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► To cite this version:

Jebrane Bouaoud, Quentin Hennocq, Giovanna Paternoster, Syril James, Eric Arnaud, et al.. Excessive ossification of the bandeau in Crouzon and Apert syndromes. *Journal of Cranio-Maxillofacial Surgery*, 2020, 48, pp.376 - 382. <10.1016/j.jcms.2020.02.022>. <hal-03490869>

HAL Id: hal-03490869

<https://hal.science/hal-03490869v1>

Submitted on 22 Aug 2022

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“Excessive ossification of the bandeau in Crouzon and Apert syndromes”

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Financial Disclosure Statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Presented at: the XVIIIth meeting of the International Society of Craniofacial Surgery in Paris, September 16th-19th, 2019

Short Running Head: Frontal bandeau thickness increases after monobloc

Author's role and participation on the manuscript

Drs Jebrane Bouaoud, Quentin Hennocq and Roman Hossein Khonsari contributed to the conception, design, acquisition, analysis and interpretation of data and the writing of the manuscript.

Drs Giovanna Paternoster and Syril James contributed to the management of the patients.

Dr Eric Arnaud contributed to the management of the patients, to the conception, analysis and interpretation of the data and the writing of the manuscript.

All the authors contributed to the writing of the manuscript and approved the final version.

Introduction

Fronto-facial monobloc advancement (FFMBA) with internal distraction is a central procedure in the management of faciocraniosynostoses (FCS) such as Crouzon and Apert syndromes (CS and AS respectively) (Arnaud et al., 2001; Arnaud and Di Rocco, 2012; Mathijssen, 2015). FFMBA acts on most of the functional and aesthetic issues occurring in *FGFR*-related faciocraniosynostoses, such as intracranial hypertension (Arnaud et al., 2016; Morice et al., 2018), oculo-orbital disproportion (Khonsari et al., 2016; Khonsari et al., 2019; Way et al., 2019), obstructive sleep apnea syndrome (Al-Saleh et al., 2011; Doerga et al., 2016; Khonsari et al., 2016; Mannelli et al., 2019) and facial retrusion with class III occlusion (Forte et al., 2014; Patel and Fearon, 2015). FFMBA is associated with high and specific morbidity (Arnaud and Di Rocco, 2012; Gwanmesia et al., 2015). Per- and post-operative issues have been partly controlled by the use of distraction osteogenesis (Arnaud et al., 2007) but a vast array of complications can still potentially occur (Arnaud et al., 2007).

Interestingly, we have clinically observed an apparent post-operative hyper-ossification of the supra-orbital bar - also known as the 'bandeau' – in FCS (Figure 1). This excess in bone formation could result from the disease itself, but also could be the consequence of FFMBA. This study aimed at assessing the variations in thickness of the supra-orbital bar in a series of patients with CS and AS before and after FFMBA.

Patients and methods

The retrospective study was designed according to the local ethical regulation and approved by the Necker - Enfants Malades ethics committee (Comité d’Ethique de Necker – Enfants Malades, Ethical approval Number 2216445 v 0).

Patients

The diagnoses of CS and AS were suspected based on clinical examination (coronal craniosynostosis midfacial retrusion with hypertelorism) (Staal et al., 2015), and confirmed by screening for *FGFR* mutations. All patients with CS and AS who underwent FFMBA with internal distraction in our team, from 2008 to 2018, with available early post-operative (before distraction), 1 month post-operative, 3 months post-operative, 6 months post-operative and 12 months post-operative digital CT-scans of sufficient quality for thickness analysis were included in the study. The following clinical parameters were collected: age, gender, date of birth, date of the surgical procedure (FFMBA), *FGFR2* mutation status.

Patients assessed for minor craniofacial trauma with no medical history of craniofacial conditions, with a normal head CT-scan, were included as a control group. All patients with developed frontal sinuses were excluded.

Surgical technique and distraction protocol

All procedures were performed by the same surgeon following a standardized protocol as

previously described (*Morice et al., 2018*) (Figure 2).

Briefly, a forehead bony flap was elevated, allowing access to the anterior skull base. After orbital and temporal osteotomies (*Arnaud and Di Rocco, 2012*), bilateral pterygo-maxillary disjunction and mobilization of the face using Rowe maxillary disimpaction forceps was performed. The skull base defect was reconstructed using periosteal flaps (*Morice et al., 2018*). Two pairs of internal distraction devices (cranial and temporo-zygomatic *Arnaud-Marchac* distractors, KLS Martin, Tuttlingen, Germany) were then implanted (*Arnaud et al., 2007*). After a latency period of 5 days, the standard distraction protocol consisted of an advancement of 0.5 mm per day for the four distractors. Both cranial distractors were generally activated up to their maximum range (22 mm). The activation of the tempo-zygomatic distractors was stopped when an occlusal overcorrection or a class I occlusion was obtained. In case of cerebrospinal fluid (CSF) leak, distraction was delayed until resolution and decompressive lumbar punctures were performed during 3 consecutive days. At the end of the distraction period, the flexible activation rods of the devices were pulled off, and the devices themselves were removed after a 5-6 month period necessary for consolidation and the prevention of relapse.

CT measurements and evaluation of bone thickness

1. 2D measurements

2D measurements were performed on sagittal sections from CT-scans according to the Half Maximum Height (HMH) protocol (*Spoor et al., 1993*) using Mimics® Innovation Suite v.21.0 and 3-matic® v.13.0 (Materialise, Leuven, Belgium). The thickness of the frontal bone was

assessed at five locations: (1) **right/left lower supra-orbital point** (5 mm above the right/left supra-orbital ridge), (2) **right/left upper supra-orbital point** (10 mm above the right/left supra-orbital ridge) and (3) **glabella (Figure 3A)**.

2. 3D measurements

The thickness of the frontal bones was furthermore measured and plotted using the Wall Thickness Analysis module of 3-matic® v.13.0 (Materialise, Leuven, Belgium) as previously described (*Khonsari et al.*, 2013). A green-yellow-red (respectively 0-5-10 mm) continuous color map for thickness values was plotted over the surface of the 3D renderings of the supra-orbital rim and frontal bone (Figure 3B).

Statistical assessment

We used two hierarchical linear models in order to account for repeated measurements in single patients and thus non-independent data. A random effect on the intercept was introduced for each individual and for the location of the measurement (right/left/glabella and upper/lower supra-orbital thicknesses). The model coefficients were compared to 0 using Student tests. The predicted variable for linear **model №1** was the quantitative change in frontal bone thickness in non-operated patients (controls or CS or AS). Two other explanatory variables were age at CT-scan and gender. Linear **model №2** was dedicated to the quantitative change of frontal bone thickness in operated patients with CS or AS. Four other explanatory variables were time point of the CT-scan, age at FFBMA, gender and the different *FGFR2* mutations. The significance of

each parameter was defined as $p < 0.05$ (Tables 1-2). Significance meant that the parameter had an effect on the explanatory variable. Assumptions of normality and homoscedasticity of errors were tested. The distributions of sex and age in the CS, AS and Control groups were tested using a logistic model and a linear model respectively. The statistical analyses were performed on **R** 3.3.2 using the *nlme* and *ggplot2* packages.

Results

We included 210 CT-scans from 25 patients with CS (141 scans), 10 patients with AS (44 scans) and 25 control subjects (25 scans).

Of the 141 scans performed on CS children, 26 (18%) were performed before FFMBA. There were 12 boys in the Crouzon group compared to 14 in the control group. The median age at CT-scan in the control group was 32 [4-48] months. The median age at FFMBA in the CS group was 42 [3.80-152] months. The median post-operative follow-up period (corresponding to the latest included post-operative CT-scan) was 12.16 [4.67-16] months. *FGFR2* mutations were found in 20/25 Crouzon children (80%). Among them, the most frequent mutations were Cys342Trp (4/20) and Cys342Tyr (4/20), followed by Ser354Cys (3/20), Phe276Val (2/20), Tyr340His (2/20), Ser347Cys (1/20), Trp290Arg (1/20), Trp290Gly (1/20), Tyr381Asn (1/20) and Cys278Phe (1/20) (Table 3).

Before FFMBA, children with CS had a significantly thicker frontal bone (+0.772 mm +/- 0.312) than controls ($p = 0.017$) (Table 1). Age at CT-scan and sex were not statistically related to frontal bone thickness ($p = 0.943$ and $p = 0.627$). A significant ($p < 0.001$) increase in frontal

bone thickness was reported at 3 months post-operatively (+ 0.637 mm +/- 0.141), 6 months post-operatively (+ 0.910 mm +/- 0.120) and 12 months post-operatively (+ 1.099 mm +/- 0.124) in Crouzon syndrome (Table 2, Figure 4). The post-operative increase in frontal bone thickness was independent of gender but was statistically related to age at FFMBA (- 0.017 mm +/- 0.006; $p=0.031$) and to Phe276Val FGFR2 mutations (- 2.253 mm +/- 0.965; $p=0.048$).

For AS children, 15 (34%) scans were performed before FFMBA. There were 4 (40%) boys in the AS group compared to 14 (56%) in the control group. The median age at FFMBA in the AS group was 26 [15-108] months. The median post-operative follow-up was 12 [3-80] months. FGFR2 mutations were found in 7/10 AS children (70%) corresponding to Ser252Trp (4/7) and Pro253Arg (3/7) mutations (Table 4).

Before FFMBA, children with AS did not have thicker frontal bones (+ 0.141 mm +/- 0.454) than controls ($p = 0.758$) (Table 5). A significant increase in frontal bone thickness was reported at 1 month post-operatively (+ 2.069 mm +/- 0.441, $p < 0.001$), 6 months post-operatively (+ 1.247 mm +/- 0.406, $p=0.003$) and 12 months post-operatively (+ 2.360 mm +/- 0.284, $p < 0.001$) after FFMBA in AS (Table 6, Figure 4). The post-operative increase in frontal bone thickness was statistically related to the age at FFMBA (+ 0.033 mm +/- 0.008; $p=0.031$) but independent of gender and FGFR2 mutations. The Ser252Trp FGFR2 mutation nevertheless seemed to be related to thicker frontal bones after FFMBA (+ 0.916 mm +/- 0.332, $p=0.07$) but larger numbers are required to confirm these trends.

Discussion

The objectives of our study were to assess the post-operative thickness of the frontal bone following FFMBA and to identify influencing factors, based on a retrospective series of infants with CS or AS homogeneously managed by the same surgeon (EA) in a single craniofacial surgery center (Hôpital Universitaire Necker - Enfants Malades, Paris, France).

Controlled reports assessing changes in orbital morphology, orbital volumes, zygoma and maxillary shape, facial growth in patients with CS and AS (Bender et al., 2013), as well as studies assessing the impact of FFMBA on orbital shape, globe position, airway parameters, facial growth, skull and zygomatic arch ossifications are available in the literature (Oyama et al., 2009; Khonsari et al., 2016; Sicard et al., 2018). Interestingly, Oyama et al. (2009) have reported differences in the re-ossification of the skull and zygomatic arches after FFMBA (Oyama et al., 2009). In their study, re-ossification of the coronal gap was considered as satisfactory (bone linkage 75%-100%) in 40.9% of cases whereas a bilateral re-ossification of zygomatic arches was observed in only 27.3% of cases. Furthermore, Hopper et al. (2010), have shown high variability in the amount of bone formed in the pterygo-maxillary region after Le Fort III osteotomies in CS and AS (Hopper et al., 2010). Recently, Cha et al. (2018), have described the case of a nine year-old AS boy who presented a horizontal groove above the supra-orbital bar 8 years after frontal calvaria distraction osteotomy (Cha et al., 2018). Fearon et al. (2018), have studied the long term aesthetic results of the supraorbital bandeau in non-syndromic craniosynostosis repair and noted undesirable bony irregularities such as regional overgrowths producing visible bumps arising from discontinuous bony segments (Fearon et al., 2018). These previous results did not allow differentiating frontal bone re-ossification issues due to the surgical procedure itself – most probably the case in non-syndromic craniosynostoses (Fearon et al., 2018) – or functional factors such as post-operative variations in intra-cranial pressure

(Arnaud et al., 2016) from re-ossification issues due to excessive *FGFR2* activation.

Fibroblast growth factor signaling pathways are involved in the formation of craniofacial mesenchymal osteogenic condensations and have key roles in regulating osteogenesis (Ornitz and Marie, 2015). In CS and AS, early suture fusion may result from an accelerated maturation of sutural osteoblasts (Gorlin, 1997; Marie, 2015). *FGFR2* function is known to be tissue-specific (Holmes et al., 2018) and spatio-temporal variations in *FGFR2* expression patterns have been reported (Britto et al., 2001).

Our results suggest that frontal bone thickening in CS and AS, both before surgery and after FFMBA, results from the interaction of intrinsic – genetics and age – factors with functional factors, among which brain growth and intra-cranial pressure are most probably at the forefront (Luo et al., 2017).

We found that the post-operative increase in frontal bone thickness of AS children was related to the Ser252Trp mutation of *FGFR2* ($p=0.07$). This mutation, which is responsible for nearly two-thirds of AS cases, impairs osteogenesis regulation in FCS (Azoury et al., 2017). However, this is the first report of its interaction with post-operative bone formation. Regarding CS, the uncommon Phe276Val *FGFR2* mutation (Roscioli et al., 2013) was statistically related to thinner post-operative frontal bones. This result is supported by a recent study showing that specific activating *FGFR2* mutations in CS impair reossification of critical size defects in CS mouse models (Alcon et al., 2018).

Regarding age at FFMBA, with the same post-operative delay, an older age at surgery was associated with thicker frontal bones for AS patients. Age at surgery is a factor commonly assessed when evaluating management protocols for craniosynostoses and is still a matter of

controversies (Taylor and Bartlett, 2017). Our study is the first reporting the effect of age at surgery on post-operative bone formation in CS and AS and suggests that earlier procedures are associated with less frontal bone overgrowth for AS.

Thick supra-orbital bars with bony irregularities can indicate secondary surgical corrections (Fearon et al., 2018). Various technique for forehead contouring and reconstruction are available depending on the extent of the deformation, ranging from lipofilling and endoscopic re-surfacing to frontal osteotomies (Capitan et al., 2015).

Despite the inherent limitations due to our retrospective data collection, and the relatively limited number of patients analyzed, our results strongly indicate that children with CS had thicker frontal bones before surgery and that CS and AS children had a significant post-operative increase of the frontal bone thickness.

Conclusion

Craniofacial surgeons should be aware of and inform CS and AS patients that there is a potentially significant increase in frontal bone thickness after FFMBA. Interestingly, specific situations expose to thick post-operative supra-orbital bars, such as AS patients operated on late and/or with Ser252Trp *FGFR2* mutations. Our results suggest that excessive *FGFR2* activation affects the thickness of the frontal bone in FCS, and that FFMBA interacts with this parameter.

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Figure legends

Figure 1. Post-operative increase of the supra orbital bar thickness in a 12 years-old girl with Crouzon syndrome height years after the FFMBA with internal distraction. (A) Per operative lateral right and (B) front of views showing this supra orbital bar thickness (green arrow).

Figure 2. Fronto-facial monobloc advancement (FFMBA) with internal distraction surgical technique. A. Pre-operative view on the CT-scan. B, C and D. Schematic representation of per operative steps showing the frontal, temporal, orbital and skull osteotomies with the two pairs of internal distraction devices (cranial and temporo-zygomatic Arnaud-Marchac dis-tractors, KLS Martin, Tuttlingen, Germany) implanted. E. Photography of the procedure at the end the surgery F. post-operative view on the CT-scan after activation of the internal distraction devices showing the advancement of the fronto-facial monobloc.

Figure 3. Thickness measurements performed on the frontal bone using sagittal sections of CT-scans. **A.** (1) right lower supra orbital point (5 mm above the right supra orbital ridge), (2) right upper supra orbital point (10 mm above the right supra orbital ridge), (3) glabella, (4) left lower supra orbital point (5 mm above the left supra orbital ridge) and (5) left upper supra orbital point (10 mm above the left supra orbital ridge). **B.** Green-yellow-red (respectively 0-5-10 mm) continuous color map for thickness values plotted over the 3D rendering of the supra-orbital rim and frontal bone.

Figure 4. Model №2. Evolution of the thickness of the frontal bandeau (in millimeters) in children with Crouzon (left) and Apert (right) syndrome, before surgery and at 1, 3, 6 and 12 months post-op. The values corresponded to the mean thickness according to our model with standard deviation, for the reference class (girls, operated on at 0 years of life, with Cys278Phe mutation for Crouzon syndrome or Pro253Arg for Apert syndrome). The stars correspond to a value significantly different from the pre-op.

Table legends

Table 1. Model №1. The reference class corresponded to controls; the intercept value (3.618) corresponded to the average values of frontal bone thickness values for girls without Crouzon syndrome, at age zero. Children with Crouzon syndrome before FFMBA had a significantly ($p = 0.017$) thicker frontal bone ($+ 0.772 \pm 0.312$) than controls. The standard deviations 'Individual', 'Lower/upper thickness', 'Left/right/glabella' corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

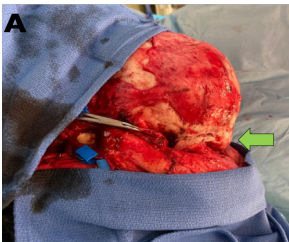
Table 2. Model №2. The intercept value (6.350) corresponded to the average values of frontal bone thickness for girls with Crouzon syndrome, immediately after FFMBA, at age zero with no *FGFR2* mutations. A significant ($p < 0.001$) increase in frontal bone thickness was reported at 3 months post-operatively, 6 months post-operatively and 12 months post-operatively. The standard deviations 'Individual', 'Lower/upper thickness', 'Left/right/glabella' corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

Table 3. Crouzon syndrome: population and clinical data. sd: standard deviation; see Figures 1-2 for other abbreviations.

Table 4. Apert syndrome: population and clinical data. sd: standard deviation; see Figures 1-2 for other abbreviations.

Table 5. Model №1. The reference class corresponded to controls; the intercept value (2.646) corresponded to the average values of frontal bone thickness for girls without Apert syndrome, at age zero. Children with Apert syndrome before FFMBA did not have a thicker frontal bone ($+0.141 \pm 0.454$) than controls ($p = 0.758$). The standard deviations 'Individual', 'Lower/upper thickness', 'Left/right/glabella' corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

Table 6. Model №2. The intercept value (2.186) corresponded to the average values of frontal bone thickness for girls with Apert syndrome, immediately after FFMBA, at age zero with no *FGFR2* mutations. A significant increase in frontal bone thickness was reported at 1 month post-operatively ($p < 0.001$), 6 months post-operatively ($p=0.003$) and 12 months post-operatively ($p < 0.001$). Age at FFMBA ($p=0.031$) was significantly related to the post-operative increase of frontal bone thickness for children with Apert syndrome. The standard deviations 'Individual', 'Lower/upper thickness', 'Left/right/glabella' corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.



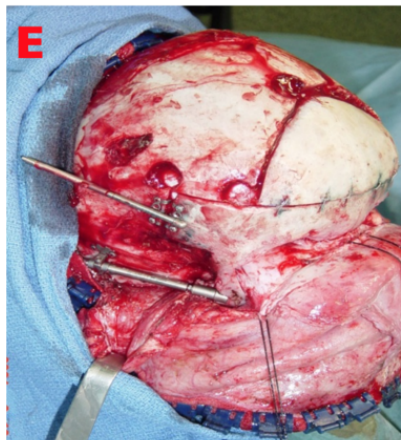
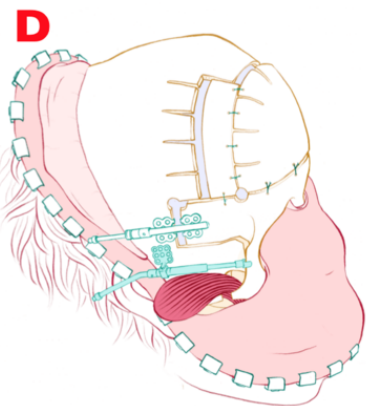
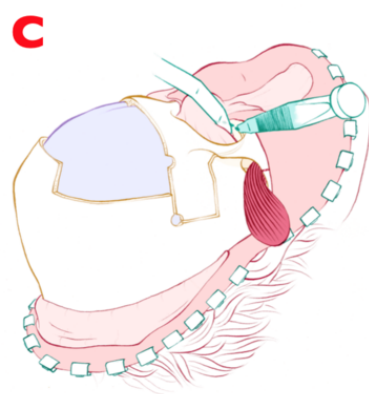
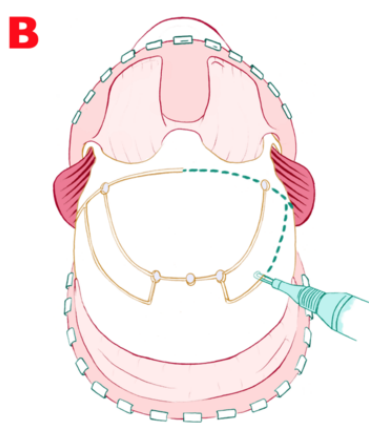
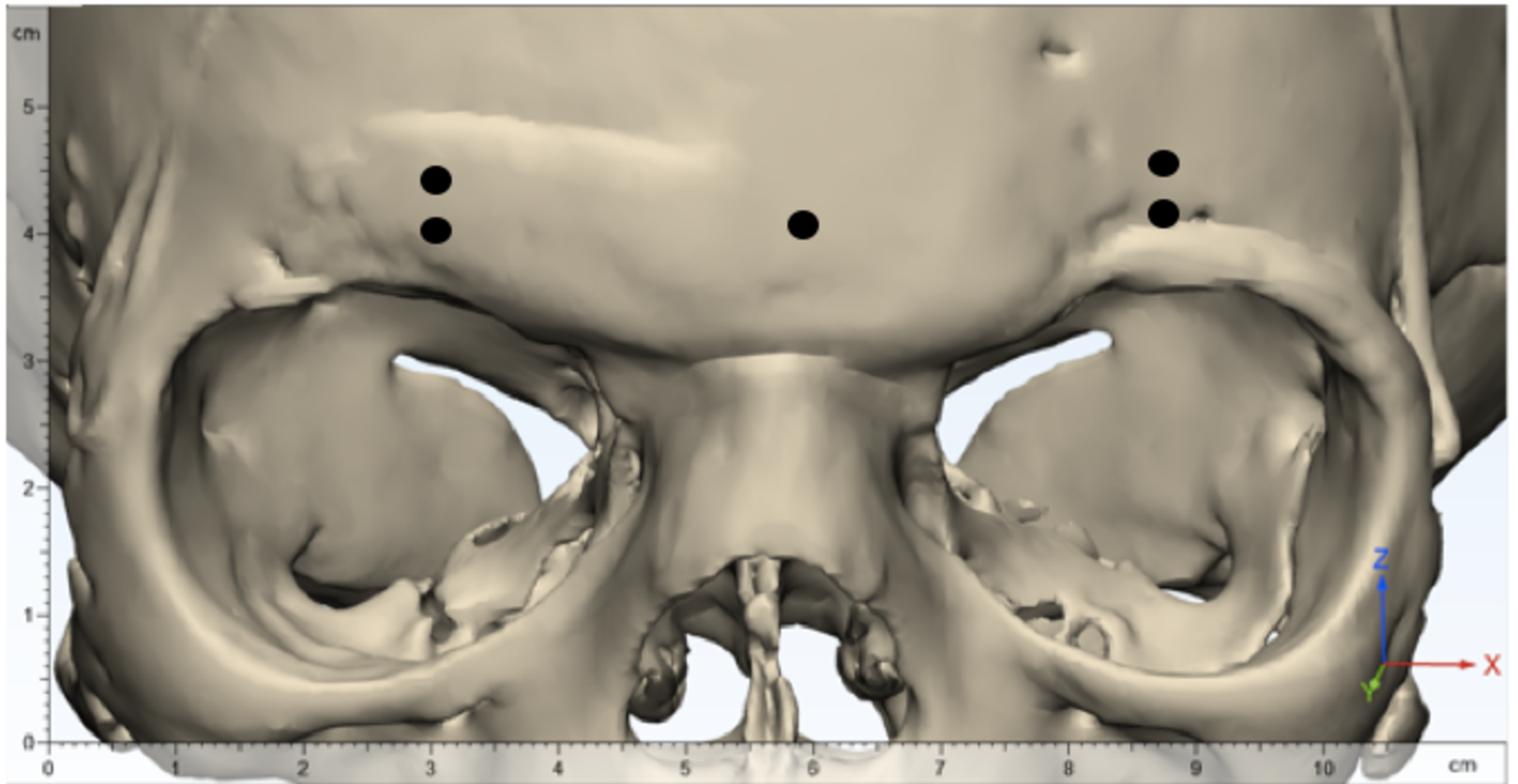
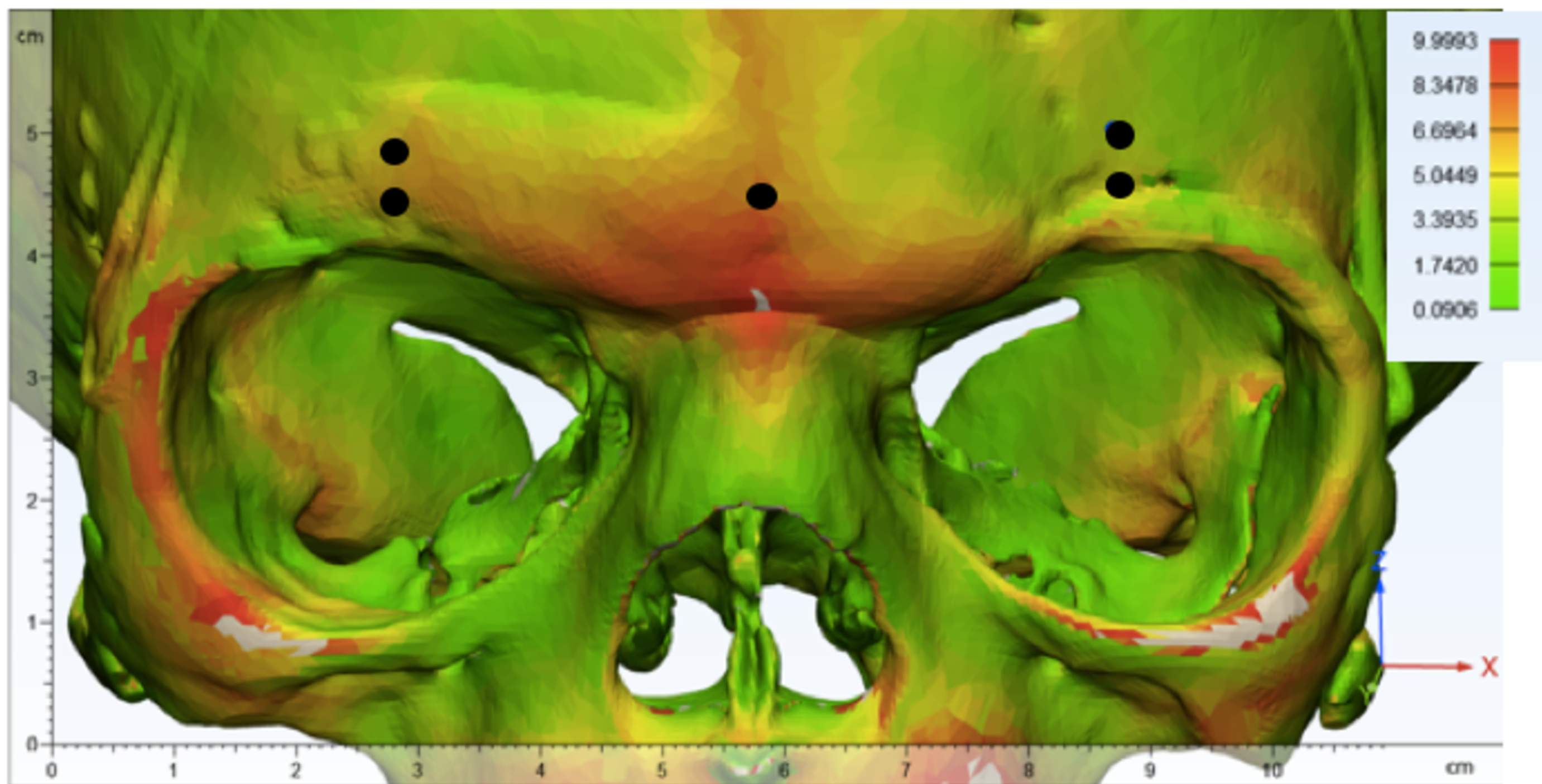


Figure 3

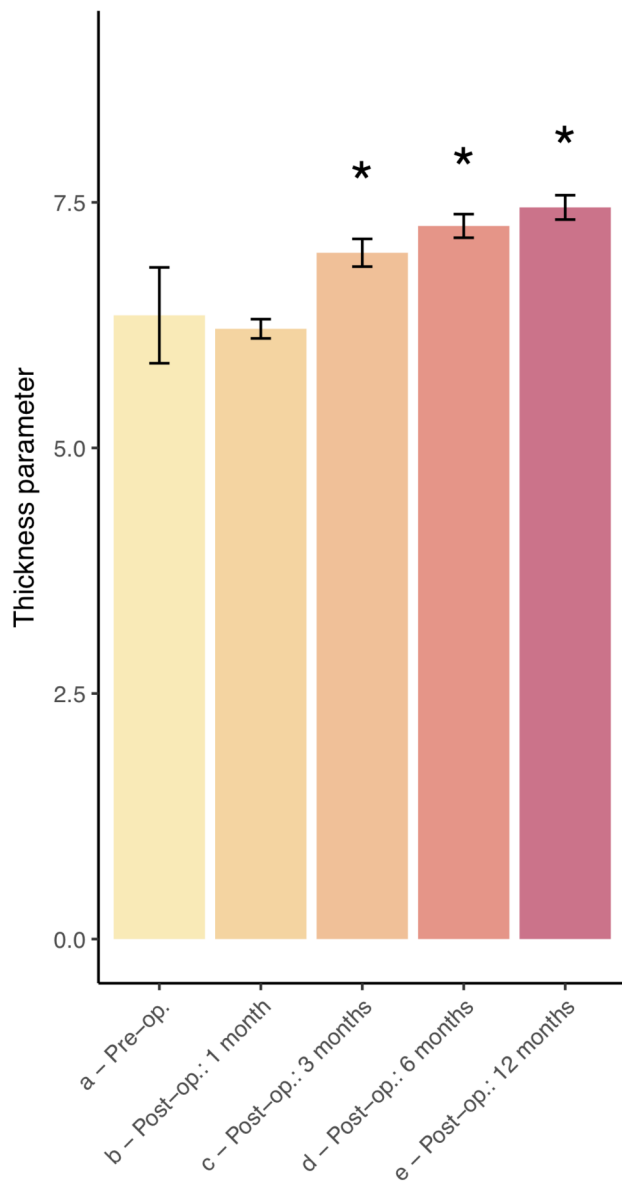
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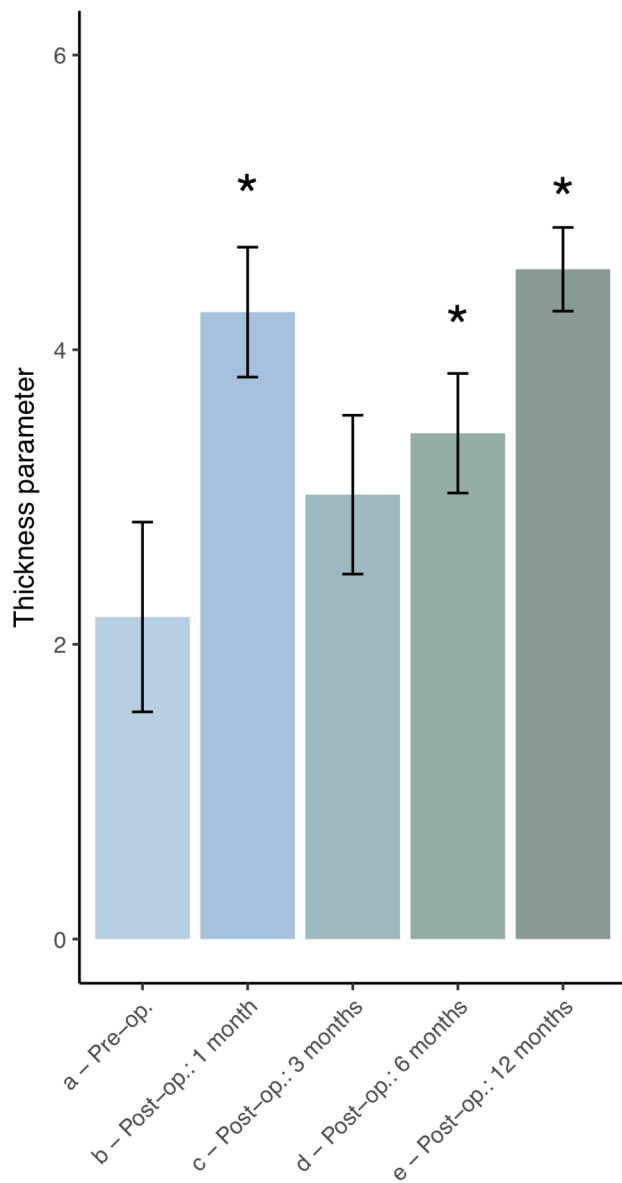
B



Crouzon syndrome



Apert syndrome



	Frontal bone thickness (mm)	Sd	p-value
Intercept	3.618	0.319	
Individual		0.813	
Lower/upper thickness		0.649	
Left/right/glabella		0.639	
Age at CT-scan	+ 0.000	0.007	0.943
Crouzon syndrome	+ 0.772	0.312	0.017
Gender: boys	- 0.143	0.292	0.627

Table 1. Model №1. The reference class corresponded to controls; the intercept value (3.618) corresponded to the average values of frontal bone thickness values for girls without Crouzon syndrome, at age zero. Children with Crouzon syndrome before FFMBA had a significantly ($p = 0.017$) thicker frontal bone (+ 0.772 +/- 0.312) than controls. The standard deviations ‘Individual’, ‘Lower/upper thickness’, ‘Left/right/glabella’ corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

	Frontal bone		
	thickness (mm)	Sd	p-value
Intercept	6.350	0.897	
Individual		0.488	
Lower/upper thickness		0.406	
Left/right/glabella		1.089	
One month post-op.	- 0.137	0.098	0.162
Three months post-op.	+ 0.637	0.141	< 0.001
Six months post-op.	+ 0.910	0.120	< 0.001
Twelve months post-op.	+ 1.099	0.124	< 0.001
Age at FFMBA (months)	- 0.017	0.006	0.031
Gender: boys	- 0.948	0.462	0.074
FGFR2: Cys342Trp	- 0.845	0.891	0.371
FGFR2: Cys342Tyr	- 0.722	0.976	0.480
FGFR2: Phe276Val	- 2.253	0.965	0.048
FGFR2: Ser347Cys	- 2.671	1.171	0.052
FGFR2: Ser354Cys	- 0.806	0.903	0.398
FGFR2: Trp290Arg	- 0.524	1.082	0.641
FGFR2: Trp290Gly	- 1.152	1.099	0.325
FGFR2: Tyr340His	- 0.620	1.089	0.585
FGFR2: Tyr381Asn	+ 0.484	1.116	0.676

Table 2. Model №2. The intercept value (6.350) corresponded to the average values of frontal bone thickness for girls with Crouzon syndrome, immediately after FFMBA, at age zero with

no *FGFR2* mutations. A significant ($p < 0.001$) increase in frontal bone thickness was reported at 3 months postop, 6 months postop and 12 months postop. The standard deviations 'Individual', 'Lower/upper thickness', 'Left/right/glabella' corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

Total population (n=50)		Crouzon syndrome	Controls
N (%)		25/50 (50 %)	25/50 (50 %)
Gender: boys		12/25 (48 %)	14/25 (56 %)
Age at FFMBA (months)	Median	42	
	Minimum	3.80	
	Maximum	152	
Number of CT-scans		141	25
	Pre-op.	26/141 (18 %)	
	Post-op. 1 month	59/141 (42 %)	
	Post-op. 3 months	14/141 (10 %)	
	Post-op. 6 months	23/141 (16%)	
	Post-op. 12 months	19/141 (13 %)	
Frontal bone thickness	Mean (sd)	4.54 (1.66)	3.58 (1.35)
	Minimum	0.82	0.75
	Maximum	10.67	6.89
<i>FGFR2</i> mutation		20/25 (80 %)	
	Cys342Trp	4/20 (20 %)	
	Cys342Tyr	4/20 (20 %)	
	Ser354Cys	3/20 (15 %)	
	Phe276Val	2/20 (10 %)	
	Tyr340His	2/20 (10 %)	
	Ser347Cys	1/20 (5 %)	
	Trp290Arg	1/20 (5 %)	

Trp290Gly	1/20 (5 %)
Tyr381Asn	1/20 (5 %)
Cys278Phe	1/20 (5 %)

Table 3. Crouzon Syndrome Population and clinical data. sd: standard deviation; see Figure 1-2 for other abbreviations.

Total population (n=35)		Apert syndrome	Controls
N (%)		10/35 (29 %)	25/35 (71 %)
Gender: boys		4/10 (40 %)	14/25 (56 %)
Age at FFMBA (months)	Median	25.95	
	Minimum	15.27	
	Maximum	108	
Number of CT-scans		44	25
	Pre-op.	15/44 (34 %)	
	Post-op. 1 month	4/44 (9%)	
	Post-op. 3 months	2/44 (5%)	
	Post-op. 6 months	4/44 (9%)	
	Post-op. 12 months	19/44 (43%)	
Frontal bone thickness	Mean (sd)	5.25 (1.83)	3.58 (1.35)
	Minimum	0.63	0.75
	Maximum	10.35	6.89
<i>FGFR2</i> mutation		7/10 (70 %)	
	Ser252Trp	4/7 (57 %)	
	Pro253Arg	3/7 (43 %)	

Table 4. Apert Syndrome population and clinical data. sd: standard deviation; see Figure 1-2 for other abbreviations.

Thickness of the frontal bone			
	(mm)	Sd	p-value
Intercept	2.646	0.376	
Individual		1.049	
Lower/upper thickness		0.528	
Left/right/glabella		1.018	
Age at CT-scan	+ 0.041	0.007	< 0.001
Apert syndrome	+ 0.141	0.454	0.758
Gender: boys	- 0.298	0.410	0.472

Table 5. Model №1. The reference class corresponded to controls; the intercept value (2.646) corresponded to the average values of frontal bone thickness for girls without Apert syndrome, at age zero. Children with Apert syndrome before FFMBA did not have a thicker frontal bone (+ 0.141 +/- 0.454) than controls (p = 0.758). The standard deviations ‘Individual’, ‘Lower/upper thickness’, ‘Left/right/glabella’ corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.

	Frontal bone thickness (mm)	Sd	p-value
Intercept	2.186	0.644	
Individual		0.000	
Lower/upper thickness		0.002	
Left/right/glabella		0.479	
One month post-op.	+ 2.069	0.441	< 0.001
Three months post-op.	+ 0.830	0.539	0.127
Six months post-op.	+ 1.247	0.406	0.003
Twelve months post-op.	+ 2.360	0.284	< 0.001
Age at FFMBA (months)	+ 0.033	0.008	0.031
Gender: boys	+ 0.298	0.407	0.517
FGFR2: Ser252Trp			
(Ref = Pro2531Arg)	+ 0.916	0.332	0.070

Table 6. Model №2. The intercept value (2.186) corresponded to the average values of frontal bone thickness for girls with Apert syndrome, immediately after FFMBA, at age zero with no *FGFR2* mutations. A significant increase in frontal bone thickness was reported at 1 month postop ($p < 0.001$), 6 months postop ($p=0.003$) and 12 months postop ($p < 0.001$). Age at FFMBA ($p=0.031$) was significantly related to the post-operative increase of frontal bone thickness for children with Apert syndrome. The standard deviations ‘Individual’, ‘Lower/upper thickness’, ‘Left/right/glabella’ corresponded to the random effects of our hierarchical model. See Figure 1-2 for abbreviations.