there are gender differences and asymmetry tends to increase with age within the general population.

Results
1. The individuals with a childhood cancer have greater facial dysmorphism than age-sex-ethnicity matched controls but no set of common dysmorphic features, not even within the tumor predisposition patterns found previously.

The heat mapped signatures in Figure 1A delineate localized individual facial dysmorphism of 12 female (row 1) and 29 male patients of Dutch descent (rows 2 to 4). This visualization of detailed face shape differences offers an objective adjunct to clinical examination. It is possible to identify small subgroups of patients with a similar heat map highlighting similar facial dysmorphism such as malar flattening (anterior red patches on cheeks of LLA_9, LLA_24, LLA_34, LLA_43), perioral insufficiency (red regions around mouths of LLA_29, LLA_45, SC_3, SC_26, LLA_29) and mid-facial hyperplasia (blue patches on midface of EF_2, EF_7, LLA_20). However, overall, there is considerable heterogeneity in the facial dysmorphism of the patient group. This is confirmed in the collapsed form of the face signature graph for controls and patients (Figure 1C and 1D) with dispersion factors of 0.94 for patients and 0.16 for controls, and the patient group’s clustering as a large number of singletons, a few duos and a quartet.

The location of patients in the periphery or as terminal nodes of the signature graph for controls and patients is as a result of their greater facial dysmorphism (Figure 1B).
Figure 1. Face signatures of patients; and signature weights and graphs for patients and controls. 

**A:** Heat mapped face signatures of 41 patients of Dutch descent. Each demarcates localized facial dysmorphism using a red/green/blue scale for “below -2SD”/zero SD/”over +2SD” contractive/coincident/expansive surface difference compared to a mean of age-sex-ethnicity matched controls.

**B:** Collapsed version of the face signature graph for patients and controls, shown as empty and filled circles respectively. The annotated dispersion rates, between 0 and 1, summarize the overall clustering of the control and patient signatures. The low value (0.16) for controls and high value for patients (0.94) suggests that the patient dysmorphism is significantly different from the majority of controls. The high value for the patient group also reflects the relatively large number of clusters into which it is decomposed and the lack of homogeneity in the facial dysmorphism of its members.
C: Face signature graph for patients (with square outline) and controls. Typically, in a signature graph the least dysmorphic individuals are located more centrally and the most dysmorphic more peripherally. The location of patient signatures largely at the periphery and terminally reflects their greater facial dysmorphism.

D: Histogram of log-transformed normalized signature weights showing greater overall facial dysmorphism in faces of patients compared to controls.
Furthermore, the associated (log transformed) face signature weight distribution (Figure 1D) confirms a significantly greater mean for patients \(M = 2.20\) compared to controls \(M = 2.14\); \(t(54) = 2.35, p = 0.02\). Inspection of the face signatures in Figure 1A suggests the LLA pattern subgroup to have more red-blue hues than green and hence to be more facially dysmorphic. Some quantitative evidence for this is seen in a control vs pattern histogram of signature weights (Supplementary Figure 1) but the relatively low numbers in the other pattern subgroups rather undermines such cross pattern comparisons.

2. The malar region is more dysmorphic in patients compared to controls

Although, as shown above, there was no discernible set of common dysmorphic features in the patient group when considering the face in its entirety, the malar region is notably painted red or blue (at 2SD) in a majority of the heat mapped signatures of Figure 1A. This clinical observation suggested that the malar region should undergo closer objective scrutiny. Given the complex geometry of the malar region, this would be impossible using linear or angular measures derived solely from landmarks. In order to investigate malar dysmorphism, a customized region was demarcated as depicted in Figure 2A.

The distribution of signature weight as a measure of dysmorphism for the malar region is shown in the histogram in Figure 2B. The malar dysmorphism score is indeed significantly higher in patients \(M = 1.81\) compared to controls \(M = 1.74\); \(t(58) = 2.93, p = 0.004\). The collapsed signature graph for the malar region for controls and patients, as was the case for the face, shows patients to be located more at the periphery, reflecting greater malar dysmorphism. The malar region dispersion factors for controls (0.16) and patients (0.92) also reflect the heterogeneity of the malar dysmorphism for the patients when considered as a whole (Supplementary Figure 2).

Interestingly, the signature graph for differences along the anterior-posterior or z-axis of the malar region for patients alone shows some stronger clustering for LLA patients compared to other pattern subgroups (Figure 2C). This is more clearly shown in the collapsed form of the signature graph and the lower dispersion factor (0.66) for LLA-pattern patients (Figure 2D). In comparison, EF-, SC- and BP-pattern patients show dispersion factors of 0.83, 0.87 and 1.00 respectively. This suggests that the LLA-pattern subgroup of these 41 patients are more similar in their malar flattening or malar prominence than patients from the other pattern subgroups (Figure 2D).

3. Patients have significantly greater facial asymmetry when compared to controls

The PCA-vector representation of each original face surface was subtracted from that for its mirrored form in the DSM generated for all original and mirrored or reflected images. The "size" of this vector difference is an estimate, or index, of the overall asymmetry of the original face surface. Facial asymmetry increases with age and at different rates for females
and males as is shown by the separate female and male scatter plots for the raw asymmetry index against age (Supplementary Figures 3A and 3B)\(^8,26\). When adjusted for age (linear regression adjusted) and z-scored for gender within the approximate patient age range of 10 to 40 years, there was significantly greater asymmetry in patients (\(M = 0.75\)) compared to controls (\(M = 0; t(52) = 2.2, p = 0.03\)).

This greater facial asymmetry for patients compared to controls can also be appreciated on an individual basis by interpreting the PCA vector difference between original and mirrored DSM PCA vectors as a surface in the DSM model. The resulting original-reflected difference for each patient can then be normalized against corresponding control differences just as for signatures for the original faces. Thus, corresponding to the gallery of face signatures of Figure 1 is another showing normalized asymmetry differences from the asymmetry of age-sex matched controls in the form of heat mapped facial asymmetry signatures (Figure 3A). Once again, it is possible to discern subgroups, this time with similar asymmetry dysmorphism. This is more easily observed by considering the induced clustering in the asymmetry signature graph of the patients alone (Figure 3B). Of the seven subclusters within the graph, subcluster 2 contains a duo of faces showing almost no difference (mostly green hue) from the asymmetry of age-sex-ethnicity matched controls. Subcluster 3 contains 8 individuals displaying a right dominant asymmetry difference from controls in the supraorbital region (blue above right eye, red above left eye). Indeed, the faces in subclusters 3, 4 and 5, below and to the left of subcluster 2, largely show right dominant asymmetry differences from controls, whereas subclusters 1, 6 and 7, above and to the right of subcluster 2, largely include individuals with more left dominant asymmetry. It also noticeable that most mandibular asymmetry occurs in the EF pattern. However, the small sizes of the pattern subgroups in this patient population somewhat undermines such attempts to hypothesize about intra-pattern similarities and inter-pattern differences.

**Discussion**

The main purpose of this study was to identify additional benefits that 3D facial morphometry might offer beyond the clinical and classical anthropometric facial analysis carried out in the origin Merks et al study\(^9\) of more than 1,000 individuals who had suffered a childhood cancer and a similarly sized group of controls. In the previous study, tumor predisposing syndrome patterns were identified by considering not just the face but other physical attributes as well. Inevitably, in this study of only faces, and in less than 3% of the original patient cohort, it was unlikely that the original patterns could be confirmed or that novel patterns might emerge. With the future study in mind of tens of thousands of individuals who have had a childhood cancer, it was more important that this study determine how best to exploit 3D facial morphometric analysis in the future on a much larger scale and in a much more heterogeneous population than has generally been undertaken hitherto.
**Figure 2.** Malar region definition, signature weight (for anterior-posterior depth axis)

**A:** A butterfly-shaped patch of the face surface was used to demarcate a malar region. The right inner canthus ($IC_R$) was connected with the right exocanthus ($OC_R$) following the lower orbit border. The right exocanthus was connected with the right lower ear attachment ($LEA_R$) and the upper ear attachment ($UEA_R$) was connected with the right cheilion ($CH_R$); their crossing formed the lateral border. For the medial border, the right cheilion was connected with the right inner canthus following the nasolabial fold. All connecting curves followed the surface. The same procedure was repeated for the left side.

**B:** Histogram of log-transformed normalized signature for the malar region of patients compared to controls.
C: Signature graph for differences along the anterior-posterior axis for the malar region. Each malar signature is annotated by an outline of a different colour depending on its pattern label: BP-green; EF-black; LLA-blue; SC-red.

D: Collapsed version of signature graph shown in C using the same colour coding of pattern labels.
Rather than investigate individual linear or angular measures derived from landmarks, we employed signature based analysis where surface shape differences at 25,000+ surface points are normalized against age-sex-ethnicity matched controls for the whole face, for face patches and for the difference between an original face and its mirrored or reflected form. We used heat maps of the signatures to delineate individual localized dysmorphism. The “weight” of the signatures was used to estimate an index of dysmorphism, through which we established statistically significant differences between the patients and controls within the same age range. Signature graphs with directed edges linking most similar signatures were used to cluster both controls and patients into subsets with similar dysmorphism i.e. shape differences from age-sex matched controls. Relative central or peripheral position in signature graphs reflected low or high levels of dysmorphism and, in the collapsed form of signature graphs, rates of dispersion quantified overall clustering rates of patients compared to controls and/or between pattern subgroups of patients.

Using the methodological approach summarized above, we detected significantly higher dysmorphism scores (signature weights) for the facial region without ears in the individuals who had cancer as a child. This was also reflected in the corresponding signature graph for controls and patients where the latter patients appeared more in the periphery and as terminal nodes. Common facial differences between patients and controls could not be identified and a high dispersal rate, reflecting lack of similarity clustering of the patient group, provided supporting evidence. Similarly, when considering patients on their own, no intra-pattern similarities or inter-pattern differences were evident in the signatures or the signature graphs.

Based on subjective evaluation of the face signatures, we hypothesized that the malar region of patients was more dysmorphic than in controls. This would be a challenging hypothesis to test using linear or angular measures derived from clinical examination or derived from landmarked photographs. It required an analysis of 3D surface shape. An experienced dysmorphologist (RCMH) defined a customized region to act as the focus for analyzing shape differences in the malar region and as a base shape for constructing DSMs. Following the same methodological sequence as for face shape analysis, we established significantly greater dysmorphism of the malar region in the patients compared to controls. Once again, shape signature graphs were used to confirm this. In terms of intra-pattern analysis of anterior-posterior malar shape difference, the LLA pattern subgroup produced a lower dispersion rate suggesting some commonality of form for malar flattening or prominence. Finally, we identified increased facial asymmetry in patients compared to controls. This could have been an effect of therapy that childhood cancer patients may have received. However, patients who had undergone radiotherapy in the facial region were excluded. Therefore, the increased facial asymmetry in patients is more likely to reflect ‘intrinsic asymmetry’ rather than asymmetry caused by external effects. Asymmetry occurs frequently in genetic conditions associated with a malignancy. For example, it is a well-known feature in Bannayan-Riley-Ruvalcaba syndrome (BRRS, OMIM: 153480) and Beckwith-Wiedemann Syndrome.
3D Morphometry enhances facial analysis of individuals with a childhood cancer

Figure 3 Facial asymmetry signatures and associated graph for patients A. Heat mapped face asymmetry signatures of 41 patients of Dutch descent. Each demarcates differences of original and reflected surfaces for each patient normalized to similar differences of matched controls using a red/green/blue scale for “below -2SD”/zero SD/“over +2SD”. Each heat map will necessarily be anti-symmetric in its red-blue colouring since the right sided differences of original surface face compared to its reflection or mirrored form will be the opposite for the left side.

B. Signature graph for the signatures in A. Colour outlines are used to identify the pattern subgroup to which an individual belongs: BP-black; EF-red; LLA-green; SC-blue.
(BWS, OMIM: 13060) 17. It should be noted that none of the patient subgroup of this study were diagnosed with established syndromes such as BRRS or BWS. Some potential for inter- and intra-pattern analysis of facial asymmetry was identified for particular parts of the face, e.g. supra-orbit and mandible, and may assist in future determination of face shape differences and even alternative tumor disposition patterns of dysmorphism.

In this project, we used 3D facial photographs and dense surface modelling morphometric techniques to characterize the facial phenotype of a cohort of patients who had cancer as a child, and in whom distinct patterns of morphological abnormalities were previously demonstrated using physical examination and anthropometry 10. The patterns consist of abnormalities located both in the face and in other body parts. As we used only the face, it is impossible to evaluate the complete morphology of patterns this way. Therefore, it was impossible to repeat the grouping of the patients using signature graphs for the complete cohort (1,073 childhood cancer patients) described by Merks et al. 10, blinded from the statistical patterns of co-occurring morphological abnormalities. The relatively small number of individuals of the various patterns and in the total cohort hampers detailed statistical analyses and prevents some subgroup analysis. Another overall limitation of our analysis could be that, in computing face signatures, the age- and sex-matched controls selected are according to a matching running mean age, which could be biased by lack of coverage of certain ages.

Despite these limitations, the 3D face image capture and subsequent analysis has shown significant added value. We conclude that dense surface modelling techniques expand the possibilities for physicians (plastic surgeons, clinical geneticists etc.) to describe and characterize the phenotype of an individual or group of individuals and allow objective comparisons to age- and sex-matched controls. The addition of the approach adopted here in a large, nation-wide study of individuals who have had cancer as a child, together with a recently developed tool to recognize individuals with a high chance to have a tumor predisposition syndrome 18 will allow recognition of larger subgroups within pediatric cancer patients, and allow further characterization of the faces and facilitate subsequent molecular analyses. Such a study is presently in preparation.

Acknowledgements

The authors would like to thank all participants of the study. PH and MS received part funding from the US National Institute on Alcohol and Alcohol Abuse (NIAAA) through a CIFASD developmental grant (www.CIFASD.org). SMJH was supported by the Tom Voûte Fund.
DEFINITIONS AND EXPLANATION OF FREQUENT USED TERMS

**LANDMARKS**: Designated soft tissue points on anatomically well-defined locations.

**DENSE SURFACE MODEL (DSM)**: The actual 3D model, which forms the basis for further 3D analysis. A DSM is built from a set of surfaces of which mean landmarks are calculated using the Procrustes algorithm. The surfaces of the individual subjects are warped to the mean landmarks, aligning them. The points on a selected face can be mapped to the closest points on each face to induce a dense correspondence of tens of thousands of images across all images. The DSM is formed from the principal components covering 99% of shape variation from the overall average based on the densely corresponded points.

**FACE SIGNATURE**: The normalized differences, typically orthogonal to the face surface, of surface point displacements from corresponding positions of the densely corresponded points on the mean surface.

**SIGNATURE WEIGHT**: The square root of the sum of the squared normalized differences for all densely corresponded points.

**FACE SIGNATURE DISTANCE (FSD)**: The Euclidean distance between the vectors representing the normalized differences across the densely corresponded points for two signatures.

**SIGNATURE GRAPH**: Graphical representation of a set of face signatures as vertices. A directed edge is drawn from one signature to another signature with the smallest FSD from the first. In a signature graph, the FSD is the length of the edge between two vertices.

**LINEAR MEASUREMENTS**: Calculations of anthropometric distances using the 3D coordinated of anatomical landmarks.

\[a\] Adapted from 6 and 2
Chapter 5

References

Supplementary data

Supplementary Figure 1
Distribution of face signature weights for controls and pattern specific subgroups of the patient group

FACE SIGNATURE WEIGHT

- BP (n=10)
- EF (n=8)
- LLA (n=17)
- SC (n=6)
- CONTROLS
Supplementary Figure 2

Collapsed signature graph for the malar region showing the dispersion rates of the control and patient groups. The low value (0.16) for controls and high value for patients (0.92) suggests patient malar dysmorphism to be different from the majority of controls. The high value for patients also reflects the relatively large number of clusters and lack of homogeneity in the malar dysmorphism of its members.
Supplementary Figure 3 A/B: Raw facial asymmetry scores
The scatter plots show the age adjusted raw facial asymmetry scores of female (A) and male (B) patients and controls.