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Craniofacial anthropometric measurements of the cohort of Egyptian male school children and their utility in detection of abnormalities

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Abstract

Background Anthropology is a scientific discipline which applies scientific methods to identify and quantitate inter-individual variations in body structure and function. Anthropometry assesses craniofacial dysmorphology in genetic disorders and helps to detect phenotypic differences in diseases with common underlying cause. This study is part of a comprehensive cross-sectional study of craniofacial and oral findings in Egyptian school children. This paper focused on establishing the norms of Egyptian male school children and its utility in determining the differences in facial measurements of a child with Prader–Willi syndrome (PWS). Thirty craniofacial measurements were taken from 55 healthy Egyptian school children aged 12–14 years with mean age 13 ± 0.64 and a PWS child aged 13.6 years. The PWS measurements were compared with healthy children of the same age using computed Z-score.

Results Morphological face height of the PWS child was within the normal range. However, upper face height and nose height were significantly lower with Z-scores of -3.18 and -2.7 , respectively; right and left mandibular body length and upper lip height were significantly higher than the mean of healthy children with corresponding Z-scores of 2.95, 2.48, and 2.33.

Conclusions By establishing the norms of Egyptian male school children and utilizing these data, we can identify the difference in facial measurements among children with abnormalities like PWS. This information can be used during periodic checkups as a simple, non-invasive, and economical method for the detection of these abnormalities.

Keywords Egyptian male children, Craniofacial norms, Clinical application, Prader–Willi syndrome

Background

Anthropometry is the quantitative assessment for the body's physical features, while anthroposcopy is a qualitative method based only on visual examination (Farkas 1994). Qualitative variation in craniofacial morphology should be represented in anthropometric findings (Krogman and İşcan 1986), which add a quantitative extent to clinician observational experience (Ward 1989). Craniofacial anthropometry techniques are based on a series of measurements with subsequent proportions and indices. These measurements aid in the characterization of phenotypic abnormalities and their quantification (Jayaratne and Zwahlen 2014). Normative anthropometric data

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are essential for diagnosis and monitoring patients with craniofacial deformity. Quantifying dysmorphology involves comparing a patient's anthropometric measurements with normative data specific to their race and gender (Farkas et al. 2005). Variations in norm values exist among different ethnic groups (Farkas et al. 2005), emphasizing the importance of utilizing ethnically specific normative data for accurate determination of facial deformities' extent (Jayaratne and Zwahlen 2014).

Prader–Willi syndrome (PWS; MIM #176270) is a rare complex genetic neurodevelopmental multifactorial disorder caused by the deletion or silencing of paternally imprinted genes on chromosome 15q11–q13 (McCandless 2011; Kalsner and Chamberlain 2015). PWS results mainly from a large *de novo* deletion on chromosome 15q11–q13 (~ 60–70% of affected individuals). Approximately 25–35% of the cases were due to maternal uniparental disomy. Defect of the genomic imprinting center occurs in less than 5% of the cases, and cases with sporadic chromosomal translocations or rearrangements were rarely identified (Butler et al. 2019).

PWS disorder is characterized by insatiable appetite leading to obesity (Angulo et al. 2015). Affected children have growth hormone deficiency, if untreated results in decrease growth velocity and subsequent short stature (Bridges 2014). Older children and adults show behavioral problems, intellectual disability, hypoplastic genitalia, small hands and feet, and dysmorphic facial anomalies including narrow forehead, downturned mouth, and almond-shaped eyes (Angulo et al. 2015).

The symptoms of the disease show great variability between patients; this depends on the size of the chromosomal deletion (Costa et al. 2019). A precise definition of the range of facial features of PWS is not available. This may be attributed to the fact that it is a rare complex genetic neurodevelopmental multifactorial disorder; prevalence of PWS ranges from 1–15,000 to 30,000 births having no sex or ethnic predilection (Butler et al. 2002; Vogels et al. 2004; McCandless 2011; Lioni et al. 2015). The disease-causing mechanisms remain unresolved (Kummerfeld et al. 2021), so individual assessment of PWS patients is required.

This endeavor aims to present craniofacial norms of Egyptian male school children and their application in identifying differences in facial measurements of a child with Prader–Willi syndrome.

Methods

A craniofacial anthropometric study was conducted on 55 apparently healthy male Egyptian preparatory school children, aged between 12 and 14 years, with a mean age of 13.1 ± 0.64 . Additionally, a 13.6-year-old PWS case (Fig. 1), who was attending the same school, participated



Fig. 1 A photograph of a male PWS case (13.6 ys)

in the study. The sample was selected from Cairo governorate Egyptian school children. Note that the 55 individuals were specifically selected from the same school as the PWS case and were meeting the defined age and sex criteria. The study objectives and methodology were explained to the participants; informed consent was obtained from their parents/legal guardians. Study ethical approval was obtained from the Medical Research Ethics Committee of National Research Center (MREC-NRC:12113 date 22/11/2016 project n: 11010176). All subjects, excluding PWS case, had acceptable occlusion with full component of permanent dentition and no history of orthodontic treatment.

Taking into consideration the experience of authors (dentists, biological anthropologists, medical geneticists, and molecular geneticist), the selection for apparently healthy children by ruling out others was done based on clinical experience documented by questionnaire signs and symptoms.

The criteria of genetic analysis that could differentiate the PWS syndrome from healthy individuals are qualitative and quantitative confirmed by molecular study. The PWS case showed obesity, short stature, dysmorphic facial anomalies including bitemporal narrowing of forehead, narrow nasal root, almond-shaped eyes, and raised ear lobules as shown in Fig. 1.

The same investigator took thirty craniofacial measurements in each child, including 1 measurement of the head [head circumference], 21 measurements of the face [maxillary arc, left maxillary arc, right maxillary arc,

mandibular arc, left mandibular arc, right mandibular arc, maximum facial breadth, mandibular breadth, right maxillary depth, left maxillary depth, right mandibular depth, left mandibular depth, right mandibular body length, left mandibular body length, right mandibular ramus height, left mandibular ramus height, morphological face height, upper face height, lower face height, anterior mandibular height, and chin height], 2 measurements of the orbit [inter-canthal width, outer-canthal width], 2 measurements of the nose [nose height, nose width], and 4 measurements of the orolabial [philtrum width, philtrum length, labial fissure width and upper lip height]. Figure 2 shows the reference points for the craniofacial measurements. To reduce intra-observer error, each measurement was taken three times to derive an average value for improved accuracy.

The craniofacial measurement of the PWS case aged 13.6 years, was obtained as part of clinical, dental, and molecular (or cytogenetic) examination of this syndrome by team of investigators at National Research Centre, Cairo, Egypt. Anthropometric measurements were taken directly from subjects using calipers and measuring tape.

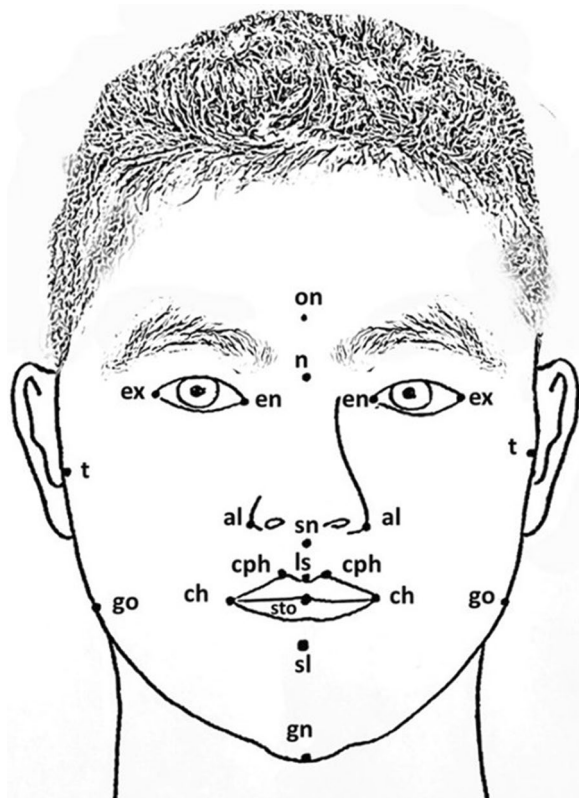


Fig. 2 Facial landmarks subnasal (sn), tragion (t), gnathion (gn), gonion (go), nasion (n), stomion (sto), sublabial (sl), endocanthion (en), exocanthion (ex), cristaphiltri (cph), Cheilion (ch), labiale superius (ls), alare (al)

Measurements techniques are explained in Kolar and Salter (1997). Same standardized landmarks were used in PWS and healthy control children (Fig. 2). Note that maximum facial breadth and mandibular breadth were not obtained for PWS due to child irritability. There are no standardized measurements for the case; measurement selection depends on visual examination and on the authors experience.

The sample size and the fact that the study included only one PWS case limited the use of conventional statistical tests. The *t* test relies on having data from two groups to assess the difference between the means and/or distributions. The *z* test for a single sample assumes a large sample size. For these reasons, we decided to use the *Z*-score for the comparison of the PWS case measurements with Egyptian school children for age and sex. The *Z*-score measures how many standard deviations a measurement is from the mean of the sample. Measurements were categorized as being abnormal for significantly smaller values (< -2 SD) or significantly high values ($> +2$ SD).

Three milliliters blood sample was withdrawn for molecular study from PWS child and control children. Methylation Specific Multiple Ligation PCR Amplification (MS-MLPA) was done using “SALSA MS-MLPA probemix ME028-C1 Prader-Willi/Angelman” supplied by MRC-Holland for copy number variation analysis and methylation analysis.

Coffalyser.Net was used for MS-MLPA data analysis and the analysis of MS-MLPA probemixes.

Results

PWS sample and healthy controls were analyzed using MS-MLPA PWS/AS probemix (MRC-Holland) for detection of copy number variations (CNVs) or aberrant methylation patterns.

Methylation analysis of our patient revealed that he had MAGEL2 gene and four from the SNRPN region of 100% methylation in comparison with the normal control of 50% methylation pattern.

The mean and standard deviation of craniofacial anthropometric measurements of apparently normal male children, for age groups (12 to less than 13 years) and (13–14 years), are shown in Table 1.

Table 2 presents a comparison between the measurements of the PWS to those of normal children aged 13–14 years. The table shows the mean and the range of the normal children. The column difference shows the difference between the PWS case and the mean of the normal children in percentage; the difference was calculated as follows $(\text{PWS value} - \text{mean}) / \text{mean} = \text{percentage}$. The column *Z*-score shows the calculated *Z*-score for the PWS case.

Table 1 Craniofacial anthropometric measurements of Egyptian school children—age groups [12,13] and [13,14]

	Male (< 13)		Male (13–14)	
	Mean	SD	Mean	SD
Head circumference	54.3	2.0	54.0	2.1
Maxillary arc	28.2	1.3	27.7	0.9
Left maxillary arc	14.2	0.7	14.0	0.6
Right maxillary arc	14.0	0.7	13.9	0.6
Mandibular arc	29.9	1.5	29.1	1.2
Left mandibular arc	15.0	0.8	14.7	0.6
Right mandibular arc	14.9	0.8	14.6	0.8
Maximum facial breadth	11.4	0.6	11.3	0.4
Mandibular breadth	10.7	0.7	10.5	0.5
Left maxillary depth	12.5	0.5	12.5	0.5
Right maxillary depth	12.7	0.5	12.5	0.6
Left mandibular depth	13.5	0.9	13.5	0.5
Right mandibular depth	13.9	3.8	13.7	0.7
Left mandibular body length	9.7	0.6	9.5	0.5
Right mandibular body length	9.7	0.5	9.4	0.5
Left mandibular ramus height	5.8	0.4	5.8	0.5
Right mandibular ramus height	5.9	0.4	5.9	0.4
Morphological face height	11.4	0.6	11.7	0.6
Upper face height	7.4	0.8	7.7	0.4
Lower face height	6.3	0.3	6.4	0.5
Anterior mandibular height	4.3	0.2	4.5	0.4
Chin height	2.8	0.4	2.7	0.3
Inter-canthal width	3.3	0.2	3.3	0.3
Outer-canthal width	9.6	0.3	9.6	0.5
Nose height	5.7	0.3	5.9	0.4
Nose width	3.5	0.2	3.4	0.2
Philtrum width	1.5	1.1	1.1	0.2
Philtrum length	1.2	0.2	1.2	0.2
Labial fissure width	4.8	0.3	4.8	0.3
Upper lip height	2.1	0.2	2.0	0.2

In the PWS case, the upper face height and nose height measurements were significantly lower than the mean of the normal population (− 16.1% and − 16.4%, respectively).

Conversely, the PWS case exhibited significantly higher measurements than the control children in the following craniofacial variables: upper lip height (22.3%), chin height (19.1%), right mandibular body length (15.1%), and left mandibular body length (12.9%).

The right mandibular length, left mandibular length, upper face height, and nose height measurements were outside of the normal range for children of that age.

Figure 3 displays the difference in craniofacial anthropometric measurements between the PWS and the mean of the normal population as a percentage.

From Table 2 the upper face height of the PWS shows the largest deviation from the mean with a Z-score of − 3.18.

Statistical analysis indicated that the upper face height and the nose height showed significant deviation from the normal children group with a Z-score − 3.18 and − 2.7, respectively. They were significantly lower than the mean of the normal children. On the other hand, statistical analysis showed that the left mandibular body length, the right mandibular body length, and the upper lip height were significantly higher than the mean of the normal children population with Z-score of 2.48, 2.95, 2.33, respectively.

Discussion

Anthropometric measurements can provide early, additional, and accurate diagnostic features of the disease. However, the lack of adequate craniofacial anthropometric comparative data for the Egyptian population is increasingly becoming a problem for analyzing patterns of dysmorphology. Craniofacial anthropometric measurements add a quantitative extent to clinician observational experience.

Prader–Willi syndrome is a rare and complex disease that presents a broad clinical spectrum of symptoms, which vary depending on the size of the chromosomal deletion (Costa et al. 2019). Therefore, individual assessment is required. This study focuses on the signs of the head and face of an Egyptian male case with PWS who was not under growth hormone therapy. Clinically, the case exhibited short stature, overweight with dysmorphic ear, peg-shaped teeth, and spaced dentition. Head circumference was within normal range. The findings were consistent with those reported in the study of Meaney and Butler (1987), where most of the values fall within normal limits. However, some linear craniofacial measurements were significantly greater than normal. Specifically, the right and left mandibular body length, the left mandibular arch, the left mandibular depth, and the chin height were at the high extreme of the normal range. These findings were consistent with those reported in the literature by Vasconcelos et al. (2022). In his study on 50 individuals with PWS divided into children group (< 12 years), young adults group (12–20 years), and adults group (> 20 years), Vasconcelos et al. (2022) reported that children and young adults groups had a retrognathic mandible, both had a skeletal class II pattern, while adults had more prognathic mandible with a skeletal class III pattern. The broad and prominent mandible in our study may be attributed to significantly longer right and left mandibular body length than normal.

However, others studies contradict our results (Schaedel et al. 1990; Belengeanu et al. 2012; Giuca

Table 2 A comparison between the PWS measurements and the apparently normal Egyptian school children aged 13–14 years

Index	Measurement	Male (13–14)		PWS	Difference (%)	Z-score
		Mean	Range [min–max]			
1	Head circumference	54.0	[50–59.5]	54	−0.1	−0.02
2	Maxillary arc	27.7	[25.5–29.5]	29	4.6	1.34
3	Left maxillary arc	14.0	[13–15.7]	14.7	5.0	1.20
4	Right maxillary arc	13.9	[12.6–15.5]	14.3	2.7	0.59
5	Mandibular arc	29.1	[26.2–31.2]	29.5	1.4	0.33
6	Left mandibular arc	14.7	[13.1–15.9]	15.8	7.5	1.75
7	Right mandibular arc	14.6	[12.8–16.9]	13.7	−6.2	−1.08
8	Left maxillary depth	12.5	[11.7–14]	12.3	−1.5	−0.37
9	Right maxillary depth	12.5	[11.7–14.1]	12	−4.4	−0.97
10	Left mandibular depth	13.5	[12.3–14.5]	14.3	5.6	1.60
11	Right mandibular depth	13.7	[12.5–15.7]	14.3	4.5	0.85
12	Left mandibular body length	9.5	[8.8–10.65]	10.7	12.9	2.48
13	Right mandibular body length	9.4	[8.5–10.5]	10.8	15.1	2.95
14	Left mandibular ramus height	5.8	[4.5–6.5]	6.2	7.2	0.91
15	Right mandibular ramus height	5.9	[4.9–6.6]	6	2.5	0.35
16	Morphological face height	11.7	[10.2–13]	11.2	−3.9	−0.73
17	Upper face height	7.7	[7–8.6]	6.5	−16.1	−3.18
18	Lower face height	6.4	[5.6–7.6]	6.2	−3.4	−0.47
19	Anterior mandibular height	4.5	[3.8–5.2]	4.8	5.9	0.68
20	Chin height	2.7	[2.1–3.5]	3.2	19.1	1.47
21	Inter-canthal width	3.3	[2.7–4]	3.2	−2.3	−0.25
22	Outer-canthal width	9.6	[8.7–10.6]	9.1	−5.4	−0.96
23	Nose height	5.9	[5.1–6.5]	4.9	−16.4	−2.70
24	Nose width	3.4	[3–4]	3.4	−1.3	−0.18
25	Philtrum width	1.1	[0.8–1.5]	1.1	−3.3	−0.24
26	Philtrum length	1.2	[0.8–1.5]	1.2	−1.4	−0.11
27	Labial fissure width	4.8	[4.2–5.6]	4.5	−6.4	−0.92
28	Upper lip height	2.0	[1.6–2.5]	2.5	22.3	2.33

et al. 2016). Schaedel et al. (1990) reported significantly smaller mandibular length in greater than 65% of PWS cases in their study on 12 adults and 8 children, but the study had a wide age range of 4.5–50 years. Belengeanu et al. (2012) studied 18 PWS cases aged 4 to 30 years and found varying degrees of reduction between patients compared to the control group. Giuca et al. (2016) also disagreed with our results, reporting a reduction in mandibular body length of PWS patients aged 10.2 ± 3 years. Prominent chin of PWS cases without growth hormone therapy was reported, and the prominence was accentuated after 12 months of growth hormone therapy (Butler et al. 1998).

Concerning measurements that were significantly smaller than normal, upper face height and nose height were found to be significantly lower than average. There seems to be general agreement in the literature that PWS patients have a smaller skeletal structure than the average population (Schaedel et al. 1990; Belengeanu et al. 2012;

Giuca et al. 2016). Schaedel et al. (1990) classified studied cases into children and adult groups. The results revealed that in both groups the bony craniofacial structure was smaller than the control group. Belengeanu et al. (2012) and Giuca et al. (2016) confirmed the small craniofacial structure and linear measurements compared to the control group.

The PWS case also showed tendency of small labial fissure width ($Z = -0.92$), but it was within the normal range. Comparing our results with other craniofacial studies of PWS is difficult due to differences in ethnicity and study design. The lack of expression of one or more genes at the PWS critical region contributes to different phenotypes (Costa et al. 2019), but how the genetic profile contributes to the clinical phenotype of PWS remains unresolved (Kummerfeld et al. 2021).

In summary, the measurements allowed for the precise identification of upper face and lower face disfigurement, including short upper face height, short nose, great upper

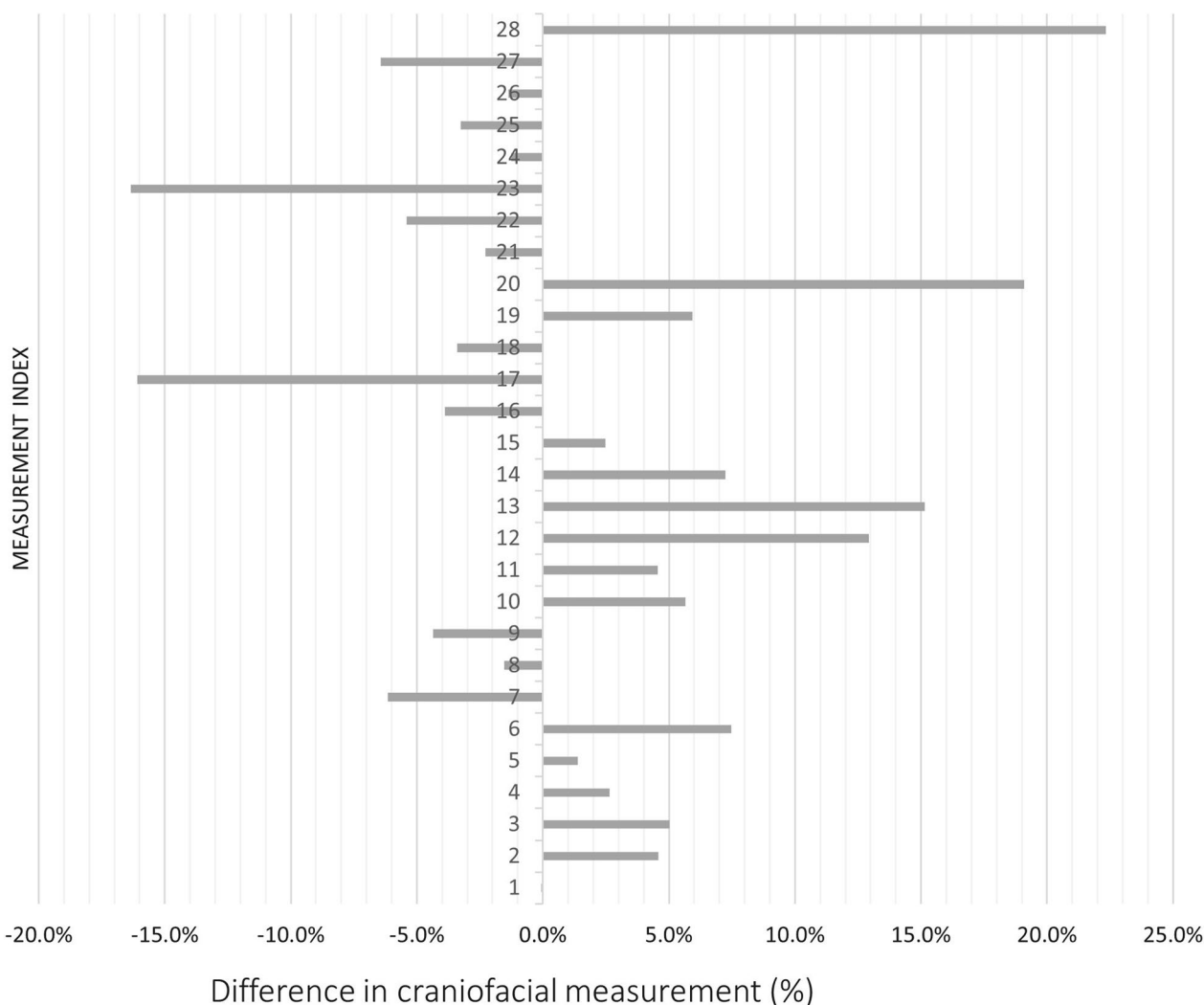


Fig. 3 Difference between the craniofacial measurements of the PWS case and normal Egyptian school children 1 head circumference, 2 maxillary arc, 3 left maxillary arc, 4 right maxillary arc, 5 mandibular arc, 6 left mandibular arc, 7 right mandibular arc, 8 left maxillary depth, 9 right maxillary depth, 10 left mandibular depth, 11 right mandibular depth, 12 left mandibular body length, 13 right mandibular body length, 14 left mandibular ramus height, 15 right mandibular ramus height, 16 morphological face height, 17 upper face height, 18 lower face height, 19 anterior mandibular height, 20 chin height, 21 inter-canthal width, 22 outer-canthal width, 23 nose height, 24 nose width, 25 philtrum width, 26 philtrum length, 27 labial fissure width, 28 upper lip height

lip height, great right and left mandibular body length, and a tendency for great chin height. However, the morphological face height was within the normal range.

Conclusions

Knowledge of the abnormalities noticed in the PWS case, may aid in refining the diagnostic criteria of the syndrome by identifying the areas of major changes as well as minor changes. Generally the upper face, nose, and mandible seem to be the location of the PWS stigmata. Detailed craniofacial anthropometric examination of the

face, direct, and indirect measurements, will identify the most variable and damaged area.

Recommendations

- Further studies with large sample size are needed to establish the validity of these findings.
- Anthropometric methods are useful as an additional clinical assessment in the diagnosis of PWS individuals.
- The presence of bioanthropologist with adequate tool in the clinical examination team, is mandatory for

accurate clinical assessment of dysmorphic characteristics.

Abbreviations

PWS Prader–Willi syndrome
CNVs Copy number variations

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Author contributions

S.M.E. was the principal investigator. S.M.E., N.L.S., M.O.H., M.M.E. conceived the study and the layout of the manuscript. S.M.E. and N.L.S. contributed to the literature research. E.H.A. suggested the appropriate field to apply the research. S.M.E., N.L.S., M.O.H., M.M.E. defined and directed the steps and the needs of the study. G.Y.E., E.H.A., S.M.E. diagnosed the PWS case. M.O.H. performed the statistics of the study. S.M.E., N.L.S., M.O.H. interpreted the results and draw the conclusions. K.S.A. performed the molecular study. All authors read and approved the final manuscript.

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Declarations

Consent for publication

Informed consent was obtained.

Availability of data and materials

All data obtained during and/or analyzed during the current study are not publicly available as it contains individuals' health information but valuable from the corresponding author for reasonable request.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The manuscript granted ethical approval from the Medical Research Ethics Committee of National Research Center, Number (MERC-NRC: 12113).

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