2D-metrics in routine dental radiographs correlate with bone supply of intraoral donor regions: A retrospective analysis

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Abstract

Background: To test the hypothesis that cephalometric parameters in two-dimensional routine dental radiographs correlate with the bone supply of intraoral donor regions.

Methods: A total of 108 radiographs (36 panoramic radiographs [PRs], 36 lateral cephalometric radiographs [LCRs], and 36 cone-beam computed tomography scans [CBCT]) of 36 patients were analysed. Cephalometric parameters (PR and LCR) were correlated with the bone supply measurement in three-dimensional CBCT scans in three different intraoral donor regions (chin, mandibular retromolar region, and zygomatic alveolar crest).

Results: Different mean bone volumes were measured for the chin ($3.10 \pm 1.11 \text{ cm}^3 \text{ SD}$), the mandibular retromolar region ($1.66 \pm 0.54 \text{ cm}^3 \text{ SD}$), and the zygomatic alveolar crest ($0.17 \pm 0.04 \text{ cm}^3 \text{ SD}$). Cephalometric parameters were significantly correlated with the bone dimensions in the chin and the mandibular retromolar region (all p-values < 0.05). Bone volume of the zygomatic alveolar crest exhibited no correlations with cephalometric parameters but significantly correlated with the mandibular retromolar bone volume (p < 0.01). No gender-specific differences were observed with respect to bone volumes in all bone harvesting regions. However, the interforaminal distance in the chin region was significantly higher in the male population (p = 0.001).

Conclusion: Routine 2D radiographs can be used during the initial consultation for primary intraoral bone donor site evaluation. This is anticipated to be helpful in defining indications and justifying further diagnostic options such as three-dimensional radiological techniques.

Background

Implant dentistry plays a vital role in masticatory function rehabilitation.¹ However, sufficient bone volume and density are required for implant placement.² A significant bone loss occurs within the first year after tooth loss.³ This bone reduction is particularly pronounced in the coronal third of the alveolus and on the vestibular half of the alveolar ridge,⁴ and it is more evident in the molar region.⁵ Therefore, additional bone augmentation is often required.⁶

Nowadays, various bone substitute materials having different origins are readily available.⁷ Most of these materials act as osteoconductive scaffolds for vascular and bone-forming cell incorporation.⁸ As osteoconductive bone formation occurs rather slowly and originates mainly from the margins adjacent to the vital bone, autogenous bone grafting is still considered the gold standard for intraoral augmentation.⁸ Vital osteoprogenitor cells and osteoblasts are transplanted with the harvested bone tissue and lead to a homogeneous new bone formation.⁸

Several intraorally achievable donor sites, such as the chin region, the spina nasalis, the zygomatic alveolar crest, the lateral cortical bone of the mandible, and the mandibular retromolar region, are suitable

for bone harvesting.⁹ Three-dimensional radiographs (e.g. cone-beam computed tomography [CBCT] scans) are often required for implant planning and adequate evaluation of bone supply in these donor regions.¹⁰ However, this is accompanied by additional radiation exposure of the patients.^{11, 12} Two-dimensional radiographs, such as the panoramic radiograph (PR) or the lateral cephalometric radiograph (LCR), are often already available during the initial consultation prior to implant planning.¹¹ In accordance with these images, bone evaluation can be performed, which could provide detailed references about the intraoral bone supply in the different donor regions already at the beginning of the treatment planning.

Therefore, this study aimed to perform a cephalometric analysis in two-dimensional radiographs (PR and LCR) and correlate these data with the bone supply measured in three-dimensional radiographs (CBCT scans) in three different bone harvesting regions (chin, mandibular retromolar region, and zygomatic alveolar crest).

Material And Methods

Patients

This retrospective analysis was performed on 108 radiographs (36 PRs, 36 LCRs, and 36 CBCT scans) of 36 patients. PRs were obtained during routine dental and oral and maxillofacial surgical diagnostics and therapy planning. LCRs were obtained for orthodontic cephalometric analysis and treatment planning. Patient population consisted of 20 women and 16 men, ranging in age from 18 to 51 years. This study's inclusion criteria were completed bone growth and the presence of all dental supporting zones according to the Eichner classification with natural dentition.¹³ Exclusion criteria were craniofacial malformations, performed maxillomandibular advancement, bone trauma, and pathological processes in the potential bone donor regions (chin, mandibular retromolar region, and zygomatic alveolar crest, respectively). Informed consent was obtained from all participants and/or their legal guardian(s). The retrospective radiological analysis was performed in accordance with the Declaration of Helsinki, approved by the local ethics committee of the University Medical Center Goettingen (vote number: DOK_342_2015).

Radiological evaluation

Two investigators independently performed all analyses. Inter-rater reliability was confirmed using Bland-Altman plots (data not shown).

In each PR, the mean value of both jaw angles (Ang. Mand.) was determined. In addition, the distances of the root tips of the mandibular middle incisors (RT1) and second molars (RT7) to the mandibular base were measured (Figure 1A). The ratio of both distances (RT1/RT7) was calculated. All PRs were evaluated using the SIDEXIS XG® software (Sirona Dental Systems GmbH, Bensheim, Germany).

In each LCR, eight different angles were measured, as seen in Table 1 and Figure 1B. The index of upper and lower face height was determined, and the structural method according to Björk modified according

to Hasund was applied (Table 1).¹⁴ The entire cephalometric analysis was performed using the ivoris®analyze software (Computer Konkret AG, Falkenstein, Germany).

All CBCT scans were analysed using the Ez3D Plus® software (Vatech Company, Hwaseong, Korea). Measurements of the chin were made by determining the horizontal and vertical bone dimension, as seen in Figure 1C. In detail, a distance of 5 mm was maintained to the dental root tips and the mental foramen, and a distance of 2 mm was maintained to the lingual and caudal surfaces of the mandibular bone. Subsequently, the distance between the root tips of the canines and the central incisors to the caudal surface of the mandible was measured (CV1 to CV3). Perpendicular to these three vertical distances, the width of the alveolar ridge was measured at three points each (CS1 to CS9). Analogous to the width measurements, the horizontal extent of the potential bone graft was measured at three locations (CH1 to CH3).

As there is no clear distal boundary in the mandibular retromolar region, the mesiodistal length was set at 20 mm for the analysis. Safety distances of 2 mm to the inferior alveolar nerve, to the second molar, and to the lingual surface of the mandibular bone were maintained. The vertical distance from the inferior alveolar nerve to the occlusal bone surface was determined at three different points (MN1 to MN3). Along the three vertical measurements, the alveolar ridge width was determined at right angles at three points each (MW1 to MW9). A schematic representation is presented in Figure 1D.

For the analysis of the zygomatic alveolar crest (Figure 1E), the symmetrically tapered envelope point was marked in the axial view of the CBCT scan. From this point, a dorsal and ventral section of 5 mm each was drawn, resulting in a total graft width of 10 mm. The caudal limit of the graft was either the floor of the maxillary sinus or the root tip of the molar located there. Starting from this plane, a cranio-caudal length of 10 mm was marked. Along the marked area with a length and width of 10 mm, the bone thickness was measured at nine points (ZA1 to ZA9). For this purpose, the coronal section plane was moved parallel to the turnover point of the zygomatic alveolar crest. The first three measurements were taken along the ventral border of the bone block at the cranial (ZA1) and caudal (ZA3) ends, as well as centrally (ZA2). This procedure was repeated along the distal border (ZA7 to ZA9). Three measurements were also taken along the envelope point (ZA4 to ZA6).

Finally, the bone volumes for all three bone harvesting regions were calculated (V_{chin} , V_{retro} , V_{crista}). In the chin region (V_{chin}), the mean values for the vertical bone height (CV), horizontal bone width (CH) and sagittal bone depth (CS) were calculated and multiplied with each other. For the volume determination of the retromolar bone block (V_{retro}), the mean values for the distance of the inferior alveolar nerve to the occlusal bone surface (MN) and the width of the bone block (MW) were calculated and multiplied by the specified length of 20 mm. The volume determination in the zygomatic alveolar crest (V_{crista}) follows the same principle. The height and width of the bone block were set at 10 mm each and were multiplied by the average thickness of the graft (ZA).

Statistical analysis

The entire data were tested for normal distribution using the Shapiro–Wilk test. Statistical analysis was performed using Student's t-test, chi-square test, linear regression, logistic regression with backward removal algorithm, and Pearson correlation. Box-whisker plots and scatterplots were used for graphical representation. All tests were performed at a significance level of $\alpha = 5\%$, using the statistical software STATISTICA® (StatSoft Europe GmbH, Hamburg, Germany) and SPSS® (IBM Corporation, New York, USA).

Results

Panoramic radiograph evaluation

In PR evaluation, higher distances between the root tips of the mandibular middle incisive (RT1) and the lower mandibular base were measured, compared to the root tips of the second mandibular molars (RT7). Overall, the average vertical bone height in the chin region was higher than that in the mandibular second molar region. However, larger standard deviations were found for the analysis in the chin region compared to those in the molar region (Table 1).

Cephalometric analysis

The detailed data of the cephalometric analysis in the LCR, along with the indices and the Hasund scores, are encapsulated in Table 1.

Bone volume analysis

Chin region

The analysis revealed that the horizontal extent of the chin region was the highest in the middle position (CH2). The highest standard deviation was measured for the horizontal expansion at CH3. With a distance of 2 mm from the mandibular base, this was the most caudal of the three horizontal measurement points and was near the bony base of the chin region, which seems to be subject to higher interindividual standard deviations. In the vertical bone analysis, the highest mean values were measured for the middle position (CV2). If a safe distance (5 mm) from the tooth apex is maintained, the chin provides more bone in the vertical dimension in the area of the lower incisors than below the canines. The analysis for the CV1 and CV3 measurement points barely showed any differences because of the lateral symmetry. This is also similar to the sagittal evaluation. The bone thickness below the canines is equally close in the lateral comparison owing to symmetry. On average, the highest bone thickness was measured at measuring point CI5. The calculations for the bone volume in the chin region resulted in a mean value of $3.10 \text{ cm}^3 \pm 1.11 \text{ cm}^3 \text{ SD}$.

Mandibular retromolar region

The average distance between the occlusal bone surface and the inferior alveolar nerve was the highest at the most distal measurement point (MN3). On average, the vestibular bone wall was thicker at the distal root (MR2) than at the mesial root (MR1) of the second mandibular molar. The buccolingual bone thickness was higher at the mesial measurement points (MW1 to MW3) than at the distal measurement points (MW4 to MW6 and MW7 to MW9). Differences were also demonstrated in craniocaudal direction. Thus, the average buccolingual bone thickness halfway between the bone surface and the inferior alveolar nerve (MW2, MW5, MW8) was higher than in the cranial (MW1, MW4, MW7) and caudal measurement positions (MW3, MW6, MW9). For the mandibular retromolar region, on average, a bone volume of $1.66 \text{ cm}^3 \pm 0.54 \text{ cm}^3$ SD was calculated.

Zygomatic alveolar crest

On average, the measurement positions at the inflexion point of the zygomatic alveolar crest (ZA4 to ZA6) had a higher bone thickness than the measurement points located on the lateral position (ZA1 to ZA3 and ZA7 to ZA9). With an average of $0.17 \text{ cm}^3 \pm 0.04 \text{ cm}^3$ SD, the zygomatic alveolar crest had the lowest bone volume among all bone harvesting regions examined.

Gender influence

The analysis revealed that gender had a significant impact on the horizontal bone thickness in the chin region (at measuring points CH2 and CH3; $p = 0.036$ and $p = 0.003$, respectively). On average, female gender showed 3.44 mm and 6.15 mm less bone thickness compared to the male gender at the CH2 and CH3 measuring points, respectively. Overall, no significant differences in the bone volumes in the three analysed bone harvesting regions were noted between the genders.

Correlation analysis

Chin region

The analysis revealed a significant negative correlation between the ML-NSL angle (LCR) and the CH3 distance (CBCT scan) (Table 2 and Figure 2A). Thus, a larger ML-NSL angle correlates with a transversely narrower chin and thus a reduced interforaminal distance. Moreover, a significant positive correlation between the ML-NSL angle and the vertical dimension of the bony chin (CV3) was observed (Table 2 and Figure 2B). A larger ML-NSL angle correlates with an increased distance between the root tip of the mandibular incisors or canines and the mandibular base. A strong correlation between RT1 and CV2 and a significant negative correlation between RT1 and CS4 were found (Table 2 and Figure 2C). The sagittal

extent of the bony chin cannot be evaluated in PR. A significant positive correlation was noted between the RT1 measuring point and the total bone volume of the chin region (Table 1 and Figure 2D).

Mandibular retromolar region

A significant negative correlation between the jaw angle (Ang. Mand.) measured in the PR and the vertical bone supply above the inferior alveolar nerve was observed (Table 3). Thus, an increased jaw angle correlates with a reduced distance between the occlusal bone surface and the inferior alveolar nerve. The distance between the root tips of the mandibular second molars and the mandibular base measured in the PR significantly correlates with the vertical bone height and the bone volume measured in the CBCT scans (Table 2).

The Gn-Go-Ar jaw angle measured in the LCR behaved analogously to the jaw angle measured in the PR with respect to its significant negative correlation with the vertical retromolar bone supply (Table 3).

A significant positive correlation between Gn-Go-Ar (LCR) and the jaw angle (PR) was found ($r = 0.89$; $p = 0.000$; Figure 2E). The basal sagittal distal jaw relation, characterised by increased ANB angle in the LCR, was positively correlated with the vertical bone supply (MN, Table 3) and the total retromolar bone volume (Vretro) (Table 3).

Likewise, the chin region, certain cephalometric growth patterns and types can be associated with CBCT measurements for the mandibular retromolar bone harvesting region. On the one hand, the basal sagittal distal relation (ANB angle enlarged), retrognathia (SNB angle reduced), and anterior rotations (Hasund score enlarged, and Gn-Go-Ar angle reduced) were significantly correlated with an increased bone supply in the retromolar region (Table 3). An increased jaw angle, on the other hand, was significantly correlated with a reduced bone supply in the mandibular retromolar region (MN3; Table 3).

Zygomatic alveolar crest

The analysis revealed a significant positive correlation between the bone volume in the zygomatic alveolar crest and the mandibular retromolar region (Table 4 and Figure 2F). A zygomatic alveolar crest with a stronger bone wall and a larger volume correlates with an increased retromolar bone supply. No significant correlations between the bone volume of the zygomatic alveolar crest and cephalometric parameters were found.

Discussion

The augmentation of intraoral bone deficiencies is a frequently performed procedure.¹⁵ Although exogenous bone substitute materials are becoming available in increasing numbers, harvesting autogenous bone crafts is still considered the clinical gold standard.¹⁶ The selection and evaluation of an

ideal donor site is an important prerequisite, and has already been described by various authors using three-dimensional radiological techniques (CBCT and computed tomography, CT).¹⁷⁻²⁰ In this study, we examined the possibility of using routine two-dimensional dental radiographs to acquire information about the bone supply of commonly used intraoral bone donor regions prior of therapy planning, which can be used during initial consultation.

The measured bone volumes in the three different donor regions differed significantly in the present analysis. While the chin region offers the largest amount of bone for augmentation ($3.10 \pm 1.11 \text{ cm}^3 \text{ SD}$), only small volumes can be obtained from the mandibular retromolar region ($1.66 \pm 0.54 \text{ cm}^3 \text{ SD}$) and the zygomatic alveolar crest ($0.17 \pm 0.04 \text{ cm}^3 \text{ SD}$).

These results are comparable to those of Zeltner and colleagues,¹⁷ who described an average bone volume of $3.5 \pm 1.3 \text{ cm}^3 \text{ SD}$ and $1.8 \pm 1.1 \text{ cm}^3 \text{ SD}$ for the chin and mandibular retromolar region, respectively.¹⁷ The slightly higher values in the retromolar region compared to this study could be explained by the fact that a proportion of studied patients had a distally shortened dentition.¹⁷ Moreover, the mesiodistal length of the bone block was not determined equally for all bone grafts.¹⁷ Thus, patients with distally shortened dentition have larger overall bone volume in the mandibular retromolar region. These patients might be particularly suitable for harvesting compacta shells, as the bone height is reduced because of local atrophy, while the mesiodistal extent of the removable bone block increases because of the missing molar.^{3, 17}

However, other characteristics besides the bone volume may influence the surgeon's decision when selecting the right donor site. In this investigation, various cephalometric parameters in the PR and LCR were found to be significantly correlated with the three-dimensionally measured bone dimensions in frequently used bone donor regions.

Patient's growth type could play a substantial role in the process of decision making. Patients with a vertical growth type have an increased vertical bone supply in the chin region between the apices of the incisive and the mandibular base. At the same time, a reduced interforaminal distance is expected in such patients. Moreover, the chin tends to be thinner in a sagittal direction in such cases, resulting in a reduced distance to the lingual cortex. Therefore, in patients with a vertical growth pattern, the interforaminal distance and the distance to the lingual cortical bone might be more limiting factors in bone harvesting than the distance between the mandibular base and the apices of the incisive, and more bone could be harvested in vertical dimension. Such a narrowing of the alveolar ridge in vertical growth-type patients has also been described by Handelman, and, together with the elongation of the mandibular incisors, represents a compensatory mechanism.^{21, 22} The involvement of the bony chin dimensions in such compensatory mechanisms has also been affirmed in previous studies.²³⁻²⁵ Although the sagittal thickness of the bony chin cannot be directly assessed in PR, a small distance between the root tip of the middle incisive and the mandibular base correlates with an extended chin in a sagittal direction. In the case of an enlarged distance between the root tip of the middle incisive and the mandibular base in the

PR, the tendency to reduce the distance to the lingual cortex must be taken into account when removing a bone block.

Significant correlations between cephalometric parameters and the bone supply were also observed for the mandibular retromolar region. Patients with a distal bite position, according to the ANB and SNB angles, in addition to a small jaw angle (Ang. Mand.), could be particularly interesting for retromolar bone block harvesting. A distal bite position could lead to a compression of the retromolar space, which results in an increased bone supply. Whether such compression possibly reduces the mesiodistal extent of the retromolar bone block was not tested in this study and should be the subject of further investigations. Compared to this study, no correlations between ANB angle and the total mandibular retromolar bone volume were demonstrated by others.^{26, 27} This suggests that bone volumes of individual mandibular regions correlate with cephalometric parameters, while other areas exhibit either no or opposite effects. The distance between the root tips of the second mandibular molars and the mandibular base in the PR significantly correlates with the mandibular retromolar bone volume. It is likely that this distance captures the vertical dimension in the mandibular retromolar region, which is significantly involved in the supplied bone volume.

The bone volume of the zygomatic alveolar crest exhibits no correlations with the measurements in the PR and LCR and only correlates with the mandibular retromolar bone volume. A plausible explanation of this observation could be that at least the bone thickness of the zygomatic alveolar crest correlates less with orthodontic growth patterns than with characteristic trajectories of masticatory loading.²⁸ As part of the vertical zygomatic pillar, the zygomatic alveolar crest is where the masticatory pressure is transmitted and distributed.²⁸ These main force lines extend over the zygomatic alveolar crest and the mandibular retromolar region, especially over the linea obliqua. Corresponding thickenings of the compacta can be formed in response to these force effects.²⁸ It has been previously demonstrated that a strongly pronounced horizontal growth type correlates with increased masticatory force delivery.²⁹ However, no statistically significant correlation between the Hasund score and the bone dimensions of the zygomatic alveolar crest was found in this study. To investigate a possible effect between the masticatory force delivery and the bone supply of the zygomatic alveolar crest, further studies should be conducted.

When examining gender-specific differences in the bone supply, no statistically significant correlations were found. Existing correlations between bone volumes and cephalometric parameters exhibited no dependence on gender. However, the interforaminal distance is significantly larger in the male population studied.

Conclusions

The added value of the most commonly used radiographic methods in dentistry and oral and maxillofacial surgery (PR and LCR) in the search for suitable intraoral bone donor regions before planning alveolar ridge augmentation was analysed. Significant correlations were found between the cephalometric growth patterns and the bone dimensions of different intraoral bone harvesting regions,

which could be helpful in finding suitable donor regions and defining indications and would justify further diagnostic options such as CBCT or CT scans.

Abbreviations

PR Panoramic radiograph

LCR Lateral cephalometric radiograph

CBCT Cone-beam computed tomography

Declarations

Ethics approval and consent to participate

The retrospective radiological analysis was performed in accordance with the Declaration of Helsinki, approved by the local ethics committee of the University Medical Center Goettingen (vote number: DOK_342_2015). Informed consent was obtained from all participants and/or their legal guardian(s).

Consent for publication

Not applicable.

Data availability

The datasets generated and/or analysed during the current study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

PB and BW were mainly responsible for interpreting the results and writing the manuscript. TS was mainly responsible for the evaluation and generation of data. HS revised the manuscript. WH was mainly

involved in the planning and implementation of the trial.

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Tables

Table 1

Descriptive statistics of PR, LCR and CBCT evaluation. Distances are given in [mm], angles in degrees [°], index in percent [%], Hasund in [score] and bone volume of each donor region in [cm³].

Parameter	N	Mean value	Minimum	Maximum	SD
RT1 [mm]	36	25.39	14.37	34.02	4.80
RT7 [mm]	36	13.19	7.50	20.53	3.28
RT1/RT7 [mm]	36	2.02	0.90	2.95	0.52
Jaw angle [°]	36	127.50	111.08	140.40	7.20
SNA [°]	36	80.16	68.70	90.90	5.26
SNB [°]	36	78.16	62.70	94.25	8.28
ANB [°]	36	1.88	-14	12.60	6.23
ML-NSL [°]	36	33.26	10.05	51.25	10.43
NL-NSL [°]	36	9.11	1.20	21.55	4.55
ML-NL [°]	36	24.15	2.15	42.65	9.22
NSBa [°]	36	131.89	117.85	168	9.30
Gn-Go-Ar [°]	36	125.33	103.05	138.95	8.57
Index [%]	36	77.36	64	101	7.97
Hasund [score]	36	2.47	-12	17	6.96
Vchin [cm ³]	36	3.10	1.59	6.16	1.11
Vretro [cm ³]	36	1.66	0.69	2.83	0.54
Vcrista [cm ³]	36	0.17	0.10	0.25	0.04

Table 2

Pearson correlation analysis between PR/LCR parameters and CBCT measurements for the chin region.

PR/LCR	CBCT	Correlation coefficient	p-value
RT1	CV1	0.75	0.000
	CV2	0.83	0.000
	CV3	0.70	0.000
	CS4	-0.48	0.003
	Vchin	0.67	0.000
RT7	Vchin	0.41	0.013
ML-NL	CH1	-0.34	0.042
	CH2	-0.44	0.007
	CH3	-0.59	0.000
	CV1	0.44	0.008
	CV2	0.43	0.009
	CV3	0.49	0.002
	CS4	-0.44	0.007
ML-NSL	CH1	-0.36	0.033
	CH2	-0.50	0.002
	CH3	-0.66	0.000
	CV1	0.45	0.006
	CV2	0.43	0.009
	CV3	0.48	0.003
	CS4	-0.50	0.002
Hasund	CH3	0.53	0.001
	CV1	-0.44	0.007
	CV2	-0.43	0.009
	CV3	-0.47	0.004
	CS4	0.46	0.005
ANB	CV3	0.43	0.009
Gn-Go-Ar	CH3	-0.41	0.012
Index	CV1	-0.46	0.005

CV2	-0.42	0.011
CV3	-0.41	0.014

Table 3

Pearson correlation analysis between PR/LCR parameters and CBCT measurements for the mandibular retromolar region.

PR/LCR	CBCT	Correlation coefficient	p-value
RT7	MN1	0.51	0.002
	MN2	0.54	0.001
	MN3	0.41	0.013
	Vretro	0.40	0.017
Jaw angle	MN3	-0.41	0.013
SNB	MN1	-0.34	0.040
	MN2	-0.45	0.006
	MN3	-0.41	0.012
ANB	MN1	0.49	0.003
	MN2	0.57	0.001
	MN3	0.34	0.044
	Vretro	0.35	0.039
Gn-Go-Ar	MN3	-0.47	0.004
Hasund	MN3	0.50	0.002

Table 4

Pearson correlation analysis between CBCT measurements of the zygomatic alveolar crest and the mandibular retromolar region.

CBCT (zygomatic)	CBCT (retromolar)	Correlation coefficient	p-value
ZA8	MN1	0.51	0.002
	MN2	0.45	0.007
	MW2	0.44	0.008
	MW3	0.35	0.039
	MW5	0.55	0.001
	MW9	0.35	0.039
ZA9	MN1	0.48	0.003
	MN2	0.45	0.002
	MN3	0.39	0.018
	MW2	0.34	0.044
Vcrista	Vretro	0.52	0.001

Figures

Figure 1

Please See image above for figure legend.

Figure 2

Please See image above for figure legend.

Supplementary Files

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- [SupplementaryFigure3.jpg](#)