

Blount disease and familial inheritance in Ghana, area cross-sectional study

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To cite: Jansen N, Hollman F, Bovendeert F, *et al.* Blount disease and familial inheritance in Ghana, area cross-sectional study. *BMJ Paediatrics Open* 2021;**5**:e001052. doi:10.1136/bmjpo-2021-001052

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bmjpo-2021-001052>).

Received 9 February 2021
Revised 31 March 2021
Accepted 4 April 2021

ABSTRACT

Objective The objective of this study is to study familial inheritance for Blount disease to create better understanding of the aetiology of Blount disease.

Methods After reviewing patient files and conventional roentgenologic imaging, 139 patients with Blount disease were included in this cross-sectional study, of which 102 patients were interviewed. During the interviews, patient characteristics and family history were collected. Blood samples were taken from five patients and three families and a whole exome sequencing was performed.

Results Although patients came from all over the country, 90% of the patients belonged to the Akan tribe. A positive family history was found in 63 families (62%), of which, almost two-third had a positive family history in a first-degree family member. In most of the cases (64%), the varus legs resolved over time. In 9%, severe bowing remained 'just like the patient'. The results of the whole exome sequencing did not show a genetic predisposition.

Conclusion This study describes a large group of Blount patients. Because of the high numbers of positive family history and the centralisation of patients in the Akan region, a familial predisposition is suggested. Further genetic research is essential for better understanding of the possible multifactorial aetiology in Blount disease.

INTRODUCTION

Blount disease is characterised by a growth arrest and disturbed endochondral ossification of the posteromedial part of the proximal tibia. This results in genu varum, internal rotation and procurvatum.¹⁻³ Three different forms of the condition are described, based on the age of onset of the condition. Infantile, or early onset, starts before the age of 4 years, juvenile onset starts between the age of 4 and 10 years and adolescent or late onset starts after the age of 10 years.^{2,4}

The aetiology of Blount disease is not well known. The best-found hypothesis is possibly a combination of factors such as obesity, early walking age, pre-existing varus and race.⁴⁻¹⁰ Although there are several hypotheses, most articles support the hypothesis of the combination of factors, often referred to as the 'increased mechanical force hypothesis'.

Most studies supporting the 'increased mechanical force hypothesis' are conducted

What is known about the subject?

- Blount disease is a rare paediatric orthopaedic disease, which results in genu varum, internal rotation and procurvatum.
- The best-found hypothesis is a combination of factors such as obesity, early walking age, pre-existing varus and race, also called 'increased mechanical force hypothesis'.

What this study adds?

- Detailed family history in a large group of patients with Blount disease.
- Large study in a sub-Saharan African country, until now most studies on the aetiology of Blount disease are conducted in high income countries.
- Two-third of the patients in the early onset group reported a positive family history for varus legs.

in high income countries, mostly the USA. The prevalence of overweight and obesity in the American population is much higher, respectively, 32% and 17%, compared with the prevalence in sub-Saharan Africa, respectively, 11% and 3%.^{11 12} This stands in contrast to earlier published work showing a strong relation between obesity and developing Blount disease in developed countries,^{6 8 13} and the relative high prevalence in the African population.^{9 14 15} Also in the USA, Blount disease was found more prevalent in the Afro-American ethnic group compared with the Caucasian ethnic group.^{4 6 7 16-20} It is suggested that Blount disease is more common in the African and Afro-American population because of the earlier walking age and the greater laxity of the knee ligaments compared with the Caucasian population.^{15 18} But this does not explain why relatively large groups of patients with Blount disease are found in Finland and Japan.^{21 22} In addition, a genetic predisposition is suggested.^{9 10 23}

Most studies describing familial occurrence of Blount disease are case reports or retrospective studies in which affected siblings



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were an incidental finding.^{10 22 24–27} The only studies which actively conducted a family history found a positive family history in 14% and 45% of the early onset Blount patients,^{21 28} and a negative family history for all adolescent Blount patients.^{19 21}

To the best of our knowledge, no studies focusing at genetic predisposition are conducted among patients with Blount disease.

In this study, we investigated the familial influences and possible familial predisposition in Blount patients. It is hypothesised that Blount disease is seen more often in children with a positive family history of Blount disease or varus legs compared with those with a negative family history and that there might be a familial predisposition.

METHODS

Patient files and conventional roentgenologic images from patients diagnosed with Blount disease seen in a mission hospital in rural Ghana between May 2010 and March 2018 were reviewed. In total, 206 patients with the diagnosis of Blount disease were selected. All patient files and X-rays were evaluated by an orthopaedic surgeon and the first author. Exclusion was based on patients younger than 2 years of age at presentation, missing patient files, diagnosis not made by an orthopaedic surgeon and no X-ray available for evaluation, X-ray did not meet the Langenskiöld classification for Blount disease.²² After exclusion, 139 cases of confirmed Blount disease were included. These patients were approached for an interview after informed consent was given. The interviews were conducted over the phone (n=74) or during a face-to-face meeting (n=28). In April 2018, 93 interviews were conducted by the first author. Because of the language barrier, the same translator was used for all the interviews. From nine patients, data conducted during interviews taken in December 2014 were used, because these patients were not reachable at the time of this research. Patients or the public were not involved in the design, or conduct, or reporting or dissemination plans of our research. The Ghanaian medical ethical committee has given ethical approval to perform this study (ref: CHRPE/AP/152/18).

Patient characteristics were collected through interviews (see online supplemental appendix 1). Tribes were allocated to one of the eight following ethnic groups: Akan, Mole-Dagbon, Ewe, Ga-Dangme, Gruma, Guan, Grusi or Mande, or assigned to 'others'.

Interviews were completed with one or both of the parents or the family member who raised the patient. In every case, the interviewee stated that there was a positive family history in the other side of the family, this needed to be confirmed by the other side of the family. A positive family history for bowed legs required to meet the following criteria; idiopathic varus deformity which started in childhood. Anamnestic cases of rachitic and polio were excluded. Self-reported family history has a sensitivity and specificity above 70% according to earlier

studies in cancer and non-communicable diseases.^{29 30} Janssens *et al*³⁰ noted that these numbers will be higher in if patients and family members are more aware of their condition. Blount disease is a visible condition and complicates daily mobilisation, this increases the awareness and therefore the accuracy of the self-reported family in Blount disease.

After the interviews were conducted, 13 families (patient and both parents) with the most comprehensive family history were selected for the genetic research in collaboration with the department of clinical genetics. From all 13 families, an extended family tree was made during a second interview, blood samples were taken and a second informed consent form was signed (online supplemental appendix 2).

From every family, two Ethylene Diamine Tetra Acetic acid (EDTA) tubes with blood were obtained per person, DNA was isolated within 7 days. Based on the extended family trees obtained from the 13 families, five patients and three families (patient and both parents) were selected for diagnostic whole exome sequencing (WES) and variant calling was performed as described.³¹ Briefly, exome capturing was done using the Agilent SureSelectXT Human All Exon v5 library prep kit (Agilent Technologies, Santa Clara, CA, USA). Libraries were sequenced on an Illumina HiSeq 4000 instrument (Illumina, San Diego, CA, USA) with 101 bp paired-end reads at a median coverage of 75× at BGI Europe (BGI, Copenhagen, Denmark). Sequence reads were aligned to the hg19 reference genome using Burrows-Wheeler Alignment version 0.5.9-r16.14. Variants were called using the unified genotype Genome Analysis Toolkit, version 3.2-2 and annotated in a custom-built annotation pipeline developed for diagnostics. WES was both used to identify potential causal variants in known Mendelian disease genes in pedigrees, and also to generate massive variant data sets of the exomes from all pedigrees which could then be compared between samples for shared identical (likely) pathogenic variants or for non-identical variation in a communal candidate disease gene. Variant interpretation and classification were done adhering to professional guidelines.³²

Continuous data are displayed as mean±SD and categorical variables are shown as a frequency and/or as a percentage.

RESULTS

Out of 139 cases with confirmed Blount disease, 102 were included for analysis. All 37 excluded patients were not included because they were not reachable for an interview (figure 1). Data presented in this study concern the interviewed 102 patients, unless stated otherwise.

Patient characteristics

Patient characteristics are displayed in table 1. Most patients were allocated to the early onset group (n=84), followed by the juvenile onset group (n=14) and the

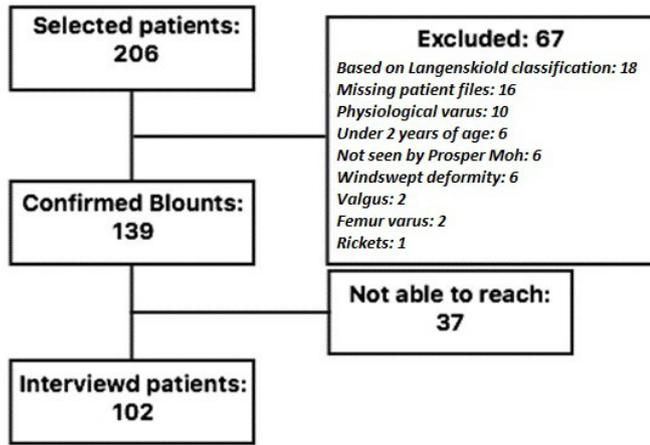


Figure 1. Flowchart patient selection

Figure 1 Flowchart patient selection.

late onset group (n=4). The male female ratio was 1:4. In 43% of the cases, the condition was bilateral and in the unilateral cases, the left and right legs were almost as often affected (30% vs 27%). In our study population, 94% needed a surgical correction.

Patients came from all over Ghana, but analysing the distribution of the patients, most patients live in the Ashanti-region (55%), Western-region (19%) or

Brong-Ahafo (17%) region and belong to the Akan tribe (88%). The Akan tribe is the biggest tribe in Ghana (48%) and consists of multiple subgroups. From the Akan patients of which we knew the subgroup (n=83), 59% was Asante (n=49). Interestingly, only 20% of all Ghanaian Akans belong to the Asante subgroup. Online supplemental appendix 3 shows a map with the distribution of patients in Ghana.

Family history

A total of 137 cases of positive family history were found in 63 families. In the early onset group, two-third of the patients reported a positive family history, of which, almost two-third had a positive family history in a first-degree family member (35 out of 56). Furthermore, in the juvenile group and late onset group, there were families with a positive family history but not as frequent as in the early onset group.

Only two cases of positive family history were confirmed Blount disease, this concerned two brothers both operated in this hospital. A patient’s cousin with anamnesticly the same disease was operated in a different hospital in Ghana. Nine other cases claimed to still have a severe, early onset, varus deformity similar to the patient, possibly having the same disease. As a result of the absence of

Table 1 Patient characteristics

		Early onset (n=84)	Juvenile onset (n=14)	Late onset (n=4)	All patients (n=102)
Gender	Female	65 (77%)	9 (64%)	1 (25%)	75 (74%)
	Male	19 (23%)	5 (36%)	3 (75%)	27 (26%)
Affected leg	Bilateral	38 (45%)	6 (43%)	0 (0%)	44 (43%)
	Left	25 (30%)	4 (29%)	2 (50%)	31 (30%)
	Right	21 (25,0%)	4 (29%)	2 (50%)	27 (27%)
Region	Ashanti	48 (57%)	6 (43%)	2 (50%)	56 (55%)
	Western	14 (17%)	5 (36%)	0 (0%)	19 (19%)
	Brong-Ahafo	13 (15%)	3 (21%)	1 (25%)	17 (17%)
	Central	8 (10%)	0 (0%)	0 (0%)	8 (8%)
	Greater Accra	1 (1%)	0 (0%)	0 (0%)	1 (1%)
	Volta	0 (0%)	0 (0%)	1 (25%)	1 (1%)
Tribe*	Akan	69 (87%)	13 (93%)	3 (75%)	85 (88%)
	Mole Dagbon	1 (1%)	0 (0%)	0 (0%)	1 (1%)
	Ewe	2 (3%)	0 (0%)	1 (25%)	3 (3%)
	Gruma	1 (1%)	0 (0%)	0 (0%)	1 (1%)
	Guan	1 (1%)	0 (0%)	0 (0%)	1 (1%)
	Other	5 (6%)	1 (7%)	0 (0%)	6 (6%)
Family history	Positive	56 (67%)	5 (36%)	2 (50%)	63 (62%)
	Negative	28 (33%)	9 (64%)	2 (50%)	39 (38%)
Family history in first degree family	Positive	35 (42%)	3 (21%)	1 (25%)	39 (38%)
	Negative	49 (58%)	11 (79%)	3 (75%)	63 (62%)

Continuous data are presented as means±SD and categorical data are shown as a frequency and/or as a percentage.

*Early onset: n=79, juvenile onset n=14, late onset n=4, total n=97.

Table 2 Cases of positive family history

	Early onset (n=56)	Juvenile onset (n=5)	Late onset (n=2)	All patients (n=63)
Resolved itself	82 (66%)	1 (14%)	5 (83%)	88 (64%)
Still mild varus	32 (26%)	4 (57%)	1 (17%)	37 (27%)
Still severe varus	10 (8%)	2 (29%)	0 (0%)	12 (9%)
Total cases in family	124	7	6	137

diagnostics and treatment in these cases, the diagnosis remains unclear. Furthermore, 37 (27%) cases claimed to still have a mild varus deformity and in 88 cases (64%), the varus deformity resolved itself during childhood, at an average age of 7 years (diverging from 2 to 17 years).

Anamnestically, one case of monozygotic twins and one case of monozygotic triplets were found in this study. All the twins and triplets' siblings had varus legs from early childhood, however none of the siblings developed Blount disease. Table 2 shows the cases of positive family history and their severity. Figure 2 shows the family tree of one of the Blount disease patients.

Genetic predisposition

The first analysis of the WES did not show a clear genetic predisposition.

Routine diagnostic WES using genomic DNA of each patient was initially performed for defined gene panels consisting of genes associated with Mendelian-inherited disorders and Skeletal Dysplasia and/or Short Stature,

including SHOX-gen (for gene panels content, see <https://order.radboudumc.nl/en/genetics/rapid-exome-sequencing>). In none of the patients did this result in the identification of a clinically relevant variant. Subsequently, the entire exome outside these gene panels was interrogated and compared between patients, in search of a biologically plausible candidate gene. This approach did not result in the identification of a candidate gene which could explain the presence of Blount disease in the study population.

DISCUSSION

This study presents high prevalence of Blount patients, including 139 Blount patients in 8 years. Although, patients came from all over Ghana, 88% belong to the Akan tribe, nationwide less than 50% of the Ghanaians belong to the Akan tribe. Furthermore, in the early onset group, two-third of the patients reported a positive family

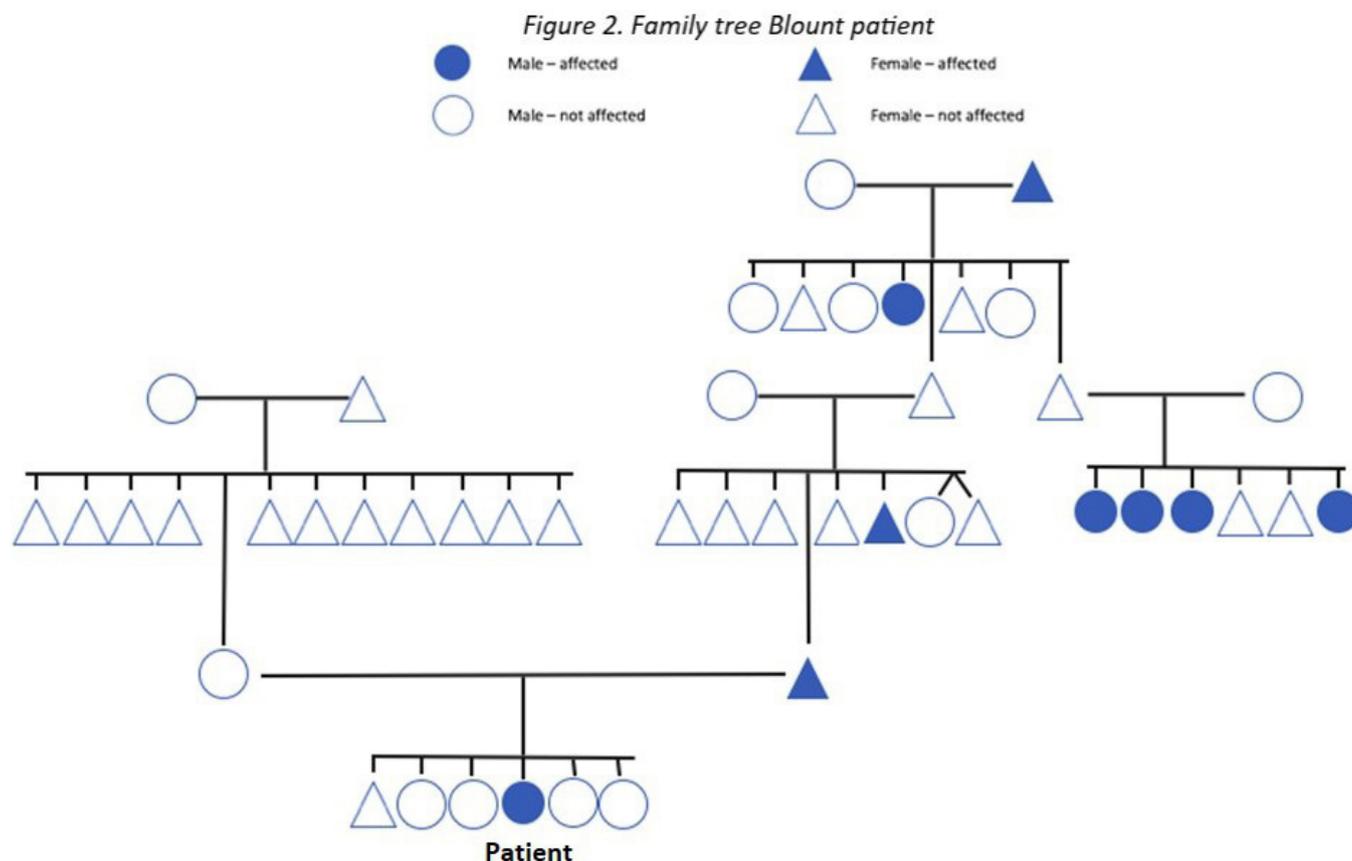
**Figure 2** Family tree Blount patient.

Table 3 Articles on familial in occurrence Blount disease

Author	Group	Year	Study type	Affected family members	Twins	Anamnestic family history
Evensen <i>et al</i> ²⁴	Early	1956	Case report	3 cousins with Blount disease of which one needed an operation and two resolved without treatment.	–	Father of one of the patients had physiological varus legs as a child.
Langenskiold and Riska ²²	Early	1964	Retrospective study	One family with four typical cases of infantile Blount disease.	–	–
Sevastikoglou and Eriksson ²⁷	Early	1967	Case report	4 siblings affected of which three needed an operation.	Yes	–
Levine and Drennan ²⁶	Early	1982	Retrospective study	Of the 22 patients, there were two pairs of siblings with Blount disease.	–	–
Schoenecker <i>et al</i> ²⁸	Early	1985	Retrospective study	–	–	45% (14 out of 31) patients had a positive family history.
Ikegawa <i>et al</i> ²⁵	Early	1990	Case report	Monozygote twins with Blount disease.	Yes	Negative family history
Schmidt <i>et al</i> ¹⁰	Early	1991	Case report	two siblings with Blount disease and a sister with physiological varus legs.	–	–
Inaba <i>et al</i> ²¹	Early	2014	Retrospective study	–	Yes, three twin cases	14% (8 out of 59) had a positive family history for varus legs.
Thompson <i>et al</i> ¹⁹	Adolescent	1984	Retrospective study	–	–	All 11 patients had a negative family history.
Schoenecker <i>et al</i> ²⁸	Adolescent	1985	Retrospective study	–	–	1 patient had a negative family history.
Inaba <i>et al</i> ²¹	Adolescent	2014	Retrospective study	–	–	All 13 have a negative family history.

history for varus legs. After analysing the interviews and literature, a relationship between the occurrence of Blount disease and familial inheritance for varus legs is suggested.

It is known that up to the age of 2 years, infants may have physiologic bowing. However, the family members with a positive family history for self-limiting varus in this study showed a relatively high age (average 7 years) for self-resolving the physiological bowing, which might suggest a more severe form of physiological varus even in the self-limiting group. In earlier bio mechanic studies, it was found that a 20° varus alignment in a 2-year-old child results in sufficient forces to reduce growth of the medial physis of the proximal tibia. For a 5-year-old child, the borderline force needed to inhibit the growth is a 10° varus alignment. These angles and forces are calculated

in patients with a normal 50th percentile weight. Forces on the medial physis increase if patients are overweight, but weight has a weaker mechanical effect on the physis than the varus angle has.³³ Our data are consistent with the hypothesis that Blount disease is primarily the result of the proximal tibial epiphysis responding to physical phenomena. Therefore, the high prevalence of familial inheritance for varus legs might explain the large population of Blount patients found in this study.

The contribution that familial inheritance for severe varus legs as an infant has on developing early Blount disease would also explain the higher number of positive family history in the early onset group compared with the juvenile group and late onset group, found in the study data and the current literature. In the juvenile case and late onset case, the bowing often started after gaining a



lot of weight or trauma,^{4 20 22 34} which could also cause changing forces on the physis.

Little is known about the prevalence of Blount disease. In the literature, one to four cases of early onset Blount disease are described per year.^{8 18 19 26 28 35 36} Juvenile and late onset Blount disease is even more uncommon.^{15 28} With 139 Blount patients in 8 years, this study presents the highest prevalence of Blount disease patients in the literature up to date.

Genetic contribution and familial influence were suggested in earlier studies but has not yet been extensively studied.^{5 9 10 19 27} Table 3 recapitulates the literature on familial occurrence in early and adolescent Blount disease. The study data show a higher prevalence of positive family history for varus legs in all groups, compared with the literature.

Research in Ghana can be challenging and therefore some limitations of this study need consideration. First, data are based on self-reported family history. But, to prevent different sides of the family accusing each other, we always needed confirmation from both sides of the family. The exclusion of rickets and polio was also based on self-reported data. Second, due to the absence of electronic patient files and digital X-rays before February 2015, we had to exclude 22 possible Blount disease patients because of missing files and, or X-rays. Finally, low resources and expensive journeys to a hospital could prevent patients from seeking medical consultation. In addition, having varus legs has some aesthetic value in Ghana. This could explain why nine out of the 12 cases with severe varus legs in the family history never visited the hospital for medical consultation.

In conclusion, this study describes a high population of Blount disease. Because of the high numbers of positive family history for varus legs, especially in the early onset group and the centralisation of patients in the Akan region, a familial predisposition for varus legs is probable. Our data are consistent with the hypothesis that Blount disease is primarily the result of the proximal tibial epiphysis responding to physical phenomena, in which varus alignment has a greater mechanical effect compared with weight. Therefore, the high prevalence of familial inheritance for varus legs and its mechanical effect on the medial physis of the proximal tibia might explain the large population of Blount patients found in this study, in a predominantly non-overweight population.

The first analysis of a routine WES-based diagnostic approach for variant filtering and selection while interrogating the entire exome and while systematically comparing the exome sequencing data between patients from different families did not show a genetic predisposition. Based on the family tree's and the WES outcome, a Mendelian inheritance was not found. Nonetheless, this study shows optimistic results for deeper interrogation of the genome using less stringently filtered raw sequencing data in a research setting. Also, more research on familial occurrence in the juvenile and late onset Blount patients

is needed, because these studied groups are rather small compared with the early onset group.

Acknowledgements We are very grateful for the help Hussein Botchway provided us to get approval from the Medical Ethical Committee of Kwame Nkrumah University Kumasi (Ghana). Furthermore, we would like to thank the whole staff St. John of God hospital in Duayaw Nkwanta (Ghana) for helping out in every possible way to make this research possible.

Contributors NJ conceptualised the study, performed the investigation, wrote, reviewed and edited the manuscript. FH conceptualised and supervised the study, wrote, reviewed and edited the manuscript. FB collected data. PM acquired the resources, supervised the study. AS analysed data. HMS conceptualised, acquired the resources and supervised the study.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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Competing interests No, there are no competing interests.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request at the corresponding author.

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REFERENCES

- Erlacher P. Deformierende prozesse der epiphysengegend bei Kindern. *Arch Orthop Unfallrich* 1922;20:81–96.
- Blount WP. Tibia vara Osteochondrosis deformans tibiae. *J Bone Joint Surg* 1937;19:1–29.
- Hollman F, Vroemen P. Infantile blount's disease: histopathological changes in the proximal tibial metaphysis. comparison between medial and lateral specimens. *International Journal of Pediatric Research* 2016;2.
- Thompson GH, Carter JR, vara L-onsettibia. Late-Onset tibia vara (blount's disease). *Clin Orthop Relat Res* 1990;255:24–35.
- Banwarie RR, Hollman F, Meijs N, et al. Insight into the possible aetiologies of blount's disease: a systematic review of the literature. *J Pediatr Orthop B* 2020;29:323–36.
- Montgomery CO, Young KL, Austen M, et al. Increased risk of blount disease in obese children and adolescents with vitamin D deficiency. *J Pediatr Orthop* 2010;30:879–82.
- Sabharwal S. Blount disease. *J Bone Joint Surg Am* 2009;91:1758–76.
- Scott AC, Kelly CH, Sullivan E. Body mass index as a prognostic factor in development of infantile blount disease. *J Pediatr Orthop* 2007;27:921–5.
- Bathfield CA, Beighton PH. Blount disease. A review of etiological factors in 110 patients. *Clin Orthop Relat Res* 1978;135:29–33.

- 10 Schmidt H, Mundlos S, Spranger JW. Sibs with a disorder resembling blount disease (tibia vara). *Pediatr Radiol* 1991;21:316–8.
- 11 Ogden CL, Carroll MD, Kit BK, et al. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA* 2014;311:806–14.
- 12 Muthuri SK, Francis CE, Wachira L-JM, et al. Evidence of an overweight/obesity transition among school-aged children and youth in sub-Saharan Africa: a systematic review. *PLoS One* 2014;9:e92846.
- 13 Dietz WH, Gross WL, Kirkpatrick JA. Blount disease (tibia vara): another skeletal disorder associated with childhood obesity. *J Pediatr* 1982;101:735–7.
- 14 Bradway JK, Klassen RA, Peterson HA. Blount disease: a review of the English literature. *J Pediatr Orthop* 1987;7:472–80.
- 15 Golding JSR, McNeil-Smith JDG. Observations on the etiology of tibia vara. *J Bone Joint Surg Br* 1963;45-B:320–5.
- 16 Henderson RC. Tibia vara: a complication of adolescent obesity. *J Pediatr* 1992;121:482–6.
- 17 Ho-Fung V, Jaimes C, Delgado J, et al. MRI evaluation of the knee in children with infantile blount disease: tibial and extra-tibial findings. *Pediatr Radiol* 2013;43:1316–26.
- 18 Loder RT, Johnston CE. Infantile tibia vara. *J Pediatr Orthop* 1987;7:639–46.
- 19 Thompson GH, Carter JR, Smith CW. Late-onset tibia vara: a comparative analysis. *J Pediatr Orthop* 1984;4:185–94.
- 20 Wenger DR, Mickelson M, Maynard JA. The evolution and histopathology of adolescent tibia vara. *J Pediatr Orthop* 1984;4:78–88.
- 21 Inaba Y, Saito T, Takamura K. Multicenter study of blount disease in Japan by the Japanese pediatric orthopaedic association. *J Orthop Sci* 2014;19:132–40.
- 22 Langenskiöld A, Riska EB. Tibia vara (OSTEOCHONDROSIS deformans tibiae): a survey of SEVENTY-ONE cases. *J Bone Joint Surg Am* 1964;46:1405–20.
- 23 Sibert JR, Bray PT. Probable dominant inheritance in blount's disease. *Clin Genet* 1977;11:394–6.
- 24 Evensen A, Steffensen J. Tibia vara. *Z Orthop Ihre Grenzgeb* 1956;26:200–10.
- 25 Ikegawa S, Nakamura K, Kawai S, et al. Blount's disease in a pair of identical twins. *Acta Orthop Scand* 1990;61:582.
- 26 Levine AM, Drennan JC. Physiological bowing and tibia vara. The metaphyseal-diaphyseal angle in the measurement of bowleg deformities. *J Bone Joint Surg Am* 1982;64:1158–63.
- 27 Sevastikoglou JA, Eriksson I. Familial infantile osteochondrosis deformans tibiae. *Idiopathic tibia vara. A case report. Acta Orthop Scand* 1967;38:81–7.
- 28 Schoenecker PL, Meade WC, Pierron RL, et al. Blount's disease: a retrospective review and recommendations for treatment. *J Pediatr Orthop* 1985;5:181–6.
- 29 Fiederling J, Shams AZ, Haug U. Validity of self-reported family history of cancer: a systematic literature review on selected cancers. *Int J Cancer* 2016;139:1449–60.
- 30 Janssens ACJW, Henneman L, Detmar SB, et al. Accuracy of self-reported family history is strongly influenced by the accuracy of self-reported personal health status of relatives. *J Clin Epidemiol* 2012;65:82–9. doi:10.1016/j.jclinepi.2011.05.003
- 31 de Ligt J, Willemsen MH, van Bon BWM, et al. Diagnostic exome sequencing in persons with severe intellectual disability. *N Engl J Med* 2012;367:1921–9.
- 32 Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical genetics and genomics and the association for molecular pathology. *Genet Med* 2015;17:405–23.
- 33 Cook SD, Lavernia CJ, Burke SW, et al. A biomechanical analysis of the etiology of tibia vara. *J Pediatr Orthop* 1983;3:449–54.
- 34 Henderson RC, Greene WB. Etiology of late-onset tibia vara: is varus alignment a prerequisite? *J Pediatr Orthop* 1994;14:143–6.
- 35 Ferriter P, Shapiro F. Infantile tibia vara: factors affecting outcome following proximal tibial osteotomy. *J Pediatr Orthop* 1987;7:1–7.
- 36 Richards BS, Katz DE, Sims JB. Effectiveness of brace treatment in early infantile blount's disease. *J Pediatr Orthop* 1998;18:374–80.

Appendix I

Interview questions family history Blount disease:

1. Date of interview:
 2. Present at the interview: PATIENT / FATHER / MOTHER /
OTHERS:.....
 3. Name patient: M / F
 4. Telephone number:
 5. Date of birth patient:
 6. Patient number:
 7. Address patient:
 8. Region of birth:
 9. Ethnic group:
 10. Age started bowing legs:
- EARLY ONSET / JUVENILE ONSET / ADOLESCENT ONSET
11. Leg(s) affected:
 12. History of Blount disease/bowed legs father: YES / NO
 13. History of Blount disease/bowed legs mother: YES / NO
 14. History of Blount disease/bowed legs siblings: YES / NO
 15. History of Blount disease/bowed legs other family members: YES / NO
 16. If yes answered on questions 12-15:
 - a. What was the age of diagnosis?
 - b. Where was it diagnosed?
 - c. Did he or she received an operation?
 - d. Did it resolve by itself? If yes, at what age?

- 17. Any older or younger siblings?
- 18. Age of mother at birth of patient?
- 19. Any further comments: (Possible to take blood from both parents and child?)
.....

Appendix II

Informed consent form 'Research genetic predisposition in Blount disease': DNA sequencing.

1. Purpose of the Project

We would like to invite you to participate in a research project called 'genetic predisposition in Blount disease'. The purpose of the research is to discover genetic changes associated with the disease. This should lead to a better understanding of the aetiology of Blount disease and later on, lead to better ways to prevent, detect, and treat the disease.

Body tissues are made up of cells. Cells contain DNA, which is your unique genetic material that carries the instructions for your body's development and function. Your DNA is a combination of the DNA from you parents. Many diseases can result from changes in a person's genetic material that cause cells to not work properly. Diseases who have a genetic predisposition can often be found in the DNA of the parents as well. They don't have to be affected by the disease but can be, so called 'carriers' who have the genetic predisposition but not the disease. Currently, researchers and doctors know some of the genetic changes that can cause some disease, but they do not know all of the genetic changes that can cause diseases. So far, they never looked into Blount disease. We think there might be a genetic predisposition in Blount disease. This is why we would like to invite you and your parents to participate in this research. We will perform this same process with some other patients and their parents who have agreed to participate in this research project. Combining these results, we will be able to say more about the possibly genetic predisposition in Blount disease.

2. Description of the Research

Collection of Samples and Medical Information:

- We will collect two samples from you by drawing about 4 tablespoons of blood from a vein in your arm for each sample. If you object to having blood drawn or are not sure if we drew enough blood, we will collect tissue from you by swabbing cells from the inside of your cheeks.
- We also will collect information from your medical records, including your age, ethnic background, diagnosis, disease history, medical treatments, and response to treatments.

Coding of Tissue Samples and Medical Information

- Your blood (or other tissue) sample and medical information will be labelled with a code.
- Only members of the research team 'genetic predisposition in Blount disease' at (Maastricht University medical centre, The Netherlands and St. John of God hospital, Ghana) will have the information that matches the code to traditionally-used identifying information, such as your name, address, phone number. The research team will keep the information that matches the code to this traditionally-used identifying information in a safeguarded database. Only very few, authorized people, who have specifically agreed to protect your identity, will have access to this database. All other researchers and personnel, including those who will be working with your samples and medical information, will not have access to any of the traditionally-used identifying information about you.

Storage and Release of Samples and Medical Information

- Your coded blood (or other tissue) samples will be sent to The Netherlands for detailed analysis. Remaining portions of your samples will be stored for an unlimited period of time for future use in research related to diseases.
- Information from analyses of your coded samples and your coded medical information will be put into a database along with information from the other research participants.

3. Financial Compensation/Costs

You will not be paid to participate in this project. Your blood (or other tissue) samples and your medical information will be used for research purposes only and will not be sold. It is possible that some of the research conducted using your samples or information eventually will lead to the development of new diagnostic tests, new drugs or other commercial products. Should this occur, there is no plan to provide you with any part of the profits generated from such products.

4. Potential Benefits of Participating in the Project

You should not expect to personally benefit from this research. The main reason you may want to participate is to help researchers and health professionals around the world to better understand the cause of your disease so that they can find better ways to prevent, detect and treat Blount disease. You may feel good knowing that you may be helping future patients. If it turns out there is a genetic predisposition in Blount disease, this could be useful information for you, knowing your children may be affected as well.

5. Potential Risks of Participating in the Project

Physical Risks

- Possible side effects from drawing the blood sample include mild pain, bleeding, bruising, and infection at the site of the needle insertion. Fainting or light-headedness can sometimes occur, but usually last only a few minutes.

Psychological or Social Risks Associated with Loss of Privacy

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measure that we will use, we cannot guarantee that your identity will never become known.

6. Confidentiality

We will make every attempt to protect your confidentiality and to make sure that your personal identity does not become known. This signed consent form will be stored in a locked file that will be accessible only to a very small number of authorized people involved in this project. We will carefully follow the coding, storage, and release plan explained in the 'Description of the Research' section of this document.

7. Project Results

In general, results from this research project will not be given back to you or put into your medical records. In some situations, the results might be important to your health or medical care. If this occurs, we will contact you to see if you want to learn more. If research from this project is published in professional journals, there will be no traditionally-used identifying

information, such as your name, address, telephone number, or insurance number, included in the publications.

8. Alternatives to Participating in the Project

The alternative option is not to participate.

9. Voluntary Participation

The choice to participate in this research by donating your tissues and medical information is completely up to you. No matter what you decide to do, your decision will not affect your medical care. Refusal to participate will involve no other penalties or loss of benefits to which you are entitled.

10. Withdrawal from the Project

Once data are generated from the samples you provided, and those data are placed in the database as described elsewhere in this consent, you will not be able to withdraw the data, only the samples. If you would like to withdraw from this project you can contact dr. H. Staal, department of orthopaedics, MUMC, The Netherlands and she will destroy any remaining tissue samples of yours that have been obtained for the study. In addition, it may be possible for her to destroy the link between you and your genetic and medical information.

However, the samples and data that have already been distributed to other research centres or placed in the research databases will not be able to be withdrawn.

11. Contact Information

If you have any questions about the project, about your rights as a research participant, or about any research-related injury, please contact N. Jansen (n.j.jansen@amc.nl).

Source:

The national human genome research institute medical sequencing program - Consent Form: Example 2 (DNA Sequencing)

Agreeing to Participate in the Project

To participate in this research, you must agree to ALL of the following statements:

- I voluntarily agree to donate two blood samples and/or a cheek tissue sample to be used for this research project.
- I agree to release information from my medical records for this research project.
- I agree to have my coded genetic information and coded medical information placed in a secure database.
- I understand that there is a risk that someone in the future might be able to use information in this database to identify me.

Please sign your name here if you agree with the above four statements.

Your signature: _____

Date: _____

Signature of Doctor/Researcher _____

Appendix III

Map of Ghana showing the distribution of patients over Ghana. Numbers indicate the number of patients coming from this city.

