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Familial Transmissability of Early Age at Initial Diagnosis in Coronary Heart Disease (CHD): Males Only, and Mediated by Psychosocial/Emotional Distress?

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In equal sized samples, a strong association between a positive Family History of Early Coronary Heart Disease (FamHx) and early Age at Initial Diagnosis (AAID) was found only for males, and thus all further analyses were restricted to males. All three scales of the self-report version of the Ketterer Stress Symptom Frequency Checklist—Revised (KSSFCR)—"AIAI" (or aggravation, irritation, anger, and impatience), Depression, and Anxiety—were associated with both a positive FamHx and early AAID. A series of regression models was used to demonstrate that the KSSFCR scales may plausibly account for 22–32% of the variance in the relationship between a positive FamHx and early AAID. Because of previously documented denial in males, the analyses were repeated in a subgroup of males for whom Spouse/Friend KSSFCRs were obtained. Spouse/Friend-reported AIAI was related to both early FamHx and early AAID, and could account for 68% of the common variance.

KEY WORDS: behavioral genetics; stress; anger; coronary heart disease.

INTRODUCTION

Familial transmission of a condition is generally taken as a requirement for asserting a genetic component to the disorder. Coronary heart disease (CHD) has a small familial component (Pyeritz, 1997) compared to disorders such as depression and schizophrenia (Bouchard *et al.*, 1990; Plomin, 1990; Plomin *et al.*, 1980). The best documented mechanism(s) that contributes to the familial transmissability of CHD are the familial hyperlipidemias (Farmer and Gotto, 1997). However, the rarity of these metabolic defects in cholesterol processing means that they cannot account for much of the familial transmission of CHD. Thus, other mediating processes must occur.

Psychosocial/emotional distress (anger, depression, and anxiety) is increasingly well established as a major risk factor for CHD (Dusseldorp *et al.*, 1999; Ketterer *et al.*, 2000c). Both depression and anxiety have moderately strong heritibility (Bouchard *et al.*, 1990; Plomin, 1990), and thus might account for some of the familial aggregation of CHD. And anger/aggression/hostility may also have a moderately strong genetic component (Carmelli *et al.*, 1988, 1990; Cates *et al.*, 1993; Costa *et al.*, 1986; Matthews *et al.*, 1984; Morell, 1993; Pederson *et al.*, 1989; Rose, 1988; Smith *et al.*, 1991). Males may be particularly likely to be at increased risk for early CHD because of anger (Chang *et al.*, 2002; Ketterer *et al.*, 2002a). To the best of our knowledge, no study has examined the role of psychosocial/emotional distress as a possible mediating factor in the familial transmission of early CHD. Raynor *et al.* (2002) recently found in twin comparisons that a single factor may account for covariation of psychosocial risk factors in CHD, consistent with our previous observation that such risk factors are confounded and nonindependent in predicting outcomes (Ketterer *et al.*, 2000a,b,c, 2002a,b).

One major problem in assessing the role of psychosocial/emotional distress as a risk factor for CHD is denial (i.e., discrepancies between what a patient reports for him/herself and what others report about him/her). We have demonstrated that "significant other" reported distress is a better predictor of coronary artery disease (CAD) severity (Ketterer *et al.*, 1996), chest pain at 5-year follow-up (Ketterer *et al.*, 1998) and Age at Initial Diagnosis (AAID) (Ketterer *et al.*, 2002a,b) than self-reported distress. Denial (spouse/friend minus self ratings) of psychosocial/emotional distress is an even more potent predictor of CAD severity (Ketterer *et al.*, 1996) and mortality (Ketterer *et al.*, 1998). This seems to be particularly true of anger ratings in males (Ketterer, 1992; Ketterer *et al.*, 1993, 2002a,b). Thus, maximally accurate quantification of psychosocial/emotional distress may require ratings from a significant other.

The present analyses of a previously described sample (Ketterer *et al.*, 2002a,b) were undertaken to examine whether the heritibility of early onset ICHD might be mediated by either known cardiovascular risk factors and/or emotional distress.

METHODOLOGY

Subjects

Records of 50 male and 50 female patients with documented CHD (history of positive catheterization and/or myocardial infarction) referred from the Cardiac Rehab Program, General Cardiology Clinics or Cardiac Catheterization Lab for stress management (and who received a standardized interview for demographic/clinical history variables, the Beck Depression Inventory, Crown–Crisp Phobic Anxiety Scale, Type D Scale, and Ketterer Stress Symptom Frequency Checklist (KSSFC)) were reviewed. Mean age of the sample was males = 57.9 and females = 56.8 ($p = 0.654$). Mean AAID was males = 53.8 females = 51.9 ($p = 0.443$). Mean years of education was male = 13.7 and females = 13.0 ($p = 0.129$).

Instruments

At initial evaluation, all patients were screened for the following clinical/demographic or risk factors: Age (in years); AAID (in years); Family History of Early Onset CHD (none *or* at least one first or second degree relative with onset or death before age 56); History of Diabetes (none, diet, oral or injection controlled); Height and Weight (to calculate Body Mass Index); Snoring (none, occasionally/lightly, usually or constantly/loudly); Years of Education; Current Marital Status (yes versus no); History of Divorce; History of Myocardial Infarction; History of Revascularization; Current Smoker; History of Hypercholesterolemia (baseline total cholesterol of 240 mg% or greater); History of Hypertension (baseline blood pressure of 139/89 or greater).

The Beck Depression Inventory (Beck *et al.*, 1961), Crown–Crisp Phobic Anxiety Scale (Crown and Crisp, 1966), and Type D Scale (Denollet, 1998) have been described elsewhere. The Ketterer Stress Symptom Frequency Checklist—Revised (KSSFCR) has also been described elsewhere (Ketterer *et al.*, 1993). It comes in two, parallel versions; one to be completed by the patient about him/herself and one to be completed by an individual chosen by the patient as "someone who knows you well." The KSSFC obtains measures of "AIAI" (aggravation, irritation, anger, and impatience),

Depression, and Anxiety/Worry. Each scale is composed of the sum of face valid items scored "0" or "1" depending upon whether the rated frequency is one standard deviation or more above previously established item norms. For example, the AIAI scale contains such items as "Over the past year, how often do you: feel or act angry; blow up; fight with coworkers; want to yell at someone; feel or act frustrated; feel or act hassled." The Spouse/Friend Version of the KSSFCR asks about the same behaviors with a different stem: "Over the past year, how often does your spouse or friend...?"

Procedures

Patients who are referred for stress management are routinely evaluated for clinical/demographic factors and cardiovascular risk factors in a standardized format, and the measures of psychosocial/emotional distress. Data were coded from clinical files without any specific identifying information.

Analysis

The $p = 0.05$ level of significance was used.

Because familial transmission of at least some forms of psychosocial/ emotional distress may be sex linked (Morell, 1993), analyses examined males and females separately. Because Family History of Early CHD was not associated with AAID for females (see Fig. 1), all further analyses were limited to males.
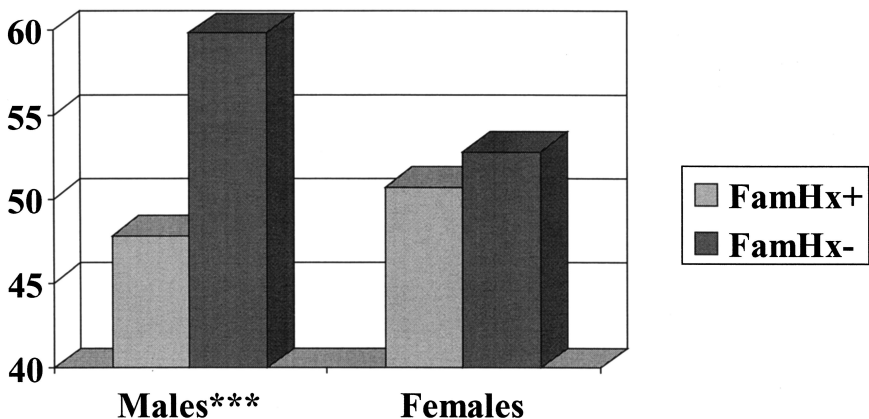

Fig. 1. Family History and AAID in 50 male and 50 female ICHD patients.

If a risk factor is to be argued to be a mediating variable for the familial transmission of early onset CHD, it must be associated with *both* Family History of Early Onset CHD and AAID. Thus, univariate statistical tests (*t* tests and chi squares) were used to test the association of Family History of Early CHD with the psychosocial/emotional measures of distress and traditional risk factors. Because of the failure of the traditional risk factors to covary with Family History of Early CHD, only the association of AAID with the psychosocial/emotional distress measures was examined.

Several multiple regressions using AAID as the dependent variable were run. Initially, Family History was used as the sole predictor to assess variance accounted for by this model. Then, forced entry of the significant univariate measures of psychosocial/emotional distress *before* entering Family History was used to see if significant variability in the relationship of Family History and AAID might plausibly be attributable to psychosocial/emotional distress.

In a subgroup for whom Spouse/Friend KSSFCRs were received, the same multiple regressions were repeated.

RESULTS

Mean AAID was about 12 years earlier for males with a positive Family History of Early CHD compared to those without such a history ($t = 3.94$, df $= 48$, $p < 0.001$). For females, there was only a 2-year difference ($t = 0.58$, df $= 48$, $p = 0.782$). This difference is displayed in Fig. 1.

Among the traditional risk factors, none were significantly different when comparing positive versus negative Family History for the males. These results are displayed in Table I.

Among the measures of psychosocial/emotional distress, the three scales of the KSSFCR were significantly different between males with a positive versus a negative Family History of Early CHD. The Beck Depression Inventory, Crown–Crisp Phobic Anxiety Scale, and Type D Scale were not significant. For those patients from whom the Spouse/Friend KSSFCRs were obtained, only the AIAI scale was significant. These results are displayed in Table II.

For the males, several measures of psychosocial/emotional distress were associated with AAID. These included all three scales of the KSSFCR in the total sample, all three scales of the KSSFCR as reported by the Spouse/Friend, and the Type D Scale. These results are displayed in Table III.

Table I. The Association of a Family History of Early ICHD, and Traditional Risk Factors in Males

	Family History of Early ICHD		
	Positive (N = 25)	Negative (N = 25)	p
t Tests			
Packyears of smoking	33.52	41.96	0.413
Diabetes	0.12	0.52	0.077
Body Mass Index	28.96	29.69	0.622
Snoring	1.36	1.16	0.512
Years of education	13.72	13.68	0.955
Chi squares			
Married	80%	84%	0.713
Hx of divorce	28%	28%	0.999
Hx of MI	84%	68%	0.185
Hx of revascularization	76%	80%	0.733
Current smoker	20%	20%	0.999
Hx of hypercholesterolemia	72%	72%	0.999
Hx of hypertension	48%	68%	0.152

The multiple regressions indicated that the self-report scales of the KSSFCR could account for about 22–32% of the variance in the Family History—AAID relationship. By contrast, Spouse/ Friend-reported AIAI on the KSSFCR accounted for over two-thirds of the variance. This is displayed in Table IV.

Table II. The Association of Family History of Early ICHD and Various Measures of Psychosocial/Emotional Distress in Males

	Family History of Early ICHD		
	Positive (N = 25)	Negative (N = 25)	p
Chi square			
Type D	28%	16%	0.306
t Tests			
Beck Depression Inventory	14.08	14.16	0.985
Crown–Crisp Phobic Anxiey Scale	3.96	7.48	0.374
Ketterer Stress Symptom			
Frequency Checklist			
Patient Version			
AIAI	5.16	2.80	0.049
Depression	4.20	2.72	0.041
Anxiety/Worry	8.12	4.88	0.048
Spouse/Friend Version	N = 18	N = 20	
AIAI	7.28	4.05	0.027
Depression	3.61	3.30	0.684
Anxiety/Worry	8.78	7.00	0.395

Table III. The Association of the Psychosocial/Emotional Distress Measures With Age at Initial Diagnosis in Males

	Total sample ($N = 50$)	Spouse/Friend subgroup ($N = 38$)
Pearson correlations		
Beck Depression Inventory	−0.073	−0.210
Crown–Crisp Phobic Anxiety Scale	0.033	0.140
KSSFC—Patients		
AIAI	−0.339**	−0.376**
Depression	−0.363**	−0.409**
Anxiety	−0.273*	−0.323*
KSSFC—Spouse/Friend		
AIAI	NA	−0.661***
Depression	NA	−0.288*
Anxiety	NA	−0.509***
t Test		
Type D	−1.91*	−1.74*

$^*p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$.

DISCUSSION

The fact that psychosocial/emotional distress succeeds as a mediating variable in the relationship between Family History and early AAID is consistent with the hypothesis that heritibility of psychosocial/emotional distress may account for some, and perhaps even most, of this relationship. The fact that traditional risk factors fail to account for significant variability in this relationship implies that their genetic influence is small compared to

Table IV. Variance in the Family History–Age at Initial Diagnosis Relationship Accounted for by Prior Forced Entry of the Psychosocial/Emotional Measures in Males

	Residual adjusted R^2	p	Variance accounted for by psychosocial measure
Total sample ($N = 50$)			
1) Family History	0.229	0.0003	
2) Depression		0.0096	32.75%
FH	0.154	0.0017	
3) Anxiety/Worry		0.0552	22.67%
FH	0.178	0.0011	
4) AIAI		0.0161	29.26%
FH	0.162	0.0014	
Spouse/Friend subgroup ($N = 38$)			
5) Family History	0.247	0.0009	
6) AIAI		<0.0001	68.02%
FH	0.079	0.0140	

psychosocial/emotional distress. This is notable for hypercholesterolemia, diabetes, hypertension, and obesity, all of which have been implicated as having a genetic component. We suspect the relatively small sample size precluded detecting the genetic effect for these factors. But the same reasoning makes the results for the psychosocial/emotional factors all that more impressive. Perhaps cardiovascular geneticists should be looking to emotional distress (i.e., acute/chronic dysfunctionalities in the autonomic nervous system and associated risk factor behavior) as the primary culprit in the heritibility of early CHD?

For the clinician, present results imply that early onset CHD should raise greater suspicion of psychosocial/emotional distress, even if the patient denies it. A careful history of personality traits in the family may raise the clinician's suspicions for the patient's own behavior. Because patient's minimize/deny stigmatized behavior (e.g., loss of temper, anger, yelling, hitting, breaking things, rudeness, etc.), a male patient who acknowledges such behavior in his father while denying it for himself might need to be approached for stress management rather than psychiatric/psychological or mental health care since this way of framing the problem destigmatizes help-seeking.

It would appear from these results that the KSSFCR captures the genetic component of CHD relevant stress better than the other scales tested. We have previously reported that the KSSFCR, or its earlier version, is a stronger correlate than several competing psychometric measures of CAD severity per angiography (Ketterer *et al*., 1996); AAID (Ketterer *et al*., 2002a,b); mortality and chest pain at 5-year follow-up (Ketterer *et al*., 1998); and inability to stop smoking (Ketterer and Maercklein, 1992). Given the strong track records of these other scales at predicting mortality in CHD patients (Ketterer *et al*., 2000a,b,c), we find this a bit surprising. The KSSFCR is a fairly "behavioral" instrument in the sense that it assesses the frequency of behaviors that are indicative of emotional state. While this rather blunt inquiry may provoke denial in some denying/minimizing patients, the critical issue of assessing the chronicity of emotional states is more directly addressed than occurs with other measures. The fact that the Spouse/Friend Version is moderately to dramatically better at predicting endpoints speaks directly to the superiority of this methodology. We increasingly suspect that maximally accurate quantification of emotional distress may require inquiry of a significant other, at least in males. To date, only the KSSFCR has captured this independent source of information in a standardized, normed, and validated manner, although similar ad hoc self versus spouse/friend comparisons have supported this hypothesis (Kneip *et al*., 1993; Siegman *et al*., 1998).

Several limitations in this study indicate the need for replication. The sample is somewhat skewed by having been referred for "stress." In fact,

some of our clinical settings refer patients only if they prescreen positive on the Hospital Anxiety and Depression Scale, and the rest refer only if the attending cardiologist believes the patient is distressed. Thus, the sample may be somewhat constrained by clinical selection bias. This might weaken, or strengthen, the observed relationships. Likewise, patients who die before detection of their CHD, are undiagnosed or who refuse referral are unavoidably excluded. The sample size here is small, making the results all that more impressive but also raising questions about whether the other psychometric scales, or the traditional risk factors, might have been significant in a larger sample. Ideally present results should be replicated in a prospective study of newly diagnosed CHD patients (e.g., first time positive catheterization patients).

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