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Unusually high prevalence of cervical ribs in an 18th-Century Hungarian town: The impact of a tuberculosis epidemic

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ABSTRACT

Tuberculosis (TB) ravaged the Hungarian town of Vác in the 18th century. Nearly all of the young and middle-aged adults buried in the Dominican Church were infected with TB. Therefore, most women were likely infected with *Mycobacterium tuberculosis* (MTB) during pregnancy. In rodents, disruptions in early gestation, when the head-to-tail patterning of the embryo occurs, often result in an increased incidence of cervical ribs. Because TB severely disrupts pregnancy, we hypothesized that these disruptions would result in an increased number of cervical ribs in Vác residents. We examined 58 skeletons and found, as predicted, that the incidence of cervical ribs is exceptionally high in this population. Cervical ribs are approximately twenty-five times more common than in the healthy general population and shifts of the thoracolumbar boundary two to five times more common. Cervical ribs are usually associated with other congenital anomalies, including other homeotic vertebral transformations. Homeotic transformations at different vertebral boundaries were usually in the same direction and sometimes involved three boundaries. This implies a prolonged disruption of pregnancy and alterations in multiple *Hox* gene expression domains. Our study emphasizes that a high incidence of cervical ribs indicates vulnerability. Our data support the idea that cervical ribs can be induced not only by genetic changes, but also by infectious diseases and thus by environmental perturbations of pregnancy.

1. Introduction

Tuberculosis (TB) has been present in the Carpathian Basin for at least 35–36 thousand years (Lee et al., 2023; Pálfi et al., 2023). It was also present in the Neolithic and Bronze Age (Masson et al., 2013; Gémes et al., 2023) and became widespread in the Avar period (6th-9th centuries) and after a lower incidence in the 10th and 11th centuries when the population was smaller (Hungarian conquest period and early part of the Árpádian dynasty), the number of cases continued to increase after the 11th century (Marcsik et al., 2006; Kiss et al., 2023). In Europe in general, the number of infections increased similarly after the Middle Ages and became epidemic in the 18th and 19th centuries (Daniel, 2006; Zürcher et al., 2016; Barberis et al., 2017). In Hungary, in the wealthy pre-industrial town of Vác, tuberculosis was found to be an epidemic among residents buried in the Dominican Church in the 18th and 19th centuries (Fletcher et al., 2003; Donoghue et al., 2011). During the renovation of the church in 1994-95, a large number of naturally mummified and well-preserved individuals was discovered in sealed crypts that had been used for burials for more than a century, between 1731 and 1838 (Pap et al., 1997, 1999). The mummies were well-documented and came from several middle-class families and clerics. Names and ages at death could be determined for 199 of the 265

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mummies, and in many cases, family relationships could be established (Pap & Szikossy, 2015). A remarkably high *Mycobacterium tuberculosis* (MTB) infection rate of 67.7 % was found in a study that examined mummified and skeletal tissues from 232 individuals for the presence of MTB DNA (Donoghue et al., 2011). Approximately half of the deceased children had infected tissues (46.5 %), while almost all deceased young and middle-aged adults were positive (89.7 %) and two-thirds of those over 65 years old (69.6 %). Some of the individuals had highly localized and probably latent infections, but at least 35 % of the individuals had active infections that had spread to several tissues. The overall high prevalence of 67.7 % is most likely an underestimate: when single sites were sampled from an individual, 55.8 % of them were found to be positive, whereas when multiple sites were sampled 78.5 % of individuals were found to be positive (Donoghue et al., 2011). Thus, a positive diagnosis is more certain than a negative diagnosis.

Tuberculosis is a serious disease and often affects pregnancy outcomes with greatly increased rates of fetal and maternal mortality and morbidity (Figueroa-Damián & Arredondo-García, 2001; Sobhy et al., 2017; Miele et al., 2020). For example, Miele et al. (2020) found a threefold increase in maternal deaths and a ninefold increase in miscarriages among pregnant women with active TB infection. As infection rates were particularly high among young deceased adults at Vác (Donoghue et al., 2011), it is likely that many of the mothers of the mummified individuals had active TB infections during their pregnancies. As a result, these pregnancies may well have been affected.

When pregnancies end in miscarriage or stillbirth, a remarkably high number has been shown to have a disturbed vertebral pattern. Cervical ribs in particular are extremely common (approximately 50 % or more, McNally et al., 1990, Galis et al., 2006; Ten Broek et al., 2012, Schut et al., 2016). Cervical ribs are ribs on the seventh, normally rib-less vertebra, indicating a homeotic transformation of a cervical rib-less vertebra into a thoracic rib-bearing one (Fig. 1). The result is a reduction in the number of cervical vertebrae. The number of cervical vertebrae in humans is normally seven, as in virtually all mammals, regardless of the length of their necks (Cuvier, 1835; Lebоucq, 1898; Starck, 1979; Varela-Lasheras et al., 2011). Deviations from this highly conserved number of seven are associated with disease, congenital anomalies and stillbirths in humans and other mammals (Gladstone & Wakeley, 1932; Adson & Coffey, 1927; Keeling & Kjaer, 1999; Tubbs et al., 2006; Bates & Nale, 2005; Steigenga et al., 2006; Galis et al., 2006; Reumer et al., 2014; van der Geer & Galis, 2017).

Cervical ribs are induced by environmental or genetic perturbations of early organogenesis, at around the time that the neck-trunk boundary is established (Galis et al., 2021). Teratology experiments in mice and rats have shown that environmental perturbations such as heat shock, boric acid, valproic acid, salicylate and retinoic acid, can induce shifts in the expression of *Hox* genes in the embryonic tissue from which the vertebrae develop (somatic mesoderm) and concomitantly in the development of the cervical ribs (Li & Shiota, 2000; Wéry et al., 2003; Chernoff & Rogers, 2004; Steigenga et al., 2006). Cervical ribs and other displacements of the cervicothoracic boundary are caused by earlier perturbations of embryogenesis than more caudal displacements (Kessel & Gruss, 1991; Rogers & Mole, 1997; Li & Shiota, 2000; Rengasamy & Padmanabhan, 2004). Therefore, when multiple regions of the vertebral column are affected by transformations, the disruption of early embryogenesis is likely to have lasted for a longer time (ten Broek et al., 2012). The timing and duration of the disruption of the vertebral patterning appear to be more important than the specific nature of the disruption (Wilson, 1965; Lubinsky, 2015).

We hypothesized that because pregnancies are severely affected by TB, we should find an increased incidence of vertebral patterning defects. Particularly in the early vulnerable period of cervical patterning, this should result in an increased incidence of cervical ribs and rudimentary or absent first thoracic ribs. In this study, we tested this hypothesis by examining the head-to-tail pattern of the vertebral column in 58 of the Vác mummies. We focused not only on changes in the number of cervical vertebrae, but also on changes in the number of thoracic and lumbar vertebrae and the total number of presacral vertebrae that are due to later disturbances of the pregnancy. Abnormalities in these latter numbers are also of interest, as we have previously found in deceased human fetuses and neonates that disturbances often occurred along a longer part of the vertebral column, indicating a longer duration of the disturbance (ten Broek et al., 2012). We found that the more vertebral regions had been affected, the stronger the association with medical problems (op. cit.). Therefore, we determined how many vertebral regions had been affected.

We also examined the hypothesis that cervical ribs may be associated with a higher incidence of positive MTB diagnosis than those without cervical ribs. The rationale is that if a pregnant mother is infected with MTB, not only is her child more likely to have cervical ribs, but the child is also more likely to be infected.

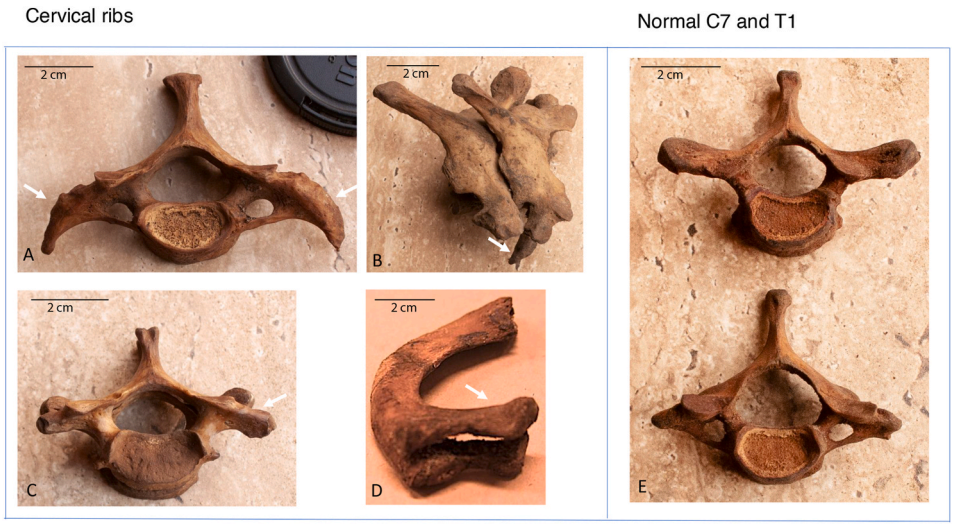

Fig. 1. Examples of cervical ribs (A–D), A) Bilateral large cervical ribs that are fused to the transverse processes of the 7th vertebra (Vác no. 195), B) Small cervical rib on the right, with fusion to the transverse process of the 7th vertebra still visible (Vác no. 153), C) Small cervical rib fused to the transverse process of the 7th vertebra on the left, D) Large cervical rib on the left, fused to the first thoracic rib, so that together they have become a forked rib (Vác no. 146), E) A normal 7th cervical and first thoracic vertebra (Vác no. 156).

2. Methods

We analyzed the vertebral columns of 58 Vác mummies kept in the Hungarian Natural History Museum. Age and sex were known for most individuals from the Dominican Church archives (Suppl. Table 1). For individuals without parish records, age and sex were estimated using standard bioarchaeological methods (Buikstra & Ubelaker, 1994). Most of the mummies, 52 (87.93 %), were adults (>20 years old), of which 20 were female, 24 were male and 7 were of unknown sex (n.a.). There were 2 young adults (18–20 years old, 1 female, 1 male) and 5 children (5–14 years old, 2 females, 2 males, 1 n. a.). Only vertebral columns where the number of cervical and/or presacral vertebrae could be determined were included in the analysis. The position of the cervicothoracic boundary could be determined for 54 skeletons (Suppl.Table 1), the position of the thoracolumbar vertebra for 55 skeletons, the position of lumbosacral boundary for 53 skeletons, and the complete presacral formula for 51 skeletons. The MTB infection status of 36 skeletons was known (raw data from Donoghue et al., 2011, listed in Suppl. Table 1).

2.1. Variations in vertebral identity and number

If a seventh vertebra had a rib, it was considered to be a transitional cervicothoracic (CT) vertebra which is an anteriorization of the CT boundary. If there was a fusion of a small rudimentary cervical rib with the transverse process of the seventh vertebra (often called an apophysomegaly), a conservative approach was taken and the vertebra was counted as a transitional cervicothoracic vertebra only if the transverse process was at least 15 % longer than that of the first thoracic vertebra (Fig. 1). We checked for rudimentary or absent ribs on the eighth vertebra, but such a posteriorization of the CT boundary did not occur.

Ribs on the 19th or 20th vertebra were considered rudimentary if they were less than half the length of the rib on the adjacent thoracic vertebra and these vertebrae were considered to be transitional thoracolumbar (TL) vertebrae (Fig. 2G). Rudimentary or absent ribs on the 19th vertebra (Fig. 2G) are an anteriorization of the TL boundary and rudimentary or full ribs on the 20th vertebra are a posteriorization of the TL boundary.

Partially sacralized lumbar vertebrae were considered transitional lumbosacral vertebrae (LS) if, on at least one side the transverse process was enlarged and fused to, or touched the adjacent sacral vertebra or ilium (Fig. 2G). Partially lumbarised sacral vertebrae were considered to be transitional lumbosacral vertebrae (LS) if, on at least one side, the transverse process had no bony connection with the adjacent sacral vertebra or ilium (Fig. 2F). A partially or fully sacralized 24th vertebra represents an anteriorization of the lumbosacral boundary, while a partially or fully lumbarized 25th vertebra represents a posteriorization of the lumbosacral boundary.

For the number of vertebrae in a vertebral region, transitional vertebrae were counted as having half the identity of the two adjacent regions, e.g., transitional cervicothoracic vertebrae were counted as half cervical/half thoracic.

The presacral number was determined as the sum of the cervical, thoracic and lumbar vertebrae. Sometimes one or more vertebrae were missing, but the absence could be determined by their shape and by fitting all the vertebrae together in order. Such missing vertebrae are indicated in Suppl. Table 1 with the actual number present followed by a "+" sign and the inferred missing number, e.g., "6 + 1″ for 6 cervical vertebrae and one inferred missing cervical vertebra.

2.2. Shifts of one or more vertebral boundaries

We coded where the vertebral boundary shifts occurred, with the presence of a cervical rib being coded as a CT shift (rudimentary or absent first thoracic ribs, which also represent a CT shift, were absent in this study, as noted above), a shift at the TL boundary as a TL shift (rudimentary or absent 12th rib, or rudimentary or complete lumbar ribs), a shift at both the cervicothoracic and thoracolumbar boundaries as CT_TL shifts, a shift at all three boundaries as CT_TL_LS, and so on; A regular presacral pattern of 7 cervical, 12 thoracic and 5 lumbar vertebrae is indicated as R (no shifts).

2.3. Statistics

Exact 95 % binomial confidence intervals (Clopper & Pearson, 1934)

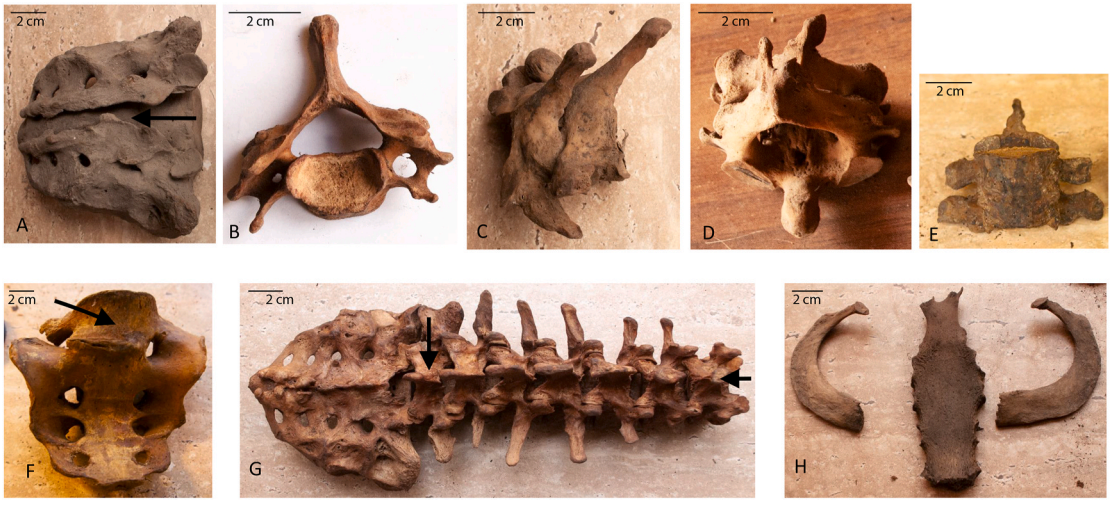

Fig. 2. Congenital anomalies associated with cervical ribs. A) Spina bifida occulta, a neural tube defect that causes the neural spines not to close (indicated by arrow; Vác no. 153), B) Asymmetric 6th cervical vertebra (Vác no. 178), C) Fused 7th cervical and 1st thoracic vertebra (Vác no. 153), D) Fused 2nd and 3rd cervical vertebrae (Vác no. 153), E) Fused 1st and 2nd thoracic vertebrae (Vác no. 180), F) Sacrum with an asymmetric transitional lumbosacral vertebra (indicated by the arrow). This is due to lumbarization of the 1st sacral vertebra on the right (i.e. the right part of the vertebra has a more lumbar shape, with the transverse process not fused laterally to the ilium and not fused caudally to the adjacent sacral vertebra; Vác no. 260), G) Part of a vertebral column showing symmetric homeotic transformations and asymmetry in the length of lumbar transverse processes. The most caudal lumbar vertebra (indicated by the vertical arrow) has been sacralized on the left (i.e. it has a more sacral shape and is fused to the sacrum) and the twelfth thoracic vertebra (indicated by the horizontal arrow) has been lumbarized on the left (on the left a lumbar transverse process and on the right a rib articulation). There is a strong asymmetry in the length of the transverse processes of the first and fourth lumbar vertebrae (Vác no. 195), H) Sternum with asymmetrical left and right first ribs (Vác no. 153).

were calculated for the probabilities of occurrence of cervical ribs in this study and compared to reported occurrences in the literature for adults of the general population, estimated from dry skeleton studies and radiographs, excluding estimates from patient populations (Galis et al., 2006).

We tested for an association between positive MTB status and changes in the number of cervical vertebrae and presacral vertebrae using Fisher's exact test (Fischer, 1934). The hypotheses were tested at $\alpha = 0.05$ significance level. Furthermore, we performed simulations to assess the power of this test for association at the given sample sizes (Script added as Supplementary Material). Data sets were simulated with different probabilities of observing a cervical rib when the MTB test was positive (values ranging from zero to one in increments of 0.01), while preserving the number of patients with and without a positive MTB test result, and keeping the probability of having a cervical rib when the MTB test result was negative constant (at 0.154). One hundred replicate data sets were simulated for each probability, and a Fisher test was applied to each data table. We plotted the percentage of significant tests as a function of the probability of having a cervical rib when the TBC result is positive. These percentages represent the dependence of the power of the test on these probabilities of association. The probability of a cervical rib among individuals with a positive MTB result was 0.304 in the data.

3. Results

3.1. Cervicothoracic boundary shifts

All cervicothoracic boundary shifts involved cervical ribs at the seventh vertebra, resulting in an anterior shift of the cervicothoracic boundary. There were no absent or rudimentary first thoracic ribs (posterior shift of the cervicothoracic boundary). In this population in which almost everyone had been infected with tuberculosis, the incidence of cervical ribs (Fig. 1) was extremely high at 24.07 % (13 of 54). This incidence is much higher than that estimated in large-scale studies of the general adult population based on dry skeletons and radiographs. Estimates from patient populations were excluded. In skeletal studies, the incidence varied from 0 to 1.07 %, with almost all shifts occurring in the cranial direction (Ancel & Sencert, 1902; Bardeen, 1904; Steinbach, 1889; Staderini, 1894; Bianchi, 1894; Paterson, 1893; Topinard, 1877; Fishel, 1906; Lanier, 1944; Spear et al., 2023). In radiological studies, the incidence was between 0.05 and 1 %, including both cranial and rare caudal shifts (Sycamore, 1944; Southam & Bythell, 1924; Steiner, 1943; Crimm, 1952; Henderson, 1913; Berner, 1944). The highest incidence reported in these studies was 1.07 % (all cranial shifts, Lanier, 1944). There is a significant difference between our results and those of Lanier's study (24.07 %, confidence interval 13.5–37.6 vs 1.07 %, confidence interval 0.39–2.32).

Cervical ribs were present bilaterally in all cases except one. In most cases, they were asymmetrical in shape and length (Fig. 1C and D).

3.2. Thoracolumbar boundary shifts

Thoracolumbar boundary shifts were as common as cervical ribs (13 out of 55, 23.64 %), and included both cranial and caudal shifts. Eleven of the 13 skeletons had rudimentary ribs on the 19th vertebra, while two had 13 thoracic vertebrae, due to the presence of ribs on the 20th vertebra (lumbar ribs). This incidence is two to five times higher than that observed in large-scale studies of the adult general population, based on dry skeletons (4.74 % Bardeen, 1904 [N = 908], 12.4 % Lanier, 1944 [N = 559], 12.34 %, 9.52 % Spear et al., 2023 [N = 893). The pairwise differences with the general populations are significant, except for the study of Lanier (1944) where there is an overlap in confidence intervals (23.64 %, confidence interval 13.23–37.02 % (our study), 4.74 %, confidence interval 3.45–6.33 % (Bardeen, 1904), 12.34 %, confidence interval 9.73–15.36 % (Lanier, 1944), 9.52 %, confidence interval 7.67–11.64 % (Spear et al., 2023).

3.3. Lumbosacral boundary shifts

Lumbosacral boundary shifts (i.e., changes in the number of presacral vertebrae) occurred in both cranial and caudal directions (Fig. 2F and G). They occurred in fewer cases than shifts of the cervicothoracic and thoracolumbar boundaries, namely in 8 out of 54 cases (14.81 %), but the probability was not significantly different from the other boundaries (Fisher's exact test $p = 0.35$ in both cases). The number of presacral vertebrae varied between 23 and 25. Most of the changes were due to a transitional lumbosacral vertebra (scored as half lumbar and half sacral, three cases of sacralization of L5 and two cases of lumbarization of S1) and three were due to an additional or missing lumbar vertebra (once 23 and twice 25). 15.09 % (confidence interval: 6.75–27.59 %) is not significantly different from the 9–13.5 % incidence found in large samples of the general population, based on dry skeletons (Bardeen, 1904; Fischel, 1906; Willis, 1923; Spear et al., 2023). Studies with patient populations were excluded, as well as studies that did not record transitional lumbosacral vertebrae as a boundary shift.

3.4. Co-occurrence and direction of vertebral boundary shifts

When all three presacral regions of an individual could be evaluated, slightly more than one-third of the skeletons (19 of 51, 37.25 %) had an abnormal number of vertebrae in at least one vertebral region (Suppl. Table 1), while 32 of the 51 skeletons (62.74 %) had a regular pattern with 7 cervical, 12 thoracic, and 5 lumbar vertebrae. In almost half of the cases with abnormal patterning (10 of 19), there was an abnormal number in only one region (5x CT, 4x TL, 1xLS), and in the remaining 9 of 19, there was seven times a shift at two boundaries (3x CT-TL, 3x TL-LS, 1x CT-LS) and twice a shift at all three boundaries (CT-TL-LS). When the cervicothoracic shifts coincided with a thoracolumbar boundary shift, they were both anteriorly oriented, i.e., with rudimentary or absent twelfth thoracic ribs at the thoracolumbar boundary. The two individuals with shifts at all three boundaries were also all in the same direction, i.e., three in anterior direction (cervical ribs and missing twelfth ribs and a decrease in the number of presacral vertebrae). All three cases with shifts at the thoracolumbar and lumbosacral boundaries also involved shifts in the same direction, once in the anterior direction (rudimentary twelfth ribs and a decrease in the number of presacral vertebrae) and twice in the posterior direction (lumbar ribs at the thoracolumbar boundary and an increase in the number of presacral vertebrae). In the one case with a shift at the cervicothoracic and lumbosacral boundaries, the shifts were in opposite directions, an anteriorization of the cervicothoracic boundary coinciding with a posteriorization of the lumbosacral boundary (increase in the number of presacral vertebrae). Thus, shifts at multiple boundaries were in the same direction in all but one case (8 out of 9).

3.5. Sex and vertebral boundary shifts

There appears to be no difference in sex and vertebral boundary shifts. In 11 of the 13 CT shifts the gender was known, 5 times female and 6 times male. The same is true for TL shifts, 5 of the 11 thoracolumbar shifts were female and 6 were male. Of the six LS shifts with known sex, three were female and three were male.

3.6. Infectious status and vertebral boundary shifts

The percentage of individuals with a cervical rib and a positive infection status was almost twice (1.83) the percentage of individuals with a cervical rib and a negative infection status (7 out of 23, 30.43 % versus 2 out of 12, 16.67 %). Despite the frequency of cervical ribs being higher, the difference was not significant (Fisher's exact test, $p = 0.427$). However, the simulations show that the power of the Fisher test only

rises above 80 % for large probabilities of having a cervical rib when the MTB test is positive, i.e. at probabilities above 0.6 (Supplementary Fig. 1). For the observed probability, the power of the test was weak (below 20 %).

Of the 7 individuals with a cervical rib and a shift over a larger part of the vertebral column (CT-TL, CT-LS and CT-TL-LS) the infectious status was only known in 3 cases (two positive, one negative).

Of the eight cases with an abnormal presacral number, six had a known infectious status, three of them were positive (50 %) and three of them negative (50 %).

4. Discussion

4.1. Extremely high incidence of cervical ribs

We hypothesized that we would find an increased incidence of cervical ribs in this population from Vác, where almost all young adults had been infected with tuberculosis. Many of the mothers of the mummified individuals were likely to have had active tuberculosis (TB) infections during pregnancy, and TB often severely affects pregnancies. Cervical ribs are known to be caused by disturbances of early pregnancy. Here we find strong support for our hypothesis. The incidence of cervical ribs is extremely high, about 25 times higher than the estimated 1 % in the healthy general population (Bardeen, 1904; Fishel, 1906; Lanier, 1944; Galis et al., 2006; Galis et al., 2021). This is despite our conservative approach of only counting the seventh vertebra as having a fused cervical rib if its transverse process was at least 15 % longer than that of the first thoracic vertebra. This 15 % safety margin is usually not taken into account in human studies. The seventh vertebra is generally considered to have a fused cervical rib if its transverse process is longer than that of the first thoracic vertebra (Pionnier & Depraz, 1956; Merks et al., 2005; Brewin et al., 2009).

In individuals with cervical ribs, it is likely that TB affected the early embryonic head-to-tail patterning and *Hox* gene expression, causing a homeotic transformation of the seventh vertebra (Gaunt, 1994; Burke et al., 1995; Deschamps & Duboule, 2017). Our results further support that cervical ribs can be induced by environmental perturbations during early organogenesis, as previously shown in rodents (Rogers and Mole, 1997; Abdulrazzaq et al., 1997, Li & Shiota, 2000; Rengasamy & Padmanabhan, 2004, Massa et al., 2005).

Homeotic transformations at the thoracolumbar boundary were about as frequent as at the cervicothoracic boundary and two or more times as frequent as in the general adult population. Homeotic transformations at the lumbosacral boundary were only slightly more common than in the general population, but not significantly so.

Overall, there were many more homeotic vertebral transformations in this population than in the general population. By far the most dramatic increase was in the presence of cervical ribs, followed by a considerable increase in shifts at the thoracolumbar boundary and no increase at the lumbosacral boundary. This can be explained by looking at the stage of organogenesis at which cervical ribs can be induced. This early stage, sometimes called the phylotypic stage, is extremely vulnerable due to the strong global interactivity throughout the developing embryo. At later stages development becomes increasingly compartmentalized and more robust to perturbations (Galis & Metz, 2001; Galis et al., 2021).

4.2. Homeotic transformations occurring simultaneously and in the same direction

It has been shown previously that homeotic transformations of vertebrae are not isolated events, but are usually accompanied by other homeotic transformations in adjacent vertebrae (Fishel, 1906; Oostra et al., 2005; Galis et al., 2006; Varela-Lasheras et al., 2011; ten Broek et al., 2012). In fact, cervical ribs are in many cases accompanied by homeotic transformations at the thoracolumbar and/or lumbosacral boundary. Thus, these transformations involved a large portion of the vertebral column, sometimes including three vertebral boundaries. This is indicative of a patterning perturbation which persisted for a long time, as perturbations affecting the cervicothoracic boundary are induced at an earlier stage than those affecting the lumbosacral boundary (Rengasamy & Padmanabhan, 2004; Rogers & Mole, 1997; Galis et al., 2021). The multiple boundary shifts also indicate that alterations in multiple *Hox* gene expression domains must have occurred (Favier & Dollé, 1997; McIntyre et al., 2007; Guerreiro et al., 2013; Deschamps & Duboule, 2017).

Interestingly, shifts at multiple boundaries were usually in the same direction (8 out of 9), also in the two cases with shifts at all three vertebral boundaries. There were 7 times anteriorizations and one posteriorization. Such simultaneous homeotic transformations in the same direction have also been found in mice that had been exposed to retinoic acid during development (Kessel & Gruss, 1991). There, anteriorizations of all four vertebral boundaries, accompanied by anterior shifts of *Hox* gene expression domains, were found when exposure occurred at the end of gastrulation and the onset of organogenesis (embryonic day 7.3). When exposure occurred about one day later (embryonic day 8.5) this induced posteriorizations of the thoracolumbar and lumbosacral boundaries.

4.3. Cervical ribs and infectious status

We hypothesized that if a mother had had TB during pregnancy, not only would her child be more likely to have cervical ribs, but the child would also be more likely to be infected. We found that individuals with positive MTB infection tests were indeed nearly twice as likely to have cervical ribs as those with negative tests. However, this difference was not significant. This lack of statistical significance, however, is not particularly informative, due to a combination of factors. First, our simulations show that the small sample size makes achieving significance nearly impossible for our data (Supplementary Fig. 1). Second, the results are confounded by the uncertainty of the negative infection status. Often only one tissue was sampled from an individual, and when more than one tissue was sampled, the infection rate was much higher (78.5 vs 55.8 %). Another confounding factor is that, when a mother is infected during pregnancy, it can occur that her child will not contract the infection (Cohen, 1946; Ormerod, 2001). Furthermore, when an individual becomes infected in utero or as a neonate, there is a considerable risk of dying shortly after birth and skeletons of such a young age were not available to us (Figueroa-Damián & Arredondo-García, 2001; Ormerod, 2001).

4.4. Cervical ribs are associated with other congenital anomalies and indicate vulnerability

Cervical ribs are often associated with other skeletal abnormalities and a variety of congenital defects and diseases in humans (Galis, 1999; Galis et al., 2006; Furtado et al., 2011; ten Broek et al., 2012; Schut et al., 2016, 2020) and a wide range of other mammalian species, including Afrotherians and Xenarthrans (Varela-Lasheras et al., 2011), racing horses (cervical ribs described as bicipital and flared first ribs, May--Davis, 2017), domestic dogs (Brocal et al., 2018), Père David deer (Cuxart Erruz et al., 2024) and extinct woolly mammoths, woolly rhinoceroses and giant deer (Reumer et al., 2014; van der Geer & Galis, 2017; Cuxart Erruz et al., 2024). The strong interactivity during the early head-to-tail patterning is most likely the cause of the frequent and variable side-effects (Galis et al., 2006; Galis, 2023). Consistently, we found not only a high incidence of cervical ribs in the skeletons of this study, but also an abundance of skeletal anomalies, including abnormally shaped bones, marked bone asymmetry, vertebral fusions throughout the spine and the other homeotic vertebral transformations mentioned above (Fig. 2). One young man, who died at the age of eighteen, had so many abnormalities that he had never been able to

walk.

The association of cervical ribs with vulnerability is also supported by the increased incidence of cervical ribs in inbred populations of humans, pedigree dogs, racehorses, minipigs and Père David deer (Palma and Carini, 1990; Breit and Kunzel, 1998; Jørgensen, 1998; Brocal et al., 2018; Cuxart Erruz et al., 2024) and shortly before their extinction or extirpation during the Late Pleistocene, woolly mammoths, rhinoceroses and giant deer (Reumer et al., 2014; van der Geer & Galis, 2017; Cuxart Erruz et al., 2024). When inbreeding depression occurs, the frequent occurrence of congenital abnormalities is thought to be due to an increase in the prevalence of homozygous genotypes of recessive deleterious alleles after a genetic bottleneck (Charlesworth & Charlesworth, 1999; Hoglund, 2009; Bundgaard et al., 2021). This increase in maladaptive genotypes is presumably involved in the disturbance of the strong interactivity during the early head-to-tail patterning (Cuxart Erruz et al., 2024).

Therefore, our data support the idea that in humans, cervical ribs and associated abnormalities can be caused by both environmental and genetic changes, as has been previously found in rodents. Our data on this population during a TB epidemic and the data on inbred humans and other mammals support the hypothesis that cervical ribs are part of a set of associated congenital defects that arise very early in organogenesis and, more generally, indicate vulnerability.

CRediT authorship contribution statement

Frietson Galis: Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Alexandra A.E. van der Geer:** Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. **Tom J.M. Van Dooren:** Data curation, Methodology, Software, Writing – review & editing. **Tamás Szeniczey:** Formal analysis, Investigation, Writing – review & editing. **Tamás Hajdu:** Formal analysis, Investigation, Writing – review & editing. **Krisztián Kiss:** Investigation, Writing – review & editing. **Ildikó Pap:** Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ydbio.2025.08.019.

Data availability

The data are in the manuscript and supplementary data

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