Genetic risk factors as possible causes of the variation in European suicide rates

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Suicide rates in Europe vary widely, with countries such as Spain, Italy and Greece reporting rates below 7 per 100 000 inhabitants per year, whereas others such as Hungary and Finland report rates in excess of 27 per 100 000 inhabitants per year (World Health Organization, 1994). In addition, since the break-up of the Yugoslav and the Soviet Federations it has become apparent that newly independent countries such as Estonia, Latvia, Lithuania and Slovenia also have high rates of suicide (Table 1).

RISK FACTORS

Risk factors for suicide are traditionally divided into medical (e.g. mental disorders), psychosocial (e.g. divorce), cultural (e.g. lack of religious commitment) and socioeconomic (e.g. unemployment). At first sight it seems plausible that sociocultural factors should be the major causes of different suicide rates across Europe. However, such a thesis fails to hold up under closer scrutiny. A more promising method for identifying risk factors for suicide is to consider that they are composed of genetic and environmental influences.

Table 1 Suicide rate (number of suicides per 100 000 inhabitants per year, standardised for age) in ten European countries with the highest suicide risk (World Health Organization, 1994)

European country	Suicide rate
Lithuania	43
Latvia	42
Estonia	38
Hungary	37
Russia	31
Slovenia	28
Finland	28
Ukraine	22
Belarus	21
Austria	21

Although scant, recent research findings support a role for genetic risk factors for suicide (Roy *et al*, 1999). An association between positive family history and risk of suicide by violent means has been reported (Linkowski *et al*, 1985), and a large community twin study has shown that genetic risk factors accounted for approximately 45% of the variance in suicidal thoughts and behaviour (Statham *et al*, 1998). Adoption studies also have shown increased rates of suicide in the biological rather than adopting relatives of adoptees (Wender *et al*, 1986).

Suicide is frequently associated with mental disorder, suggesting the possibility of shared susceptibility factors, and recent molecular genetic studies have focused on serotonin transmission and suicidal ideation. An association has been found between a tryptophan hydroxylase (TPH) polymorphism and suicidal ideation, the severity of the suicide attempt and alcoholism (Nielsen *et al*, 1998). Also, Mann *et al* (1997) have reported positive associations with the same polymorphism among suicide-attempting depressed patients.

This evidence suggests an important role for genetic factors in suicidal behaviour. Could genetic differences, at least in part, account for the varying rates of suicide in Europe, for example genetic and environmental risk factors acting additively under a multi-factorial polygenic mode of inheritance? First, we will argue that it is not possible to explain the differences in suicide rates across Europe by sociocultural differences alone. Second, we will explore the case for shared genetic risk factors influencing the rates of suicide in high-risk European countries, using evidence from population genetics. Third, we will speculate on the role of possible interactions between exposure to alcohol and genetic vulnerability.

SOCIOCULTURAL FACTORS: SLOVENIA AS A 'BLACK SWAN'

Part of the variation in suicide rates across Europe could be due to different practices in the recording of cause of death. However, most contemporary researchers now agree that these errors are randomised, at least to the extent that allows valid cross-national comparison (Diekstra, 1993). If the variation in European suicide rates reflects genuine differences, we can argue that Slovenia provides in the Popperian sense a 'black swan' that refutes conventional predictions. (Popper argued that the appropriate test of the hypothesis 'all swans are white' was to attempt refutation by finding a black swan.) According to psychosocial predictors, Slovenia should share the same low rate with its Mediterranean neighbours such as Italy. Also, about 70% of its population are Roman Catholic – a religion where suicide is strictly forbidden. However, Slovenia has a high suicide rate of 31 per 100 000 per year. Also, the annual suicide rate in Slovenia has remained remarkably stable (Marušič, 1999), despite recent profound political and social change. According to sociological theories, such changes should have led to yearly variations in the Slovenian suicide rate (Diekstra, 1993). Moreover, high rates of suicide in the native rather than the immigrant population (Marušič, 1999) also contradict the theory that social and ecological risk factors are the major influence on suicide statistics.

POPULATION GENETICS AND SUICIDE RATES

This suggests that factors other than environmental stressors alone may be implicit in determining the high suicide rate in Slovenia and other high-rate countries. Such factors could include genetic predisposition and some shared genetic vulnerability between neighbouring populations, for example between Slovenia and Hungary. An example of shared genetic predisposition can be found in the Hungarians in central Europe and the Finns and Karelians in the north, who belong to the same ethnic group (Finno-Ugrians). Both Hungary and Finland report high suicide rates (Table 1) and other members of this ethnic group elsewhere in Europe also have high suicide rates, for example

https://doi.org/10.1192/bjp.179.3.194 Published online by Cambridge University Press

in Sweden and the Urals. It has been suggested that high suicide rates in Finno-Ugrians (Kondrichin, 1995) could be due to the fixation in the gene pool of certain behavioural traits predisposing to suicide during the early stages of ethnogenesis. It is also noteworthy that both Finns and Hungarians share the same proportion of European (90%) to Uralic (10%) genes (Cavalli-Sforza *et al*, 1994).

More detailed national suicide data now are available following the emergence of the new Republics after the break-up of Yugoslavia and the Soviet Union. It is possible now to link nations with high suicide rates along a J-shaped curve from Finland to Austria, identified in Fig. 1 by shading those European countries with rates above 20 per 100 000 per year. This J-curve pattern also supports the thesis that genetic predisposition could have influenced the suicide rates in these neighbouring countries. In addition, now that new data are available for the Baltic States indicating that these countries also have high suicide rates (Table 1), it is possible that the people in these neighbouring countries may share similar proportions of Uralic genes to those of the Finns and Hungarians.

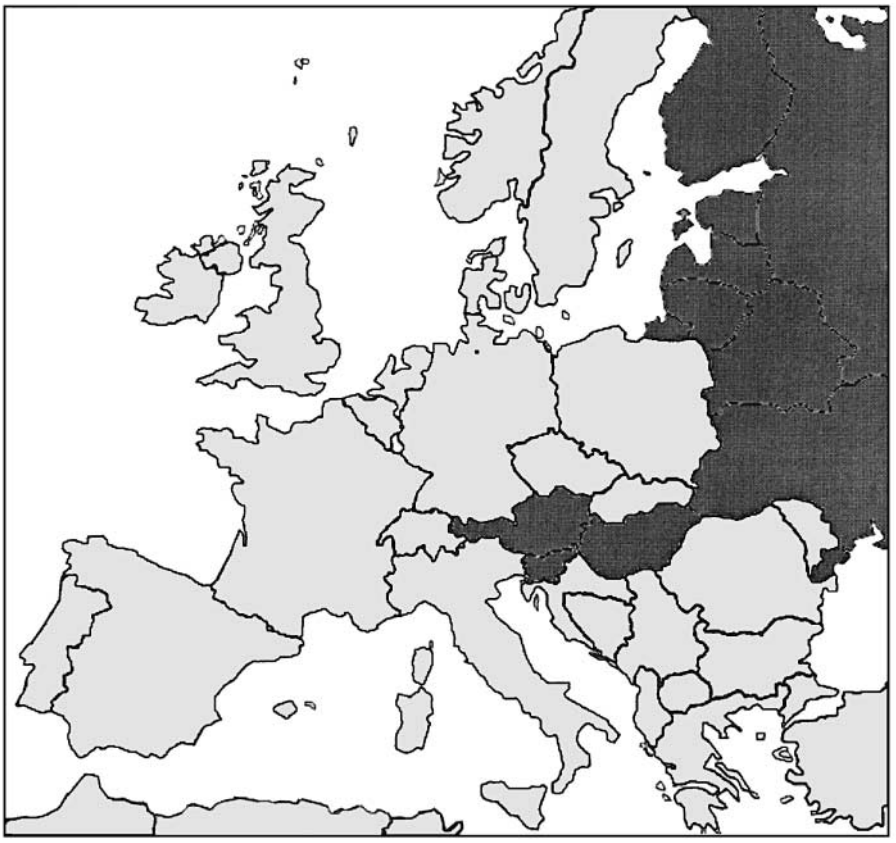

Fig. 1 The J-shaped area of 10 neighbouring countries with the highest suicide rates in Europe: above 20 per 100 000 per year (World Health Organization, 1994).

GENETIC CONSTITUTION AND EXPOSURE TO ALCOHOL: A MALIGNANT INTERACTION

Another aspect of possible genetic risk factors for suicide relates to the association between alcohol consumption and suicide. In countries such as Sweden the suicide rate is more highly correlated with consumption of alcohol than in countries such as France (Norstrom, 1995). Indeed, the relationship between alcohol consumption and the suicide rate is not straightforward. Wine-producing countries with high alcohol consumption tend to have low suicide rates (e.g. Portugal, France and Italy). Slovenia is also a wine-producing country, so why does Slovenia have such high rates of suicide instead of the low rates associated with other Mediterranean countries? A brief examination of the history of vine-growing in Slovenia allows a possible explanation in terms of gene–environment interaction.

Vine-growing in the region, established by the Romans, almost died out during the time that Slavic and Magyar tribes occupied the area, and wine production remained limited until the 12th century. One explanation is that these tribes, whose genetic constitution was not suited to alcohol consumption and whose descendants also have the highest suicide rates in Europe, contributed to the genetic make-up of the local people. Once religious and other environmental factors led to the re-establishment of vine-growing, the region's inhabitants who were genetically unsuited

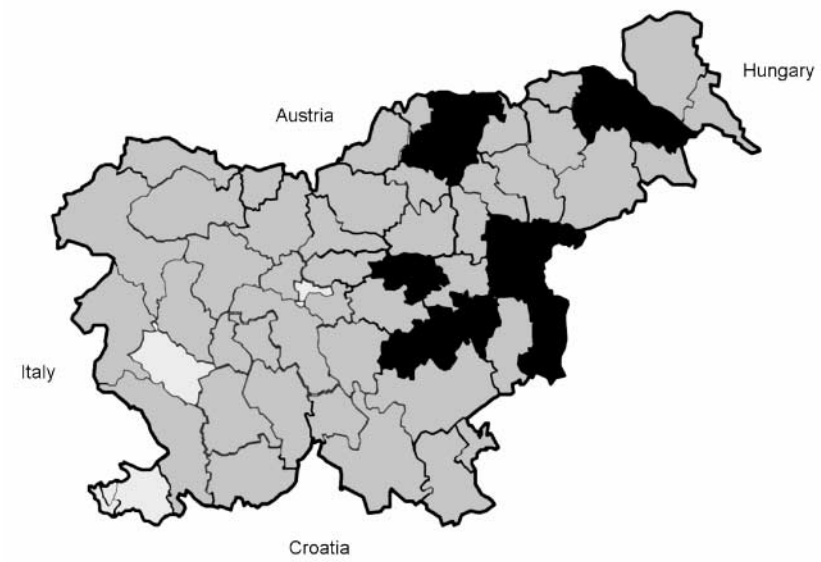

Fig. 2 Regional suicide rate (number per 100 000 per year) distribution in Slovenia, with 18 out of 60 communes outside the range of the mean (1 s.d.) suicide rate in Slovenia (5 below and 13 above) in the decade 1985–1994: □, less than 21.3; ▒, 21.3–41.1; ■, more than 41.1.

https://doi.org/10.1192/bjp.179.3.194 Published online by Cambridge University Press

to alcohol consumption soon developed the highest rates of both consumption- and alcohol-related psychiatric disorders. This adverse combination of genetic propensity and high alcohol consumption led to the high rates of suicide noted in the region today. Indeed, the suicide rates in parts of the north-east of Slovenia bordering on Hungary are the same as in Hungary and about twice the rates in the west of Slovenia (Fig. 2) (Marušič, 1999).

In addition, alcohol consumption and annual death rates from chronic liver disease and cirrhosis in Slovenia are among the highest in Europe, and 28% of completed suicides have a diagnosis of alcohol-related psychiatric problems (Marušič, 1999). Accordingly, the prevalence of alcohol-related psychiatric disorders was the best predictor of the regional variation in Slovenian suicide rates (Marušič, 1999). This supports the theory that there is a malignant interaction between high alcohol consumption in genetically vulnerable individuals, leading to high suicide rates.

CONCLUSIONS

We consider that there is sufficient evidence to support the need for more genetic research into suicide. To date, this has been a relatively under-investigated area of research. The proposal that there is a genetic aetiological component to suicidal behaviour does not mean that psychosocial and other risk factors also are not important. If anything, it would make it even more necessary to control environmental risk factors in populations of high genetic risk. However, we contend that unless both genetic as well as environmental risk factors are taken into account it is unlikely that any suicide reduction intervention will be effective. A radical rethink of research strategies is needed and it is our view that molecular genetic research is an obvious next move, because this may allow targeting of psychosocial or pharmacotherapeutic interventions at persons of high suicide risk.

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(First received 28 July 2000, final revision 14 February 2001, accepted 12 March 2001)

DECLARATION OF INTEREST

None.

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https://doi.org/10.1192/bjp.179.3.194 Published online by Cambridge University Press