www.AUSTRALIANACADEMICPRESS.com.au

ARTICLE AVAILABLE ONLINE
Twin Research and Human Genetics
Volume 15 ▮ Number 2 ▮ pp. 166–169

Feeling of Cold Hands and Feet is a Highly Heritable Phenotype

Yoon-Mi Hur[1], Jeong-Ho Chae[2], Ki Wha Chung[3], Jung Jin Kim[2], Hoe-Uk Jeong[1], Jong Woo Kim[4], Sung Yum Seo[3], Kyung Soo Kim[5]

[1] *Mokpo National University, South Korea*
[2] *Department of Psychiatry, Seoul St. Mary's Hospital, The Catholic University of Korea*
[3] *Department of Biological Science, Kongju National University, South Korea*
[4] *College of Oriental Medicine, Kyunghee University Hospital, South Korea*
[5] *Department of Family Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea*

The prevalence of the feeling of cold hands and feet (FCHF) is high in the general population but the etiology of FCHF is largely unknown. The aim of the present study was to explore whether the FCHF is heritable. Eight hundred and ninety-four pairs of twins completed a question about FCHF. Tetrachoric correlations for FCHF were .58, .29, .67, .52, and .04 for monozygotic male, dizygotic male, monozygotic female, and dizygotic female twins, respectively. Model-fitting analyses suggested that in the best fitting model, additive genetic and nonshared environmental variance including measurement error were 64% (95% CI: 55%-72%) and 36% (28%-45%), respectively. Sex differences in genetic and environmental influences were not significant.

■ **Keywords:** cold hands and feet, genetics, twin, environment, Raynaud's Phenomenon

Although complaints of cold hands and feet are common in the general population, especially in women, surprisingly few investigations have been performed to investigate the genetic etiology of the feeling of cold hands and feet (FCHF). One of the normal physiological responses to cold temperature (or emotional stress) is to lower the skin temperature to preserve body heat and maintain a normal body core temperature. A diagnosis of Raynaud's phenomenon (RP) can be made when color changes occur to the skin of the digits of the hands or feet in response to cold temperatures or emotional stress (Levein, 2010). RP is known to be caused by transient cessation of blood flow to the digits of the hands or feet (Cooke & Marshall, 2005). Prior studies have shown that RP is associated with various diseases such as rheumatoid arthritis, scleroderma, dematomyositis, hypertension, and migraine (Gayraud, 2007). However, RP can occur in the absence of these disorders, which is called primary RP. Age of onset of primary RP is generally younger than 30 years (Wigley, 2002). Although the pathophysiology of primary RP remains poorly understood, increased α_2 sympathetic receptor activity on vessels, endothelial dysfunction, deficiency of calcitonin gene related peptide, protein-containing nerves and some central thermoregulatory defect have been suggested to contribute to the development of primary RP (Boin & Wigley, 2005; Cooke & Marshall, 2005;).

Twin and family studies of primary RP are scarce. However, a few existing studies consistently suggested the importance of genetic factors in primary RP. For example, Freedman and Mayes (1996) found a higher prevalence of primary RP in the families and relatives of patients with primary RP as compared to the control group. In a large, population-based, female adult twin sample (age: 30-60 years), Cherkas et al. (2007) showed that heritability estimates of RP and severe RP were 55% and 53%, respectively. Although Cherkas et al. excluded patients with rheumatism from their analysis, because they did not divide their twin subjects into primary and secondary RP

RECEIVED 06 January, 2012 ; ACCEPTED 13 February, 2012.

ADDRESS FOR CORRESPONDENCE: Yoon-Mi Hur, Mokpo National University, 61 Dorim-ri, Muan-gun, Jeonnam, South Korea. Email: ymhur@mokpo.ac.kr

groups, genetic influences they found include some of the genetic factors for diseases other than rheumatism. In the Cherkas et al. study, shared environmental influences were not statistically significant and all nongenetic variance was attributed to nonshared environmental variance including measurement error.

Even though the relationship between RP and FCHF is not well understood, given the genetic influence found for RP, it is conceivable that FCHF also has genetic underpinning. The main goal of this study was to explore genetic and environmental contributions to individual difference in the FCHF in a sample of healthy adolescent and young adult South Korean twins. As far as we understand, the present study is the first to report genetic and environmental influences on FCHF.

Methods

Sample and Measure.

The sample included 894 twin pairs [234 male and 385 female monozygotic (MZ) pairs; 70 male, 82 female, and 123 opposite-sex dizygotic (DZ) pairs] drawn from the South Korean Twin Registry (Hur et al., 2006). The age of twins ranged from 12 to 24 years, with a mean of 16.9 years (SD = 2.8 years). The greater number of MZ than DZ twins in the present sample reflect twin birth rates in the South Korean population (Hur & Kwon, 2005). Twins' zygosity was determined by questionnaire, which has been shown to be over 90% accurate in East Asian samples as compared to DNA analysis (Ooki et al., 1993). The twin data used in this study were collected through mail and telephone surveys that included a single item about the FCHF. On the item, twins were instructed to check one of the two options: 'My hands and feet are usually cold' and 'My hands and feet are usually warm'.

Statistical Analyses

To explore genetic and environmental influences on FCHF, tetrachoric correlations were computed for the five groups of twins and biometrical model-fitting analyses were carried out on raw ordinal data using Mx (Neale et al., 1999). The raw ordinal biometrical model used in the present study includes additive genetic (A) and shared (C) and nonshared (E) environmental factors that influence FCHF, while allowing sex differences in these factors. Measurement error is confounded with nonshared environmental factors. Additive genetic factors, the sum of the average effect of all genes that influence a trait, correlated at 1.0 and 0.5 for MZ and same-sex DZ twins, respectively. For OSDZ twins, however, the correlation for additive genetic factors was allowed to vary between 0 and 0.5, assuming that some of the genes that determine FCHF may be qualitatively different between males and females. Shared environmental factors were set at 1.0 for both MZ and DZ twins in both sexes. Finally, nonshared environmental factors were those environmental factors unique to each member of a twin pair, and thus uncorrelated between the two members of a twin pair.

Two criteria were used to choose the best-fitting, most parsimonious model: the likelihood ratio test (LRT) and the Akaike information criterion (AIC = X^2 – 2df). The raw data option in Mx calculates twice the negative log-likelihood (–2LL) of the data. As the difference in –2LL is chi-square distributed with degrees of freedom equal to the difference in degrees of freedom, LRT was applied to evaluate the significance of the constraint when two models were nested. A nonsignificant change in chi-square between the full and constrained models suggests that the reduction in parameter is acceptable, whereas a significant change indicates that the parameter should be retained in the model. AIC quantifies the information content of a model in terms of the joint criterion of fit and parsimony (Akaike, 1987). Thus, the smaller, the AIC, the better the fit of the model to the data. When two models were not nested, the model that yielded a lower AIC was chosen as a more parsimonious model. A baseline model where prevalences, variances and covariances were allowed to vary was set to compare with the full model.

Results

Prevalence Rates by Sex and Zygosity and Tetrachoric Twin Correlations

Table 1 presents prevalence rates and tetrachoric correlations in the five twin groups. For both MZ and DZ twins, FCHF was significantly more prevalent among females than males ($X^2 = 45.2$, $p < .001$ for MZ twins; $X^2 = 20.8$, $p < .001$ for DZ twins). However, there was no significant difference in prevalence between MZ and DZ twins in any of the two gender groups ($X^2 = 0.11$, $p = .42$ for males; $X^2 = 0.00$, $p = .52$ for females), suggesting no zygosity effect on FCHF.

TABLE 1

Sample Size, Prevalence Rates, and Tetrachoric Correlations (95% CI) for the Coldness of Hands and Feet for the Five Twin Groups

	MZM	DZM	MZF	DZF	OSDZ
Pair No.	234	70	385	82	123
Prevalence %	42.7%	44.3%	62.3%	62.2%	51.2%
Tetrachoric Correlation	.58 (.41-.71)	.29 (-.01-.60)	.67 (.55-.76)	.52 (.20-.76)	.04 (-.24-.31)

Note: MZM = monozygotic male twins, DZM = dizygotic male twins, MZF = monozygotic female twins, DZF = dizygotic female twins, OSDZ = opposite-sex dizygotic twins.

Older twins reported coldness slightly but significantly ($r = -.15$, $p < .01$) more often than did younger twins.

MZ twin correlations were greater than DZ twin correlations in both sexes, indicating that genetics play a large role in the etiology of FCHF. However, the difference between MZ and DZ twin correlation was greater in males than in females, suggesting that genetic influences were higher and shared environmental influences were lower in males than in females. Opposite-sex DZ (OSDZ) twin correlation was lower than same-sex DZ twins, suggesting that genes related to FCHF may be qualitatively different between the two sexes. These observations were tested using model-fitting analyses.

Model-Fitting

Table 2 shows the results of model-fitting analyses. As expected from Table 1, the prevalence of FCHF could not be equated between males and females (Model 1), confirming that the incidence is significantly greater in females than in males. Genetic correlation for OSDZ twins (r_g) could be equated to that for same-sex DZ twins (Model 2). In addition, additive genetic (A), shared environmental (C), and nonshared environmental (E) variance components could be constrained to be equal across males and females (Model 3). Models 4 and 5 eliminated shared environmental (C) and additive genetic (A) effects respectively from Model 3. Neither model yielded a significant change in chi-square. However, AIC was lower in Model 4 than in Model 5, suggesting that the former is better than the latter. When both additive genetic and shared environmental effects were removed from Model 3 simultaneously, the model-fit was significantly worsened (Model 6), suggesting that nonshared environmental factors alone cannot explain individual difference in FCHF. Thus, Model 4 was chosen as the best-fitting model. The estimates of additive genetic and nonshared environmental influences including measurement error in Model 4 were 64% (95% CI: 55% to 72%) and 36% (95% CI: 28% to 45%), respectively.

Discussion

The present study showed that the FCHF is a highly heritable phenotype. Heritability estimate in the best-fitting model was similar to that for RP found in the Cherkas et al. study (2007). Our full model showed some hint of shared environmental influences in females but not in males. Shared environmental factors relevant to FCHF may include temperature in the house, nutrition shared by family members, and family socioeconomic status. Although the prevalence of FCHF is much higher in females than in males, it is difficult to explain why these shared environmental factors are important only for females. However, as shared environmental factors in our full model did not attain statistical significance perhaps due to small sample size, studies with a large sample in the future will be necessary to determine sex differences in genetic and shared environmental influences on FCHF.

Our finding of substantial genetic influences on FCHF suggests a possibility that FCHF may be a biological marker of RP. FCHF may be a mild, early manifestation of RP and predictor of many diseases related to RP. It is possible that common genetic factors may underlie RP and FCHF. Multivariate genetic analyses using RP and FCHF simultaneously will help elucidate the genetic architecture of the relationship between RP and FCHF. A locus for hereditary vascular retinopathy (HVR) haplotype on chromosome 3p21.1-p21.3 has been suggested to be involved in RP (Hottenga et al., 2005). Future research

TABLE 2

Model-Fitting Results

Model	Description	Goodness-of-fit index						Parameter Estimates					
								Male			Female		
		-2LL	df	AIC	ΔX^2	Δdf	*p*	A	C	E	A	C	E
Full	$A_m \neq A_f$, $C_m \neq C_f$, $E_m \neq E_f$ $r_g \neq 0.5$, $t_m \neq t_f$	2125.8	1656	–1186.2				0.56 (.0,.71)	0.01 (0,.60)	0.42 (.29,.59)	0.33 (.0,.76)	0.34 (.0,.72)	0.33 (.23,.45)
1	$A_m \neq A_f$, $C_m \neq C_f$, $E_m \neq E_f$ $r_g \neq 0.5$, $t_m = t_f$	2134.4	1657	-1179.6	8.6	1	.00	0.58 (.01,.72)	0.01 (.0,.60)	0.41 (.29,.58)	0.32 (.0,.75)	0.34 (.0,.72)	0.34 (.24,.46)
2	$A_m \neq A_f$, $C_m \neq C_f$, $E_m \neq E_f$ $r_g = 0.5$, $t_m \neq t_f$	2125.8	1657	-1188.2	0	1	0.99	0.56 (.0,.71)	0.01 (.0,.59)	0.42 (.29,.59)	0.33 (.0,.76)	0.34 (.0,.72)	0.33 (.23,.45)
3	$A_m = A_f$, $C_m = C_f$, $E_m = E_f$ $r_g = 0.5$, $t_m \neq t_f$	2127.7	1660	-1192.3	1.9	4	0.76	0.46 (.01,.71)	0.18 (.0,.60)	0.36 (.28,.46)	0.46 (.01,.71)	0.18 (.0,.60)	0.36 (.28,.46)
4	**$A_m = A_f$, $E_m = E_f$ $r_g = 0.5$, $t_m \neq t_f$**	**2128.3**	**1661**	**-1193.7**	**2.4**	**5**	**0.79**	**0.64 (.55,.72)**	**—**	**0.36 (.28,.45)**	**0.64 (.55,.72)**	**—**	**0.36 (.28,.45)**
5	$C_m = C_f$, $E_m = E_f$ $r_g = 0.5$, $t_m \neq t_f$	2131.7	1661	-1190.3	5.9	5	0.32	—	0.59 (.50,.67)	0.41 (.33,.50)	— —	0.59 (.50,.67)	0.41 (.33,.67)
6	$E_m = E_f$ $r_g = 0.5$, $t_m \neq t_f$	2255.7	1662	-1068.3	129.9	6	.00		—	1.00[a]	—	—	1.00[a]

Note. rg = genetic correlation for OSDZ twins, t = prevalence rate; subscripts 'm' and 'f' indicate male and female, respectively. — : fixed to be zero. The best-fitting model is indicated in bold. 95% CI are in the parenthesis. a = 95%CI cannot be calculated. MZM = monozygotic male twins, DZM = dizygotic male twins, MZF = monozygotic female twins, DZF = dizygotic female twins, OSDZ = opposite-sex dizygotic twins.

should investigate if this haplotype is also associated with FCHF in the general population.

A subsample of the present study (N=1558) completed six personality scales (neuroticism, extraversion, psychoticism, venture, impulsivity, and empathy) of Eysenck Personality Scale (Eysenck & Eysenck, 1991) and reported their height and weight. While FCHF was not significantly correlated with any of the six personality scales ($-.07 < r < .06$), it showed a significant correlation with body mass index (BMI) calculated from self-report of height and weight, indicating that warmer hands are associated with higher BMI. Given the high heritability found for BMI (Hur et al., 2008), it would be interesting in future research to explore shared genetic relationship between BMI and FCHF.

There are a few limitations in the present study that need to be addressed. First, the results of the present study were on the basis of self-report and therefore, heritability estimates found in this study may not be accurate. However, subjectively estimated finger temperature has been shown to be closely related to the finger temperature measured objectively by infrared thermometer (Polunina et al., 2011). A bivariate genetic analysis would be informative to determine common genetic and environmental etiologies between perceived and objectively measured hand temperature. Secondly, our findings may not be generalizable to other populations because prevalence of RP has been shown to be different across various ethnic groups (Nakamura et al., 2000). Finally, differences in -2LL in Table 2 are relatively small, which perhaps reflects low statistical power associated small sample sizes. As categorical analyses require a large sample (Neale & Cardon, 1992), it is necessary to replicate our findings with larger samples.

Acknowledgments

This work was supported by the National Research Foundation grant funded by the Korean government (MEST) (No.20110027738).

References

Akaike, H. (1987). Factor analysis and AIC. *Psychometrica, 52,* 317-332.

Boin, F., & Wigley, F.M. (2005) Understanding, assessing, and treating Raynaud's phenomenon. *Current Opinion in Rheumatology, 17,* 752–760.

Cherkas, L. F., Carter, L., Spector, E. D., Howell, K. J., Black, C. M., & MacGregor, A. J. (2003). Use of thermographic criteria to identify Raynaud's phenomenon in a population setting. *The Journal of Rheumatology, 30,* 720-722.

Cooke, J. P., & Marshall, J. M. (2005). Mechanism of Raynaud's disease. *Vascular Medicine, 10,* 293-307.

Eysenck, H. J., & Eysenck, S. B. G. (1991). *Manual of the Eysenck Personality Scales.* London: Hodder & Stoughton.

Freedman, R. R. & Mayes, M. D. (1996). Familial aggregation of primary Raynaud's disease. *Arthritis and Rheumatism, 39,* 1189 -1191.

Gayraud, M. (2007). Raynaud's phenomenon. *Joint, Bone, Spine: Revue du Rhumatisme, 74,* e1-8.

Hottenga, J. J., Vanmolkot, K. R., Kors, E. E., Kheradmand Kia, S., de Jong, P. T., Haan, J., Terwindt, g. M., Frants, r. R., Ferrari, M. D., & van den Maagdenberg, A. M.(2005). The 3p21.1-p21.3 hereditary vascular retinopathy locus increases the risk for Raynaud's phenomenon and migraine. *Cephalagia, 12,* 1168-1172.

Hur, Y-M., Shin, J. S., Jeong, H-U, & Han, J. Y. (2006). The South Korean Twin Registry. *Twin Research and Human Genetics, 10,* 838-843.

Hur, Y-M., & Kwon, J. S. (2005). Changes in twinning rates in South Korea; 1981-2002. *Twin Research and Human Genetics, 8,* 76-79.

Hur, Y. M., Kaprio, J., Iacono, W. G., Boomsma, D. I. McGue, M., Silventoinen, K. Martin, N. G., Luciano, M., Visscher, P. M., Rose, R. J., He, M., Ando, J., Ooki, S., Nonaka, K., Lin, C. C. H., Lajunen, H., Cornes, B. K., Bartels, M., CEM van Beijsterveldt, Cherny, S. S., & Mitchell, K. (2008). Genetic influences on the difference in variability of height, weight and body mass index between Caucasian and East Asian adolescent twins. *International Journal of Obesity, 32,* 1455-67.

Levien, T. L. (2010). Advances in the treatment of Raynaud's phenomenon. *Vascular Health and Risk Management, 6,* 167-177.

Nakamura, Y., Shinozaki, N., Hirasawa, M., Kato, R., Shiraishi, K., Kida, H., Usuda, K., & Ishikawa, T. (2000). Prevalence of migraine and Raynaud's phenomenon in Japanese patients with vasospastic angina. *Japanese Circulation Journal, 64,* 239-242.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families.* London: Kluwer.

Neale, M. C. (1999). *Mx: Statistical modeling* (5th ed.). Box 126 Medical College of Virginia, Richmond, VA 23298: Department of Psychiatry.

Ooki, S., Yamada, K., & Asaka, A. (1993). Zygosity diagnosis of twins by questionnaire for twins' mothers. *Acta Geneticae Medicae et Gemellologicae, 42,* 17–22.

Polunina, A.; Gugleta, K.; Kochkorov, A.; Katamay, R.; Flammer, J., Orgül, S. (2011). Relationship between peripheral blood flow in extremities and choroidal circulation. *Klin Monatsbl Augenheilkd, 228,* 302-305

Wigley, F. M. (2002). Raynaud's phenomenon. *New England Journal of Medicine, 347,* 1001-1008.