ORIGINAL

Y chromosome haplogroups are associated with birth size in Japanese men

Youichi Sato

Department of Pharmaceutical Information Science, Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan

Abstract : The Y chromosome is classified into haplogroups (A-T) based on a combination of several DNA polymorphisms. Japanese men are mainly classified into haplogroups C, D, and O, which have been further subdivided. The distribution of Y-chromosome haplogroups varies by ethnicity. The phylogenetic age, origin, and migration also differ. I hypothesized that Y chromosome haplogroups may be associated with height and/or weight at birth. An association analysis of height and weight at birth with Y chromosome haplogroups was performed in 288 Japanese men. Men belonging to haplogroup O1b2 were significantly associated with short stature at birth (beta = −1.88, standard error (SE) = 0.55, *P* = 0.00076), and those belonging to D1a2a-12f2b were significantly associated with increased birth weight (beta = 174, SE = 64, *P* = 0.0069). Y chromosome haplogroups are associated with physical birth characteristics in modern Japanese men. J. Med. Invest. 71 : 129-133, February, 2024

Keywords **:** *birth height, birth weight, Japanese population, Y chromosome haplogroup*

INTRODUCTION

The Y chromosome does not undergo genetic recombination and is passed on to the son as an intact chromosome. Occasional mutations occur, and combinations of DNA polymorphisms are classified into haplogroups (A-T) (1). Haplogroups are characterized by ethnicity and region, with Japanese men primarily classified into haplogroups C, D, or O (2). Haplogroups C and D were reported to have expanded into Japan approximately 12,000 to 20,000 years ago, and haplogroup O is subdivided into O1b and O2a, of which O1b was reported to have expanded 4,000 years ago (3, 4). Therefore, I hypothesized that there may be a relationship between the Y chromosome haplogroup and the physical characteristics of Japanese men.

Recently, a genome-wide association study (GWAS) of 5.4 million individuals reported 12,111 independent single nucleotide polymorphisms (SNPs) significantly associated with height, representing nearly all of the SNP-based common heritability (5). Thus, human height is largely a function of genetic background. In addition, many GWAS of body weight have been conducted, and more than 1,100 loci associated with obesity have been reported (6).

The physical characteristics of adults vary greatly depending on environmental factors such as age and lifestyle. However, compared with adults, the physical characteristics of children at birth are thought to be less influenced by the environment. In the present study, I examined the relationship between Y chromosome haplogroups and birth size (height and weight) in Japanese men.

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Address correspondence and reprint requests to Youichi Sato, Ph.D., Department of Pharmaceutical Information Science, Tokushima University Graduate School of Biomedical Sciences, 1-78-1 Sho-machi, Tokushima, Tokushima 770-8505, Japan and Fax : +81-88-633-7253. E-mail : youichi.sato@tokushima-u.ac.jp

MATERIALS AND METHODS

This study was approved by the Ethics Committees of the University of Tokushima and St. Marianna Medical University.

Samples from Japanese men and genotype of Y chromosome haplogroup

The subjects have been described previously (2, 7). Briefly, participants were recruited from the partners of pregnant women attending obstetric clinics in Sapporo, Osaka, Kanazawa and Fukuoka cities in Japan from 1999 to 2002. Multiple cohorts were analyzed to increase the sample size. Of the 792 participants, 288 Japanese men who self-reported birth weight and height were included in this study. Supermales or other syndromes that affect height were not tested. The Y chromosomes of all subjects were defined as 15 haplogroups according to the Y Chromosome Consortium (YCC) nomenclature (1) using 24 Y chromosome markers (YAP, M174, M15, M55, 12f2b, RSP4Y, M8, M217, M213, M9, M214, LLY22g, M175, MSY2.2, M119, P31, M95, SRY465, 47z, M122, M324, JST021354, M134, and JST002611), as previously described (2). The primer sets, PCR amplification conditions, and restriction enzymes are also described previously (2). The haplogroups were renamed according to the International Society of Genetic Genealogy (ISOGG) phylogenetic tree on April 19, 2019 (https://isogg.org/tree/).

Statistical analysis

Associations between Y chromosome haplogroups with frequencies > 0.05 and birth weight and height were assessed using linear regression analysis. No adjustment for covariates was made, because the only variables were height and weight. Statistical analyses were performed using R version 4.0.3 (The R Project for Statistical Computing ; http://www.r-project.org), and statistical significance was set at $P < 0.025$ (0.05/2 test : birth height and weight) to account for multiple testing.

RESULTS

Y chromosome haplogroups and birth height and weight in Japanese men

The mean birth height and weight of the 288 subjects were 50.1 ± 2.5 cm and 3180.5 ± 399.1 g, respectively. To investigate the association between Y chromosome haplogroups and birth height and weight, I typed Y chromosome haplogroups using 24 Y chromosome markers. Participants belonged to 15 haplogroups and their haplogroup distributions are shown in Table 1. The haplogroup O1b2a1a1 was the most dominant, and C1a1, C2, D1a2a-M55, D1a2a-12f2b, O1b2, O2a2b1, and O2a1b had frequencies > 5% among the participants. The frequency distributions of the subjects was similar to those of other cohorts (8-11). The means and standard deviations of birth weight and height for each haplotype are also shown in Table 1.

I then analyzed the associations between these eight Y chromosome haplogroups and birth weight and height using linear regression analysis. I found that men belonging to haplogroup O1b2 were significantly associated with shorter stature at birth (beta = −1.88, standard error (SE) = 0.55, $P = 0.00076$) than other haplogroups, and men belonging to D1a2a-12f2b were significantly associated with higher birth weight (beta = 174, SE = 64, $P = 0.0069$) than other haplogroups (Table 2). Birth

Table 1. Numbers and percent frequencies of Y chromosome haplogroups and means and standard deviations of birth weight and height for each haplotype in 288 Japanese men

Y chromosome haplogroup	Numbers (%)	Birth height (cm)	Birth weight (g)
		Mean ± SD	Mean ± SD
C1a1	17 (5.9)	50.2 ± 2.2	3082.1 ± 530.5
C2	22 (7.6)	49.9 ± 1.7	3233.0 ± 311.5
D1a2a-M55	37 (12.8)	49.5 ± 2.8	3079.1 ± 449.0
D1a2a-12f2b	45 (15.6)	50.4 ± 2.0	3327.4 ± 412.2
F*	2 (0.7)	48.5 ± 2.1	2601.5 ± 252.4
K*	12 (4.2)	511 ± 2.3	3146.7 ± 368.4
N1	4 (1.4)	49.3 ± 0.5	3005.0 ± 310.4
O1a	6 (2.1)	50.6 ± 2.6	3276.7 ± 461.2
O1b1a1a	3 (1.0)	49.5 ± 2.5	3063.3 ± 77.7
O1b2	21 (7.3)	48.3 ± 3.4	3081.3 ± 374.9
O1b2a1a1	63 (21.9)	50.4 ± 2.7	3188.6 ± 324.3
O2	7 (2.4)	49.5 ± 2.1	2932.1 ± 428.6
O2a2	8 (2.8)	49.7 ± 3.1	3152.1 ± 287.6
O2a2b1	24 (8.3)	50.7 ± 2.3	3254.6 ± 420.5
O2a1b	17 (5.9)	50.5 ± 1.4	3265.9 ± 436.5

Table 2. Association analysis between Y chromosome haplogroup and height and weight at birth in 288 Japanese men

Y chromosome haplogroup	Birth height			Birth weight		
	Beta	(SE)	*P*-value	Beta	(SE)	*P*-value
C1a1	0.11	(0.62)	0.86	−105	(100)	0.30
C2	−0.22	(0.55)	0.69	57	(89)	0.52
D1a2a-M55	−0.71	(0.44)	0.10	−116	(70)	0.098
D1a2a-12f2b	0.44	(0.40)	0.27	**174**	**(64)**	**0.0069**
F*	−1.53	(1.76)	0.38	−583	(281)	0.039
K*	1.10	(0.73)	0.13	−35	(118)	0.77
N1	−0.84	(1.25)	0.50	−178	(201)	0.38
O1a	0.52	(1.02)	0.61	98	(165)	0.55
O1b1a1a	−0.58	(1.44)	0.69	−118	(232)	0.61
O1b2	**−1.88**	**(0.55)**	**0.00076**	−107	(90)	0.24
O1b2a1a1	0.46	(0.35)	0.19	10	(57)	0.86
O2	−0.56	(0.95)	0.56	−255	(152)	0.096
O2a2	−0.40	(0.89)	0.66	−29	(143)	0.84
O2a2b1	−0.65	(0.53)	0.22	81	(85)	0.34
O2a1b	0.50	(0.62)	0.42	91	(100)	0.36

Data are shown as estimated linear regression statistic beta, standard error (SE), and *P*-value.
Numbers in bold indicate significance ($P < 0.025$).

weight is known to have decreased over the last 30 years (12). To confirm that age may be a factor, I analyzed age as a covariate. The association between men belonging to D1a2a-12f2b and higher birth weight remained significant after adjusting for age (beta = 179, SE = 64, $P = 0.0051$).

DISCUSSION

In this study, compared with men belonging to the Y chromosome haplogroups, those belonging to the O1b2 haplogroup were associated with shorter birth height, and those belonging to haplogroup D1a2a-12f2b were associated with higher birth weight in the Japanese population. Haplogroup O1b2 expanded approximately 4,000 years ago (3, 4) and is frequently found in Korea outside of Japan (13). To date, the phenotypic manifestation of O1b2 has been unclear ; this study is the first to show that O1b2 is associated with short stature at birth. The O1b2 marker SRY465 is an SNP with a synonymous substitution in the sex-determining region Y (*SRY*) gene (14). *SRY* is required for male determination ; however, it is unclear how it relates to height at birth. A gene on the Y chromosome linked to SRY465 may influence birth height ; however, further studies are required to clarify this phenomenon.

D1a2a-12f2b, which has been shown to be associated with higher birth weight, is a haplogroup found only in the Japanese population. Previously, we found that men belonging to haplogroup D1a2a-12f2b had higher levels of luteinizing hormone (LH) (15) and lower semen quality (16). Furthermore, the frequency of haplogroup D1a2a-12f2b was found to be significantly higher in patients with azoospermia than in controls (17). LH is a hormone secreted by the pituitary gland in the brain that contributes to sperm production by inducing testosterone biosynthesis and secretion in testicular Leydig cells (18, 19). These results indicate that men belonging to haplogroup D1a2a-12f2b have low spermatogenic potential. Several studies have reported the association between birth weight and infertility in men. Francois *et al*. reported that low birth weight correlated with unexplained subfertility (20). Kahn *et al*. reported that birth weight percentile during gestation was positively correlated with square root sperm concentration (21). Therefore, low birth weight appears to be associated with infertility and poor sperm quality. However, this was in contrast to our finding that men belonging to haplogroup D2a1 were associated with lower sperm quality and higher weight at birth. This discrepancy may be due to differences between the epidemiological and genetic association studies.

A limitation of this study is that it relies on self-reports of birth weight and length, and it is unclear how accurate these are. Data collection on important factors that may influence variables such as length of pregnancy and maternal health is also lacking. In addition, only 288 of the original sample of 792 adult males responded to the survey. The use of 288 samples in 15 haplogroups is considered a reasonable number compared to a sample size of over 100,000 SNPs, as in a GWAS. However, the sample size also needs to be increased and will be addressed in future studies.

CONCLUSIONS

Although several limitation needs to be overcome, this study provides the first evidence of a relationship between Y chromosome haplogroups and physical characteristics in Japanese men.

CONFLICT OF INTEREST STATEMENT

The author declare no conflict of interest.

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