

Craniofacial Anthropometry in Roberts Syndrome in a Sample of Egyptians

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Arabic Summary

متلازمة روبرتس هي اضطراب وراثي نادر ناتج عن طفرات في جين ESCO2. من بين أكثر من 150 حالة دولية تم الإبلاغ عنها ، هناك 16 حالة مصرية بما في ذلك المرضى المبلغ عنها حالياً. أبلغنا عن خمسة مرضى جدد مصابين بمتلازمة روبرتس من خمس عائلات مصرية من أقارب و من غير الأقارب. ثم عرض المتوسط و أحصائيات للتغيرات فى القياسات الأنثروبومترية المطلقة والمؤشرات المشتقة للوجه و الرأس للمرضى بالمقارنة بالأطفال الطبيعيين لتقييم نسبة التشوه ، كما تم عرض كلا الجنسين فى مجموعة مشتركة حيث لم تكن هناك فروق بين الجنسين.

Abstract

Roberts syndrome is a rare autosomal recessive genetic disorder caused by mutations in ESCO2 gene. Among over 150 reported international cases, 16 cases are Egyptian including the presently reported patients. We report five new patients with Roberts syndrome from five unrelated consanguineous Egyptian families. The mean and standard deviation of the absolute anthropometric measurements and derived indices are presented. The comparative mean, standard deviation and P values for syndrome versus the normal Egyptian control group are shown. Both sexes were collectively presented as there were no differences between sexes.

Keywords: Craniofacial, Anthropometry, Roberts syndrome, dysmorphic syndrome, Consanguinity



Introduction

Craniofacial anthropometry is applied using the traditional method to collect craniofacial datasets by direct manual anthropometry, with the use of tools as calipers and tape measurers (**Craig et al., 2011; Saari, 2015**). These direct anthropometric measurements of the face taken from living subjects have been always considered as a valuable source of data, as it has many advantages including its noninvasiveness, relative simplicity, low cost, high internal validity, 3D nature, and its suitability (**Collaboration, 2009**).

Craniofacial anthropometry has a great role in the identification of dysmorphic manifestations which shifts the description of certain malformations to a quantitative discipline instead of qualitative descriptive data which creates a big difference in genetic counseling, as reaching more accurate identification of the dysmorphism is the key point in the differential diagnosis of craniofacial syndromes (**Nagle et al., 2005**).

Roberts syndrome (MIM268300) is a rare genetic disorder. According to **Temtamy & McKusick, (1978)** any child with limb deficiency and craniofacial malformations should be considered in the differentials of this syndrome. The syndrome represents only a small proportion of the total number of individuals with limb deficiency, still it has to be identified in order to give accurate genetic counselling including recurrence risk in siblings and possible prenatal diagnosis (**Library, 1970**).

Roberts Syndrome is characterized by skeletal deformities particularly symmetrical limb reduction with more affection of the upper limbs than lower limbs, craniofacial anomalies, microcephaly, wide-set eyes, shallow orbit, hypoplastic nasal alae, cleft lip and palate, micrognathia, frontal encephalocele (defect in neural tube characterized by sac-like protrusions of the brain and the membranes that cover it through openings in the skull), with prenatal and postnatal growth retardation. Some of these features are represented in Figure (1). Photos of patients are taken with permission from the Limb Malformations and Skeletal Dysplasia Clinic, Center of

Excellence for Human Genetics, National Research Centre after written consent agreement from their parents.

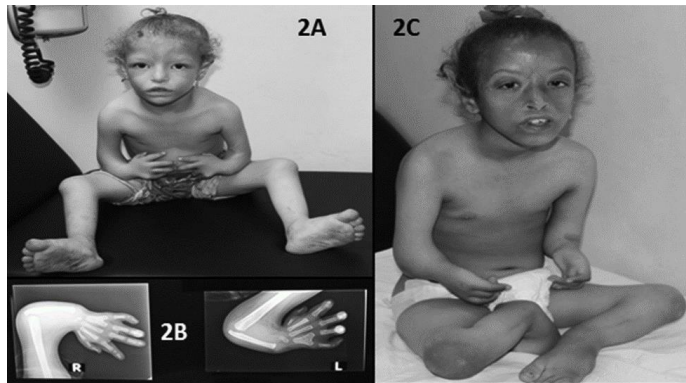


Figure 1 - A) Frontal view of case 6 at the age of 4.5 years, note the hypo pigmented sparse scalp hair and fair skin color. B) X-ray of both hands showing absent radius, hypoplastic thumbs, short ulna and fusion of 4th and 5th metacarpals. C) 6 years with symmetric mesomelic shortening of all four limbs and bilateral absent thumbs. The patient has severe contractures of knees and ankles and was unable to walk, note the patch of skin hyperpigmentation at the ventral surface of the left elbow region. (Ismail et al., 2016)

Investigators have determined that Roberts syndrome is caused by disruptions or mutation in ESCO2 gene which contains 11 exons and is located on chromosome 8p21. The protein product of ESCO2 gene is required for the establishment of sister chromatid cohesion during S phase and has acetyltransferase activity. Also, the chromosomal analysis of RBS/SC patients detected heterochromatin repulsion (HR) with consistent puffing (sister chromatids exhibited a localized premature separation usually but not exclusively at or near the centromeres) especially chromosomes 1, 9 and 16, splitting and premature centromere separation (PCS) (Afifi et al., 2016).

Subjects and methods

The study included five patients (two females and three males) with Roberts syndrome selected from the Limb Malformations & Skeletal Dysplasia Clinic (LMSDC), National Research Centre. Patient cooperation was not always obtained.



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The patients' age ranged from 0 - 14 years, of both sexes. The sex and age matched control group consisted of 48 normal individuals with Caucasian features recruited from Dental National Research Centre Clinics. Data obtained from this group was used as normal facial anthropometric standards for comparing measurements obtained from the patient group.

Approval of the Medical Research Ethics Committee at NRC was taken prior to the start of the study. A written informed consent was signed from patients' legal guardians after a full explanation of the study.

Cases were subjected at the LMSDC to the following: detailed history and full clinical examination, three generation pedigree construction, skeletal survey including skull, vertebrae and long bones, other investigations whenever needed, and oral cavity examination to determine the presence of intra oral manifestations associated with the studied syndromes

Fifteen direct anthropometric measurements and two calculated indices were taken for both the patients and the Egyptian control group using landmarks and techniques as described by (Hall et al., 2006).

Head circumference is measured with a tape measure extending from the middle of the forehead to the farthest part in the rear of the head, **head length** is measured at the maximum dimension on the sagittal axis between the glabella and the opisthorion, the measurement is taken from profile view, and **head width** is measured as the maximum biparital diameter. **Facial width** is measured as the distance between the most lateral points of the zygomatic arches (zygion) which is localized by palpation, and **facial height** is measured as the distance from the root of the nose (nasion) to the lowest median landmark on the lower border of the mandible (gnathion). **Nose length** is the distance from nasion – root of the nose to sub-nasion – deepest point of concavity at the base of the nose, and **nasal width** is measured as the distance between the most lateral aspects of alae nasi, with the nostrils in the rest position without compression of soft tissue. **Inner canthal distance** is the distance between the inner canthi of the two eyes with the eyes facing forward in the presence

of epicanthal folds, and **outer canthal distance** which is the distance from the most lateral corner of one eye to the most lateral corner of the other eye, in a straight line avoiding the curvature of the face. **Ear width** is measured transversely from the anterior base of the tragus through the region of the external auditory canal to the margin of the helical rim at the widest point. The head should be held erect with the eyes facing forward. With cupped or protuberant ear, the ear should be pressed firmly against the head, and **ear length** is the distance from the superior aspect of the outer rim of the helix to the most inferior boarder of the ear pinna parallel to the ear insertion line. The facial profile should be vertical and the subject viewed from the side. **Philtrum** length is the distance between base of the nose and the border of the upper lip in the midline. The observer should be lateral to the subject, and **philtrum width** is the distance between the philtral ridges, measured just above the vermilion border, mouth width, bigonial breadth or mandibular width. As well as the calculated **cranial index** (Head width / head length x 100), and **facial index** (Face height / face breadth x 100).

Standardized equipment used for this study were digital Vernier Caliper that measures linear projective distances between two landmarks in the same plane or in neighboring planes, spreading caliper used when the projective linear distance has to be determined between distant surfaces and various planes, and non-stretchable tape used for determining the tangential linear distances taken along the skin surface between two landmarks to the nearest 1mm. The instruments used were inspected before each setting and each single measurement was taken 3 times and an average was taken for higher accuracy.

Statistical analysis were made using the statistical package for the Social Sciences (SPSS) version 26. Data was summarized using mean and standard deviation for quantitative variables and comparisons between groups were done using unpaired t test. P-values less than 0.05 were considered as statistically significant.



Results

The genetic and clinical manifestations of Roberts syndrome cases in our study were as follows: all cases as parental consanguinity, abnormalities of radii and ulnae which varied from being curved or absent, thumb deformities and clinodactyly, four cases had frontal hemangioma, three cases showed syndactyly bilaterally, and bilateral limited knee extension, camptodactyly was represented in two cases, and clitromegaly was present in a single case.

Facial features presented were high fore head, eye abnormalities as hypertelorism, microphthalmia and bilateral epicanthal folds, pinched bulbous nose and bilateral low set or cupped ears in all patients. Dysmorphic facies were present in four cases as well as thin arched eyebrows, and two cases had antimongoloid eye slanting.

Oro-dental manifestations as thin lips, philtrum shape varied from thin in two cases, short in a case and broad in a case. Highly attached labial frenum was illustrated in three cases and double upper labial frenum with short lingual frenum in a single case. Three cases had high arched palate. Microstomia in three cases and macrostomia in another case. Rudimentary uvula was recorded in a single case. Tongue changes were present in three cases and crowded teeth in a single case.

The mean values of all anthropometric parameters are smaller in Roberts syndrome group but only head length, head width, ear length, nasal width, mouth width, and philtrum length shows a statistical significant difference from the normal Egyptian control group with P values below 0.05. Philtrum width is the only parameter which is larger in Roberts than in the normal control group. These results are illustrated in (figure 2). Roberts syndrome group has higher cranial and facial indices than the normal control group, but only the difference in facial index is statistically significant as shown in (figures 3).

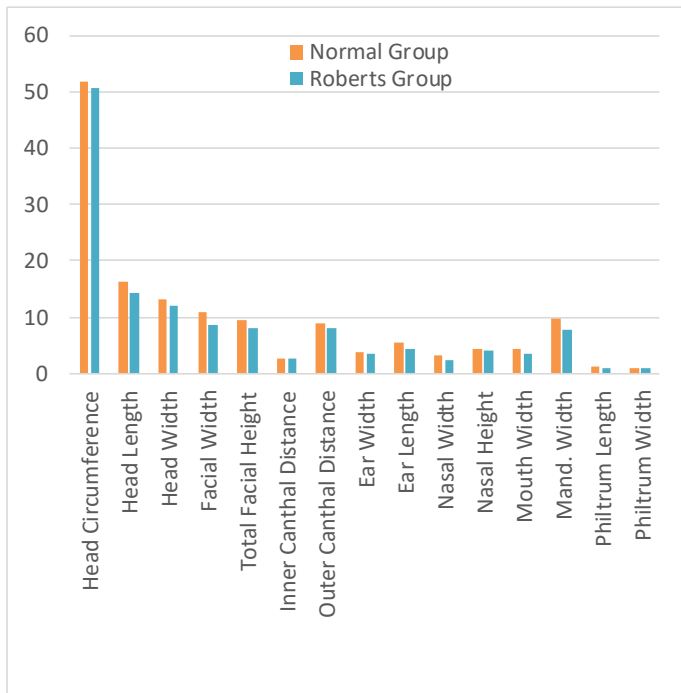


Figure 2: Bar chart showing mean of anthropometric measurements of Roberts syndrome group in comparison to normal Egyptian control group.

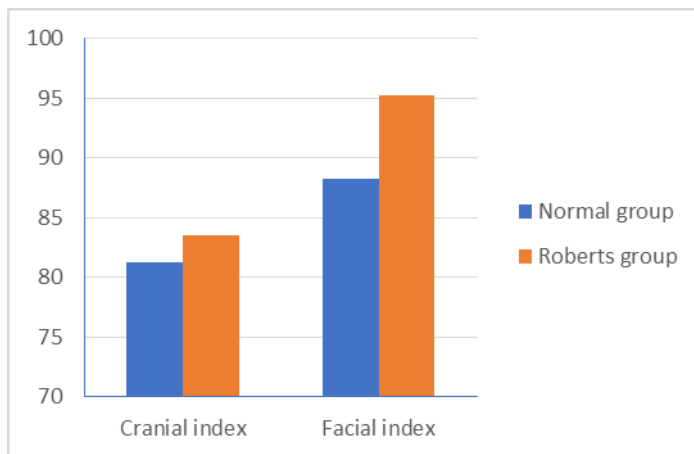


Figure 3: Bar chart showing mean of anthropometric indices of Roberts syndrome group in comparison with the normal Egyptian control group.

Discussion



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In this study, we discuss the craniofacial anthropometric aspects of Roberts syndrome using direct anthropometric methods comparing it with an Egyptian control group. Up to our knowledge, the facial anthropometric findings in our study were not previously reported.

Roberts syndrome (RBS, MIM#269000) is a rare congenital malformation syndrome. The affected children are diverse and spread worldwide. Most reported patients born with growth retardation, severe craniofacial and limb defects have died early in childhood. While those with less severe defects have better prognosis (**Abbas et al., 2011**).

Temtamy et al. (2006) previously reported four Egyptian patients with RBS, and suggested that its allele could be frequent among Egyptians, as the authors stated that among over one hundred and fifty reported cases worldwide, sixteen cases were Egyptians. The five cases demonstrated in this study were evenly distributed over Egypt covering different demographic conditions, also they were from five unrelated families. All were offspring of consanguineous parents supporting the reported autosomal recessive inheritance pattern (**Temtamy et al., 2006; Vega et al., 2010**).

Facial hemangioma is considered a major characteristic feature of RBS patients and was present in 4/5 in our study as mentioned in other studies (**Temtamy et al., 2006**). The study made by **Afifi et al. (2016)** stated that prenatal and postnatal growth retardation and craniofacial anomalies such as; microcephaly, facial hemangioma, hypoplastic nasal alae, and cleft lip/palate, were evident in most of their cases.

Ismail et al. (2016) illustrated that 75% of their RBS sample had the typical characteristics of craniofacial dysmorphism. They also pointed out that individuals with mild limb abnormalities also have mild craniofacial malformations, while those with severely affected limbs present with extensive craniofacial abnormalities. Dysmorphic facies were present in our patients including; thin arched eyebrows, hypertelorism, epicanthal folds, anti mongoloid slanting, pinched narrow nose and dysplastic short cupped ears.

One of the major chief complains by RBS patients are limb shortening or complete absence. The limb-defect pattern in RBS is mostly symmetrical, and is usually more severe in the upper limbs as stated by **Schüle et al. (2005)**. Another study by **Temtamy et al. (2006)** showed retardation in the size of upper limbs and it was more prominent than lower limbs, where the radius was absent in 2 cases in the right side , and another case had severe hypoplastic radius. These results support our findings as all our cases had short, hypoplastic radius and ulna or even absent radius in some cases.

In this study, all cases had clinodactyly of 5th fingers, three cases had soft tissue syndactyly, while camptodactyly was present in 2 cases. These results were comparable to the study of **Vega et al. (2010)**. The authors also reported clitromegaly in 45% of their cases and no male genital anomalies, one of our two studied female cases had clitromegaly.

For complete definition of RBS phenotype and proper management of the patients, orodental evaluation has an important role as most of the orodental anomalies observed in our patients were previously reported but not emphasized enough. We particularly noted that there was high frequency of orodental anomalies while cleft lip and palate associated with RBS patients were relatively rare as stated by **Ismail et al. (2016)**. Also, **Schüle et al. (2005)** described a patient, who had no clefting of lip or palate comparable to our results.

The following orodental findings were noted, in different frequencies, in our patients: microstomia (3/5), macrostomia (1/5), thin lips (4/5), fissured lips (1/5), abnormal philtrum (4/5), highly attached labial frenum (3/5), thick labial frenum (2/5), macroglossia (1/5), malposed teeth (1/5), bifid tongue tip with partial ankyloglossia (1/5) and rudimentary uvula (1/5).

Ismail et al. (2016) noticed similar associated orodental manifestations in Egyptian cases with RBS. They found macrostomia in 2/5 cases, 2/5 cases with thin lips, 2/5 cases with fissured lips, and 2/5 cases with thick alveolar ridge. The high arched palate was observed in 3/5 of our studied cases, and was suggested by



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Hennekam et al. (2010) to result from constriction of the upper jaw. High arched palate was reported to be associated with RBS in previous studies (**Temtamy et al., 2006; Goh et al., 2010**). This can lead to a range of difficulties, such as disrupted sleep due to obstruction of the nasal passages, speech problems, and dental problems later in life, such as crowding of teeth.

Characteristic facial appearance may be diagnostic or at least an important clue for the diagnosis of dysmorphic syndromes. The present study aimed to make a quantitative analysis to dysmorphism in RBS in order to aid in its differential diagnosis from other dysmorphic syndromes or from dysmorphism which occur in an isolated pattern, as well as covering all RBS criteria which is important for syndrome management and prognosis. This quantitative analysis was represented by the anthropometric measurements, and calculated indices which were compared to their corresponding normal comparable control group for better objective analysis.

Our results showed that the mean values of all measured anthropometric parameters: head circumference, head length, head width, facial width, total facial height, inner canthal distance, outer canthal distance, ear width, ear length, nasal width, nasal height, mouth width, mandibular width and philtrum length were smaller in the RBS group, but only head length, head width, ear length, nasal width, mouth width and philtrum length showed statistical significant difference from the normal group with P values below 0.05. Philtrum width is the only parameter which was larger in Roberts group than the normal control group. Thus, the subjective impression of short narrow face, short ears, pinched narrow nose, microstomia and short philtrum in our patients was supported by the statistically significant anthropometric parameters.

According to the calculated indices the crania of RBS patients showed tendency towards brachycephaly, where their cranial index was higher from the normal control group but not in a significant manner. The facial index was significantly higher from the normal group ($P = 0.023$), giving a hyperlyptoprosopic

face type versus mesoprosopic face type for the normal group. This categorization depended on the study previously discussed by **(Franco et al., 2013)**.

Vega et al. (2010) reported microcephaly in all of his studied cases of RBS patients rather than brachycephaly. While a case report of 22 days old male baby from the province of Punjab had micro-brachycephalic skull which is closer to this study results **(Abbas et al., 2011)**.

Conclusion

Proper and early diagnosis of congenital anomalies enables the clinicians to provide best possible care and proper counseling regarding the pathogenesis, prognosis and recurrence risk to syndromic patients and their families. Anthropometric techniques can be used for detecting association studies between specific facial features and genetic variants which permit a better understanding of their etiopathogenesis.



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