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ORIGINAL ARTICLE

FGFR2 is associated with hair thickness in Asian populations

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Hair morphology is one of the most differentiated traits among human populations. A previous study has shown that a nonsynonymous single nucleotide polymorphism (SNP) in the *EDAR* gene, *EDAR* 1540T/C, is strongly associated with hair thickness in Asian populations. However, the contributions of other genes remain to be elucidated. In this study, 12 SNPs on 10 hair formation-related genes with high differentiation between Asian and other populations were examined to further identify genes associated with hair morphology. A multiple regression analysis adjusted for age, sex, population and the effect of *EDAR* 1540T/C revealed an SNP in intron 9 of *FGFR2*, rs4752566, to be significantly associated with hair thickness (cross-sectional area; *P*-value=0.0052, small diameter; *P*-value=0.029 and large diameter; *P*-value=0.0015). In the genomic region containing the *FGFR2* gene, rs4752566 was not in strong linkage disequilibrium (LD) with the surrounding SNPs, indicating that the significant association of rs4752566 with the hair thickness is not due to LD with polymorphisms of the other genes. The rs4752566-T allele of *FGFR2*, associated with thicker hair, was also shown to be associated with higher mRNA level of *FGFR2* (*P*-value=0.0270). These results suggest that the *FGFR2* polymorphism affects the variation in hair thickness in Asia through alteration in the expression level of FGFR2.
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INTRODUCTION

Hair morphology is one of the most divergent traits among human populations. Africans and Melanesians have twisted hair, and Asians have thicker hair than people of the other continents.[1] To discover genes involved in human hair morphology, 21 candidate genes were previously picked up based on their functions and genetic differentiation between populations. Among these candidate genes, a nonsynonymous single nucleotide polymorphism (SNP) in *ectodysplasin A receptor* (*EDAR*), *EDAR* 1540T/C (rs3827760), which is highly differentiated between Asian (HapMap-CHB+JPT) and other populations (YRI and CEU), was found to be strongly associated with hair fiber thickness.[2,3] In addition, the chromosomal region of the *EDAR* gene showed a strong signature of recent positive selection in East Asian populations[2,4–9] These results led to the conclusion that *EDAR* is a major genetic determinant of Asian hair thickness and is likely to play an important role in adaptation to the local environments of East Asia.

As the variation in hair thickness cannot be explained solely by *EDAR* 1540T/C,[3] there might be other genetic variants associated with hair thickness. In the previous studies, however, only *EDAR*, but not other candidate genes, was evaluated. In addition, genes associated with the shape of cross-sectional area or hair index have not been identified yet. To further identify genes associated with hair morphology, this paper examined the possible association between hair morphology and 10 candidate genes including *ectodysplasin A* (*EDA*).

MATERIALS AND METHODS

Subjects

As described in the previous studies,[2,3] DNA samples and hair morphological data were obtained from 189 Japanese (JPN), 121 Indonesian (IDN) and 65 Thai-Mai (THM) individuals. Hair cross-sectional area, small diameter, large diameter and hair index, that is, the ratio of small diameter to large diameter, were used as the measure of hair fiber thickness and that of the shape of hair fibers.

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SNP selection and genotyping

In the previous study, 21 candidate genes were shown to be highly differentiated.[2] Of these genes, we subjected *LEF1, MSX2, DLL1, EGFR, CUTL1, NOTCH1, FGFR2, KRT6IRS, GPC5, AKT1, MYO5A, TGM3, EDA2R* and *EDA*, which are highly differentiated between HapMap-CHB+JPT and other HapMap populations (YRI and CEU). For *ectodysplasin A2 receptor* (*EDA2R*), a nonsynonymous SNP (rs1385699) was genotyped, because rs1385699 was recently reported to be involved in androgenetic alopecia.[10,11] In total, 17 SNPs of the 14 candidate genes listed in Table 1 were genotyped using either the DigiTag2 method[12] or PCR-direct sequencing.

Association of candidate SNPs with hair morphology

The allele frequencies were estimated by gene counting. SNPs with minor allele frequency less than 0.1 in all the studied populations (that is, JPN, IDN and THM) were excluded from the subsequent association analyses. As the previous study did not show the significant difference in phenotype of hair morphology between IDN and THM,[2] these populations were merged and designated as the Southeast Asian population (SEA) in the following multiple regression analysis. Associations between the candidate SNPs and hair morphology (cross-sectional area, small diameter, large diameter or hair index) were evaluated by a multiple regression analysis with the number of the major allele in the CHB+JPT population (that is, 0, 1 or 2) of each SNP, age, sex and population (SEA or JPN) as independent variables. As the hair of Asians has a larger cross-sectional area, larger small diameter, larger large diameter and a higher hair index than African and European populations, alleles associated with an increase in hair thickness and/or hair index were assumed to have higher population frequencies in the CHB+JPT population than the YRI and the CEU populations. Therefore, the *P*-values were calculated by a one-sided test. A multiple regression analysis considering the effect of *EDAR* 1540T/C was also performed, in addition to the other factors. To compare the goodness of fit between a statistical model including *EDAR* 1540T/C and that not including *EDAR* 1540T/C, we used Akaike's informational criteria (AIC) as guidance. For testing the association of X-linked genes, the multiple regression analyses were performed for male and female participants separately.

F_{ST} values and structure of linkage disequilibrium in FGFR2

F_{ST} values in the *FGFR2* region were calculated based on the HapMap data. The structures of linkage disequilibrium (LD) in a 200 kb genomic region containing *FGFR2* in the CHB+JPT population were assessed using pairwise D' and r^2 values between SNPs with minor allele frequency of more than 0.05.

Association of FGFR2 genotype with mRNA expression level

The association between an SNP of *fibroblast growth factor receptor 2* (*FGFR2*), rs4752566 and the mRNA expression level was evaluated using a simple regression analysis with the number of rs4752566-T as an independent variable. Normalized mRNA data from Epstein–Barr virus-transformed lymphoblastoid cell lines derived from 44 JPT and 45 CHB HapMap subjects were obtained from the database of the Gene Expression Variation (GENEVAR) project (http://www.sanger.ac.uk/humgen/genevar/).[13] The mRNA expression data detected by GI_13186256-I probe for *FGFR2* were used in this study.

RESULTS

The allele frequencies of 17 SNPs listed in Table 1 were investigated in JPN, IDN and THM. Five SNPs including rs1385699 of *EDA2R* showed minor allele frequency of less than 0.1 in all the studied populations (data not shown). Such SNPs with low minor allele frequency were excluded from the subsequent association analyses because the association test was not expected to attain enough statistical power.

The association *P*-values for the remaining 12 SNPs on 10 genes are summarized in Table 2. Of these, a G/T SNP (rs4752566) in the 9th intron of *FGFR2* showed the strongest associations with cross-sectional area (*P*-value=0.0330 and *P*-value=0.0052 when considering the effect of *EDAR* 1540T/C; Table 2), small diameter (*P*-value=0.116 and *P*-value=0.029 when considering the effect of *EDAR* 1540T/C; Table 2) and large diameter (*P*-value=0.0074 and *P*-value=0.0015 when considering the effect of *EDAR* 1540T/C; Table 2). These significant associations were observed in IDN, but not in the other

Table 1 Candidate SNPs with high population differentiation for the association study

				HapMap							
				Allele		Frequency of allele A			F_{ST} value		
rs	Chr	Pos	Gene	A	B	CEU	YRI	CHB+JPT	F_{ST}_cy[a]	F_{ST}_ya[b]	F_{ST}_ca[c]
rs12643511	4	109339428	*LEF1*	A	G	0.333	0.881	0.017	0.315	0.754	0.173
rs10057011	5	174093855	*MSX2*	A	G	0.186	0.792	0.011	0.367	0.635	0.086
rs4710714	6	170422927	*DLL1*	A	G	0.983	0.633	0.382	0.197	0.063	0.417
rs12668421	7	55076671	*EGFR*	A	T	0.705	0.974	0.082	0.134	0.798	0.407
rs11766798	7	55091813	*EGFR*	A	G	0.312	0.000	0.901	0.185	0.820	0.362
rs10259964	7	101322644	*CUTL1*	A	G	0.112	0.250	0.878	0.032	0.401	0.587
rs382270	7	101509556	*CUTL1*	A	G	0.583	0.000	0.967	0.411	0.936	0.211
rs3124602	9	138526312	*NOTCH1*	A	G	0.050	0.000	0.674	0.026	0.508	0.421
rs4752566	10	123257621	*FGFR2*	G	T	0.542	0.908	0.090	0.168	0.669	0.236
rs659695	12	51215819	*KRT6IRS*	A	G	0.350	1.000	0.989	0.481	0.006	0.461
rs1336220	13	91008260	*GPC5*	A	C	0.588	0.009	0.831	0.400	0.693	0.072
rs2494746	14	104328764	*AKT1*	C	G	0.083	0.442	0.699	0.166	0.067	0.398
rs4238390	15	50372597	*MYO5A*	A	T	0.233	0.883	0.933	0.428	0.007	0.504
rs214815	20	2246616	*TGM3*	C	T	0.817	0.100	0.944	0.518	0.714	0.038
rs6132532	20	2263543	*TGM3*	A	G	0.983	0.185	0.145	0.655	0.003	0.714
rs1385699	X	65741711	*EDA2R*	C	T	0.211	1.000	0.000	0.652	1.000	0.118
rs1938023	X	69079859	*EDA*	C	T	0.056	0.233	0.742	0.063	0.259	0.491

99th and 95th percentile values of mF_{ST} in the empirical distributions are 0.736 and 0.569 for F_{ST}_cy, 0.818 and 0.634 for F_{ST}_ya, and 0.582 and 0.398 for F_{ST}_ca, respectively.
[a]F_{ST} value CEU vs YRI.
[b]F_{ST} value CHB+JPT vs YRI.
[c]F_{ST} value CHB+JPT vs CEU.

Table 2 Results of the association analysis between SNP genotypes and hair morphology

					DNA samples			Association							
				Allele		Frequency of allele A			Cross-sectional area		Small diameter		Large diameter		Hair index
rs	*Chr*	*Pos*	*Gene*	*A*	*B*	*JPN*	*IDN*	*THM*	P-*value*[a]	P-*value*[b]	P-*value*[a]	P-*value*[b]	P-*value*[a]	P-*value*[b]	P-*value*[a]
rs4710714	6	170422927	*DLL1*	A	G	0.382	0.214	0.373	0.890	0.926	0.672	0.733	0.942	0.959	0.082
rs12668421	7	55076671	*EGFR*	A	T	0.134	0.162	0.298	0.158	0.266	0.064	0.126	0.282	0.381	0.098
rs11766798	7	55091813	*EGFR*	A	G	0.874	0.814	0.715	0.264	0.347	0.162	0.227	0.396	0.462	0.141
rs10259964	7	101322644	*CUTL1*	A	G	0.851	0.699	0.555	0.862	0.796	0.924	0.887	0.757	0.679	0.714
rs382270	7	101509556	*CUTL1*	A	G	0.984	0.877	0.885	0.585	0.551	0.465	0.423	0.653	0.629	0.264
rs3124602	9	138526312	*NOTCH1*	A	G	0.613	0.415	0.172	0.650	0.469	0.349	0.178	0.860	0.779	0.07
rs4752566	10	123257621	*FGFR2*	G	T	0.105	0.208	0.421	0.033*	0.0052**	0.116	0.029*	0.0074**	0.0015**	0.91
rs1336220	13	91008260	*GPC5*	A	C	0.675	0.679	0.469	0.518	0.515	0.468	0.439	0.571	0.597	0.451
rs2494746	14	104328764	*AKT1*	C	G	0.573	0.277	0.683	0.930	0.930	0.943	0.947	0.895	0.884	0.655
rs4238390	15	50372597	*MYO5A*	A	T	0.937	0.942	0.869	0.438	0.508	0.513	0.593	0.688	0.732	0.411
rs6132532	20	2263543	*TGM3*	A	G	0.184	0.186	0.213	0.111	0.173	0.292	0.403	0.041*	0.067	0.89
rs1938023	X	69079859	*EDA*	C	T	0.746	0.593	0.508	0.169/0.661	0.0995/0.567	0.372/0.825	0.273/0.273	0.0529/0.438	0.029*/0.386	0.306/0.200

SNPs with minor allele frequency less than 0.1 in all the populations were not assessed in the association analyses.
[a]Age, sex and ethnicity were used as independent variables.
[b]Age, sex, ethnicity and the number of *EDAR* 1540C alleles were used as independent variables. *P*-values of the X-linked SNPs (rs1938023) were represented as male/female. *P-value$<$0.05, **P-value$<$0.01.

two populations, when the test was performed in each population (data not shown). SNPs on the *TGM3* and *EDA* genes were weakly associated with large diameter (Table 2). However, no associations were detected for the other genes.

The estimated per-copy effects of the rs4752566-T allele (that is, regression coefficient of rs4752566) on cross-sectional area, small diameter and large diameter were 206.3 μm^2, 2.8 μm and 2.8 μm, respectively. When considering the effect of *EDAR* 1540T/C, the per-copy effects of the rs4752566-T allele on cross-sectional area, small diameter and large diameter were 274.3 μm^2, 1.4 μm and 3.4 μm, respectively. The per-copy effects of rs4752566-T were smaller than those of *EDAR* 1540C (578.4 μm^2 for cross-sectional area, 4.2 μm for small diameter and 4.5 μm for large diameter). A power calculation revealed that a high statistical power (>0.8) is difficult to be achieved in this study if the per-copy effect of an allele is half of *EDAR* 1540C (data not shown). Thus, the possibility that a false negative may have occurred for SNPs with small effect cannot be excluded.

For the associations of rs4752566 with cross-sectional area, small diameter and large diameter, model evaluation using AIC suggested that a regression model including *EDAR* 1540T/C as one of independent variables fits the data better than that not including *EDAR* 1540T/C (AIC=5195.21 vs 5233 for cross-sectional area; AIC=1536.29 vs 1576.2 for small diameter; AIC=1838.34 vs 1858 for large diameter). As the association of rs4752566 with large diameter was still significant after stringent multiple testing correction (Bonferroni-adjusted *P*-value=0.018 when considering the effect of *EDAR* 1540T/C) and the association of rs4752566 with cross-sectional area was marginal (Bonferroni-adjusted *P*-value=0.062 when considering the effect of *EDAR* 1540T/C), we focused on rs4752566 in the following analyses.

The rs4752566-T, which is derived and a major allele in the HapMap-CHB+JPT population, was associated with the increase in the cross-sectional area. A multiple regression analysis also revealed the significant effect of population (SEA or JPN) on the cross-sectional area (*P*-value$<$0.0001) even when considering the effects of *EDAR* 1540T/C and rs4752566. This implies the presence of other genes, which account for the variation in the cross-sectional area in Asians, although unknown environmental factors, which are different between Southeast Asia and East Asia, may have an important role in hair formation.

To examine whether *FGFR2* has a number of SNPs highly differentiated between CHB+JPT and YRI, F_{ST} values of the SNPs on *FGFR2* were calculated (Figure 1a). No SNPs with a higher or equal F_{ST} value more than the 95th percentile other than rs4752566 were found in the *FGFR2* region. To evaluate the extent of LD from rs4752566, the structure of LD in a 200 kb genomic region where rs4752566 was located at the center was investigated in the HapMap-CHB+JPT population (Figures 1b and c). In this region containing only the *FGFR2* gene, rs4752566 was not in strong LD with the surrounding SNPs, suggesting that the significant association of rs4752566 with the hair thickness is not due to LD with polymorphisms of the other genes. Therefore, a polymorphism associated with hair thickness appears to be located at least in the *FGFR2* region, although rs4752566 may not be a causative SNP.

The association between the genotypes of rs4752566 and mRNA expression level of *FGFR2* was evaluated to determine the functional role of rs4752566-T, which was associated with thicker hair. The number of rs4752566-T was significantly correlated with the level of expression (*P*-value=0.027) in EBV-transformed lymphoblastoid cell lines from the CHB+JPT individuals (Figure 1d). As no significant difference in the mRNA expression level was observed between GT and

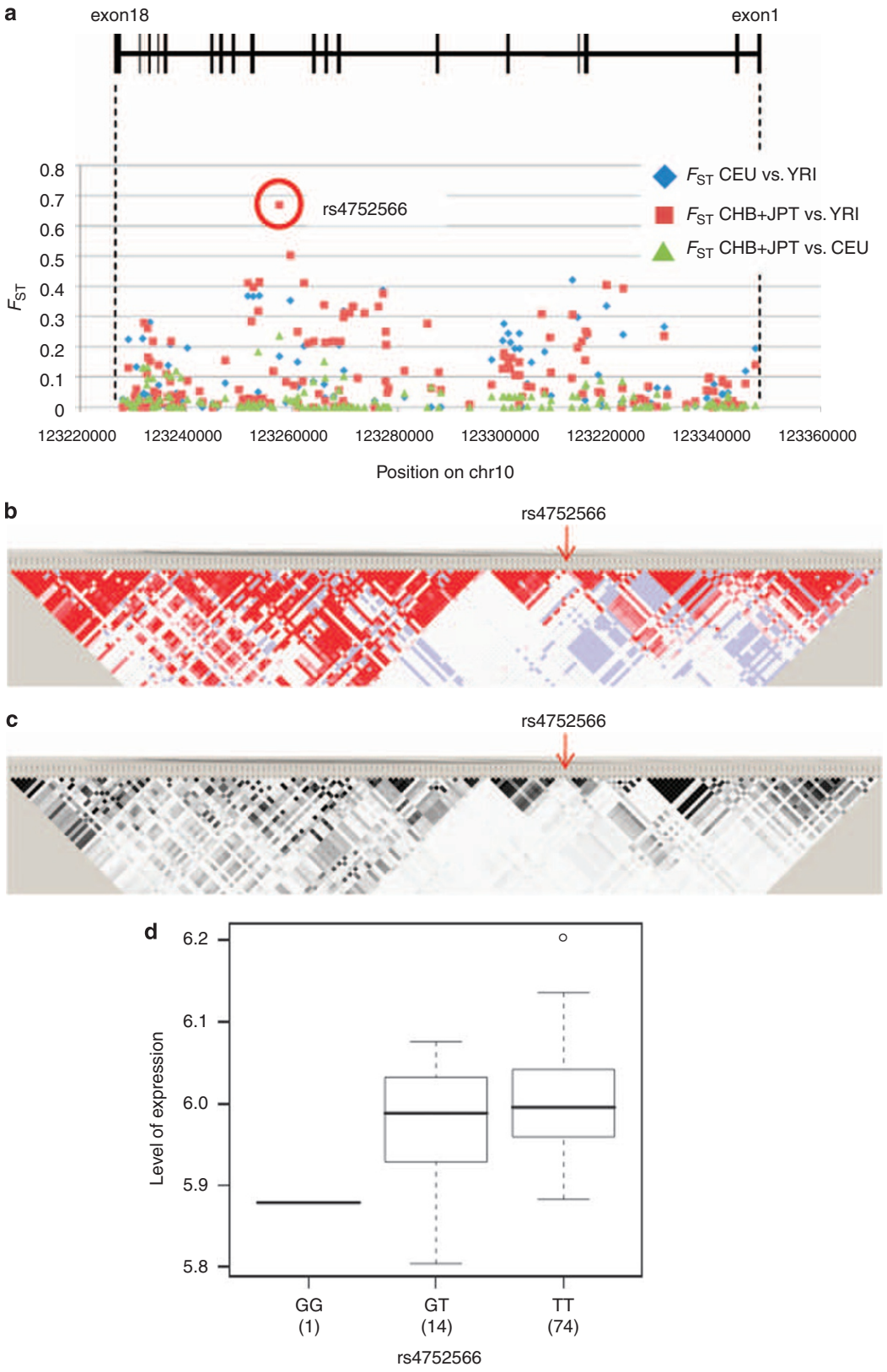

Figure 1 F_{ST}, LD and expression of *FGFR2*. (**a**) Structure of the *FGFR2* gene and F_{ST} values in the *FGFR2* gene. (**b**) Pairwise LD measured with D' between SNPs in a 200 kb genomic region including the *FGFR2* gene. Bright red squares indicate high D' values ($D'=1$) and high LOD scores (LOD >=2), and light blue squares indicate high D' values ($D'=1$) and low LOD scores (LOD < 2). For other cases, the D' value is shown in each square. (**c**) Pairwise LD measured with r^2 between SNPs in a 200 kb genomic region including the *FGFR2* gene. Black squares indicate high r^2 values ($r^2=1$), gray squares indicate intermediate r^2 values ($0<r^2<1$) and white squares indicate no LD ($r^2=0$). (**d**) The association between rs4752566 genotypes and the expression level of *FGFR2* in the HapMap-CHB+JPT population. The number of samples for each genotype is presented in parentheses.

TT genotypes, the influence of rs4752566 on the *FGFR2* expression level seems to be modest, and an apparent correlation may have come from small sample size of the GG genotype. The present results therefore need to be confirmed in larger samples.

DISCUSSION

In this study, an SNP in intron 9 of *FGFR2*, rs4752566, was found to be significantly associated with hair thickness after multiple testing correction, and to be significantly correlated with the mRNA expression level of *FGFR2*. It is known that *FGFR2* has an essential role in the proliferation of epidermal cells,[14,15] thus rs4752566 itself or a polymorphism in LD with rs4752566 would influence hair thickness through alternation in the expression level of *FGFR2*. As no significant correlations between rs4752566 and the *FGFR2* expression were observed in EBV-transformed lymphoblastoid cell lines from the CEU and YRI populations (data not shown), rs4752566 may not be a causative SNP and there might be an Asian-specific causative polymorphism near rs4752566. As the association of rs4752566 with hair thickness was not strong and much weaker than that of *EDAR* 1540T/C, it is necessary to conduct a replication study to confirm the association of *FGFR2* with hair thickness.

The candidate genes included two *EDAR*-related genes, *EDA* and *EDA2R*; two different isoforms of EDA, EDA-A1 and EDA-A2, specifically bind to EDAR or EDA2R.[16] They also harbored SNPs with high population differentiation.[2,7,10] Especially, rs1385699 in *EDA2R* is a nonsynonymous SNP with high population differentiation, in which the derived allele of rs1385699 was not observed in YRI, whereas it reached the population frequency of 79.8 and 100.0% in CEU and CHB+JPT, respectively.[7] Although rs1385699 in *EDA2R* is a promising candidate for the hair morphology-determining gene, the association cannot be tested because of a low minor allele frequency in the studied Asian populations. Association studies in European populations would be appropriate for examining the effect of *EDA2R* on hair morphology. The other EDAR-related gene, *EDA*, also showed a high differentiation between HapMap-CEU and HapMap-CHB+JPT, and a significant association of the *EDA* polymorphism, rs1938023, with large diameter was detected in male participants (*P*-value=0.029 when considering the effect of *EDAR* 1540T/C; Table 2). However, no significant association was observed in female participants. Thus, the association of the *EDA* polymorphism with large diameter requires to be re-examined in future studies.

Unlike *EDAR* 1540C allele, no extended LD was observed from rs4752566-T allele of *FGFR2* in CHB+JPT (Figures 1b and c), suggesting that the higher population frequency of rs4752566-T in CHB+JPT than YRI and CEU has not been attained by recent positive selection. As rs4752566-T is observed in YRI (Table 1), a mutation of rs4752566-T appears to predate the 'out-of-Africa' event of modern humans. Thus, high interpopulation differentiation of rs4752566 may have been caused by random genetic drift, although it is difficult to fully exclude the possibility of positive selection having acted in ancestors of East Asian origin because the extended LD, as a signature of positive selection, is difficult to be detected for a standing allele such as rs4752566-T.[6]

As *EDAR* 1540C allele is almost absent in African and European ancestors,[7] the mutation is considered to have occurred in the ancestors of Asian after the split from the ancestors of European origin. Thus, the possibility of local adaptation or positive selection related to hair thickness in non-Asian populations could not be discussed in our previous study.[2,3] If thicker hair is always advantageous in humans, an allele associated with thicker hair is expected to be highly frequent in all the populations where it exists. The rs4752566-T allele, which was found to be associated with hair thickness has lower population frequency in YRI and CEU (Table 1), implying that thicker hair may have been less advantageous in the African and European than in East Asian populations or selection intensity may be different among populations.

In this study, no strong genetic determinants of hair morphology aside from *EDAR* 1540T/C were detected. Since polymorphisms associated with hair thickness or hair index are not always a high population differentiation, it is therefore necessary to analyze the other hair-related genes to identify further genetic variants associated with hair thickness.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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