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Genetic Influences on Suicide and Nonfatal Suicidal Behavior: Twin Study Findings

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Abstract

It has been well established that suicidal behavior is familial. Twin studies provide a unique opportunity to distinguish genetic effects from other familial influences. Consistent with findings from previous twin studies, including case series and selected samples, data from the population-based Swedish Twin Registry clearly demonstrate the importance of genetic influences on suicide. Twin studies of suicidal ideation and suicide attempts also implicate genetic influences, even when accounting for the effects of psychopathology. Future work is needed to evaluate the possibility of age and gender differences in heritability of suicide and nonfatal suicidal behavior.

Keywords

suicide; suicidal ideation; suicide attempt; concordance; twin studies; heritability

1. Introduction

1.1 Suicide

A million individuals die by suicide each year, most of whom suffer from affective disorder or another form of psychopathology [13]. Thus, suicide represents a major public health problem. Efforts to understand the causes of suicidal behavior are urgently needed so that at-risk individuals can more effectively be identified and treated.

Family studies clearly demonstrate that suicide is familial [2]. What is not clear from these studies, however, is the extent to which familial influences represent genetic factors as opposed to shared familial environment. Twin studies provide an opportunity to distinguish these effects. In this paper, we describe how twin studies can contribute to our understanding of suicidal behaviors, review results from existing twin studies, and provide new data.

1.2 Twin Methods

Twin studies evaluate the importance of genetic influences on a phenotype (heritability) independent of other familial factors by comparing twin similarity within monozygotic (MZ) and dizygotic (DZ) pairs [1]. When MZ twins are twice as similar as DZ twins for a given phenotype within a given population, genetic influences are implicated and can be estimated. Shared familial influences are suggested when the MZ:DZ similarity ratio is less than 2:1. This method rests on the assumption of equal environments for MZ and DZ twins, an assumption that has generally been supported with respect to mental health phenotypes [9].

Twin studies that include unlike-sex pairs also provide the opportunity to evaluate the relative magnitude of genetic effects in women and men, as well as the presence of differential gene expression in women in men. Twin studies also allow investigators to evaluate the extent to which genetic effects for a given phenotype may be shared with other traits [1].

Twin studies can also be a vehicle for evaluating environmental influences. Co-twin control designs provide information about the importance of specific risk factors independent of genetic confounding. Further, twin studies can be used to evaluate the presence of gene by environment interaction by studying MZ twins discordant for specific environmental exposures.

Finally, twin populations can also be useful in molecular genetic investigations. A surviving co-twin of an MZ twin who died by suicide provides a unique opportunity to examine the genetic makeup of the deceased individual.

2. Twin Studies of Suicide

2.1 Review of prior studies

One method for estimating the relative importance of genetic effects on a phenotype is to compare probandwise concordance rates for MZ and DZ twins. Calculated as the number of affected twins in concordant pairs divided by the total number of affected twins, this rate can be interpreted as a twin's risk given the co-twin is affected [11]. Table 1 summarizes concordance rates from published reports.

In an early paper, Haberlandt (cited in Roy and Segal [16]) combined information from published twin suicides. Among 149 twin pairs in which at least one twin died by suicide, nine MZ pairs were concordant, yielding a 30% probandwise concordance rate. A study of suicides in the population-based Danish Twin Registry [7] reported four concordant MZ pairs among 19 MZ pairs with at least one affected twin (35%) and no concordant DZ pairs.

Roy, Segal, Centerwall, & Robinette [17] reported on twin suicides from two sources: cases solicited through a published letter (11 pairs) and data from the National Academy of Sciences/National Research Council (NAS/NCR) Twin Registry (165 pairs). There were seven concordant MZ pairs and two concordant DZ pairs in the combined sample, giving

probandwise concordance rates of 20% (MZ) and 3% (DZ). McGuffin and colleagues [12] estimated heritability of suicide to be 43% based on these data.

2.2 Suicide in Swedish Twins

We examined twin concordance for suicide in the Swedish Twin Registry (STR). The STR, established in the late 1950s, is the world's largest population-based twin register with 85,000 twin pairs born 1886–2000 [10]. Data have been gathered through questionnaires, telephone interviews, health examinations and register linkage. Zygosity was determined by questionnaire and verified in a subsample to be 99% accurate. For the current analyses, we included twins born 1886–1958 for whom zygosity could be established (38,469 pairs). Suicides through December 31, 2003, were established by linkage with the Swedish Death Register. We classified deaths as suicides (ICD7: E970-E979; ICD8/ICD9: E950-E959; ICD10: X60-X84) or undetermined (ICD8/ICD9: E980-E989; ICD10: Y10-Y34). Analyses were conducted using suicide as the outcome, and then repeated using both suicides and undetermined deaths, since this category has been shown to include misclassified suicides [14]. Because results were similar, we report suicide results only.

There were three MZ pairs concordant for suicide and 98 discordant, giving an MZ concordance rate of 5.8%. In contrast, there were two concordant DZ pairs and 223 discordant (1.8% DZ concordance rate). The concordance rate for unlike sex dizygotic twins was 3.5% (three concordant and 166 discordant pairs). Examining female and male pairs separately, differences appear to emerge, with a greater difference between MZ and DZ concordance rates for women (MZ = 11%, DZ = 0%) than for men (MZ = 3%, DZ = 2%).

Thus, findings from studies of fatal suicidal behavior vary widely. Given the relatively low base rate of suicide, concordance rates are likely to be more stable in larger samples. In addition, population based samples like the STR are less subject to ascertainment bias. Despite differences, however, existing studies are consistent in finding a large differential between MZ and DZ concordance rates. Segal and Roy [19] demonstrated that differential concordance rates could not be explained by differential grief reactions in MZ compared to DZ twins. Taken together, these results suggest an important role for genetic effects on fatal suicidal behavior.

3. Twin Studies of Suicidal Ideation and Attempt

Table 2 summarizes findings from twin studies of nonfatal suicidal behavior, including suicidal ideation and attempts. Roy, Segal and Sarchiapone [18] evaluated lifetime history of suicide attempts in co-twins of a selected sample of twins who had died by suicide. Among 26 MZ co-twins, 10 had attempted suicide, yielding a concordance rate of 56%. None of the 9 DZ co-twins had attempted suicide. In a replication using the same method, Roy and Segal [16] gathered information on an additional 28 co-twins of twins who had died by suicide. Of the 13 MZ co-twins, three had attempted suicide and 1 died by suicide. None of the DZ co-twins had engaged in suicidal behavior. Although these samples were not representative, the studies provide support for a genetic influence on suicide attempts.

Statham and colleagues [20] investigated suicidal behavior in the voluntary Australian National Health and Medical Research Council Twin Registry (ATR). The sample included 2,718 twin pairs and 559 singletons aged 27–89. Structured diagnostic telephone interviews assessed lifetime history of any suicidal thoughts, persistent suicidal thoughts (lasting more than one day), suicidal plans and suicide attempts. Concordance for each category was higher in MZ than in DZ pairs, suggesting genetic effects. Structural equation twin models yielded heritability estimates of 43% for any suicidal thoughts, 44% for persistent thoughts, plans or minor attempt, and 55% for serious suicide attempt. In logistic regression analyses, the effect of co-twin suicidal behavior was independent of the effects of psychopathology and traumatic life events.

Glowinski and colleagues [5] conducted structured diagnostic telephone interviews with 3,416 females aged 12–23 from the Missouri Adolescent Female Twin Study. Among the 143 twins who reported a lifetime history of suicide attempt, there were 12 concordant pairs, with a higher concordance rate for MZ (25%) than DZ (13%) twins. Logistic regression analysis showed that genetic effects were independent of psychopathology. Heritability of suicide attempt was estimated at 48%.

Fu and colleagues [4] investigated suicidal ideation and attempts in the Vietnam Era Twin Registry of male US veterans of the Vietnam War aged 33–55 at time of interview. A series of structural equation twin models examined heritability of suicidal ideation and attempts independent of the effects of demographic variables, psychopathology and combat exposure. Results implicate the same genetic effects for suicidal ideation as for suicide attempts in this middle aged male sample. In unadjusted models, heritability estimates for suicidal ideation and attempt were 47% and 30%, respectively. After adjustment, estimates were 36% and 17%. Shared family environmental effects explained 19% of the variance in liability for suicide attempt. Thus, this study is consistent with the results of other behavior genetic investigations of nonfatal suicidal behavior that show genetic effects independent of psychopathology.

Cho and colleagues [3] evaluated suicidal ideation and attempts in a genetically-informative subsample of the representative US National Longitudinal Study of Adolescent Health. Among 53 MZ pairs and 77 DZ pairs in which one or both members endorsed suicidal ideation in the past 12 months, seven MZ pairs and seven DZ pairs were concordant, yielding probandwise concordance rates of 23% and 17% for MZ and DZ pairs (with 9% for like-sex DZ pairs). Among the 13 MZ and 21 DZ pairs in which one or both twins had made a suicide attempt, there were three concordant MZ pairs and two concordant DZ pairs, giving MZ and DZ probandwise concordance rates of 38% and 17% (with 25% for like-sex DZ pairs). Although differences were not statistically significant, they are consistent with other studies in suggesting genetic influence on nonfatal suicidal behaviors.

These studies suggest that concordance rates may be higher for suicidal ideation and attempts than for death by suicide. Whether concordance rates differ for suicidal ideation vs. attempt is less clear. These studies also demonstrate the presence of genetic vulnerability to nonfatal suicidal behaviors that cannot be fully explained by genetically-influenced psychopathology.

4. Molecular Genetic Studies Using Twins

As noted above, twin studies can also contribute to molecular genetic investigations of suicide. An example from the Swedish Twin Registry (STR) is a study by Roy and colleagues evaluating the role of serotonin-related genes in suicide by interviewing and genotyping the surviving cotwins of MZ twins who had died by suicide [15]. The tryptophan hydroxylase 17 779C allele was significantly more frequent in the surviving co-twins than in controls. There was a trend toward greater frequency of the C/A or C/C genotype (rather than the A/A genotype) in surviving MZ cotwins. No difference was found for frequency of the serotonin transporter linked polymorphic region (5-HTTLPR) short (S) or long (L) allele or genotype in surviving MZ cotwins vs. controls, although lack of significant results may be due to relatively low power. This study highlights the possibilities for molecular genetic research on suicide using twin samples.

5. Discussion

It can be concluded that genetic factors play an important role in suicidal behavior. Concordance rates vary substantially across studies, as would be expected given the statistical rarity of suicide and the instability of concordance rates in small samples. Even in the STR, with 38,469 pairs, there were only eight concordant affected pairs. Nonetheless, in each study, the MZ concordance rate was substantially greater than the DZ concordance rate, implying genetic effects.

Results from the Swedish Twin Registry (STR) suggest that suicide may be more heritable in women than in men. Due to small numbers of concordant pairs (especially for women, among whom suicide is less prevalent than among men), these findings should be interpreted with caution. These findings are interesting, however, given prior work in the STR showing greater heritability of depression for women than for men [8].

These studies also provide clues to the genetics of nonfatal suicidal behavior. Twin studies suggest that heritability may be greater for suicidal ideation and attempts than for death by suicide. There may also be differences in the magnitude of genetic effects for suicidal ideation and attempts, although these results are less clear. These suggestive findings lend support to the notion that suicidal ideation, attempts and deaths may be partly distinct, albeit overlapping, phenotypes.

6. Conclusion

Twin studies have much to offer to the study of suicide. Large, population-based twin registries like the Swedish Twin Register can be particularly helpful. Future work evaluating possible moderators of genetic influence, including testing for age and gender differences in heritability, should provide additional guidance for suicide researchers.

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Table 1

Probandwise concordance rates for suicide

Authors	Sample	N pairs	Concordance
Haberlandt et al., 1967 ^a	Pooled data	MZ = 51 DZ = 98	MZ = 0.30 DZ = 0.00
Juel-Nielsen & Videbech, 1970	Danish Twin Registry, population based	MZ = 19 DZ = 58	MZ = 0.35 DZ = 0.00
Roy et al, 1991	Combined	MZ = 62 DZ = 114	MZ = 0.20 DZ = 0.03
	Solicited	MZ = 9 DZ = 2	MZ = 0.36 DZ = 0.00
	NAS/NRC twin reg. male veterans, USA	MZ = 53 DZ = 112	MZ = 0.17 DZ = 0.04
Swedish Twin Registry	Swedish Twin Registry, population based, birth cohorts 1886–1958	MZ = 9811 DZ = 16496 OZ = 12162	MZ = 0.06 DZ = 0.02 OZ = 0.035
	Men	MZ = 4537 DZ = 7723 OZ = 6094	MZ = 0.03 DZ = 0.024
	Women	MZ = 5274 DZ = 8773 OZ = 6068	MZ = 0.11 DZ = 0.00

Note. MZ = monozygotic, DZ = dizygotic, OZ = unlike sex pairs

^aIncludes 4 concordant MZ pairs from Juel-Neilsen & Videbech (1970).

Table 2

Probandwise concordance rates for nonfatal suicidal behavior

Authors	Sample	N pairs	Outcome	Concordance
Roy et al, 1995	Co-twins of completers	MZ = 26 DZ = 9	Suicide attempt (lifetime)	MZ = 0.38 DZ = 0.00
Roy & Segal, 2001	Co-twins of completers	MZ = 13 DZ = 15	Suicide attempt (lifetime) or completion	MZ = 0.47 DZ = 0.00
Statham et al., 1998	Australian Twin Registry, aged 27–89	Men	Any suicidal thoughts (lifetime)	MZ = 0.41 DZ = 0.31 OZ _M = 0.34
			Persistent thoughts, plans, minor attempt (lifetime)	MZ = 0.35 DZ = 0.15 OZ _M = 0.17
	Women	Serious attempt (lifetime)	MZ = 0.12 DZ = 0.00 OZ _M = 0.00	
		Any suicidal thoughts (lifetime)	MZ = 0.44 DZ = 0.26 OZ _F = 0.32	
		Persistent thoughts, plans, minor attempt (lifetime)	MZ = 0.27 DZ = 0.21 OZ _F = 0.17	
		Serious attempt (lifetime)	MZ = 0.29 DZ = 0.00 OZ _F = 0.00	
Glowinski et al, 2001	Missouri Adolescent Female Twin Study (USA), aged 12–23	3401 individuals (55% MZ)	Suicide attempt (lifetime)	MZ = 0.25 DZ = 0.128
Cho et al., 2006	National Longitudinal Study of Adolescent Health (USA), grades 7–12, genetically informative subsample	MZ _M = 141 MZ _F = 141 DZ _M = 131 DZ _F = 114 OZ = 197	Suicidal ideation (past 12 months)	MZ = 0.23 DZ+OZ = 0.17 DZ = 0.9
			Suicide attempt (past 12 months)	MZ = 0.38 DZ+OZ = 0.17 DZ = 0.25

Note. MZ = monozygotic, DZ = dizygotic like-sex, OZ = dizygotic unlike-sex