GENETIC VULNERABILITY AS A DISTAL RISK FACTOR FOR SUICIDAL BEHAVIOUR: HISTORICAL PERSPECTIVE AND CURRENT KNOWLEDGE

GENETSKA RANLJIVOST KOT ODDALJEN DEJAVNIK TVEGANJA ZA SAMOMORILNO VEDENJE: ZGODOVINSKI VIDIK IN ZNANJE DANES

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Received/Prispelo: Sep 4, 2014
Accepted/Sprejeto: Feb 17, 2015

Review article/Pregledni znanstveni članek

ABSTRACT

Introduction. Suicide is a multidimensional problem. Observations of family history of suicide suggest the existence of a genetic vulnerability to suicidal behaviour.

Aim. Starting with a historical perspective, the article reviews current knowledge of a genetic vulnerability to suicidal behaviour, distinct from the genetic vulnerability to psychiatric disorders, focused on clinical and population-based studies, and findings from recent molecular genetics association studies.

Method. The review includes peer-reviewed research articles and review papers from the professional literature in English language, retrieved from PubMed/Medline and PsycINFO.

Results. The research literature confirms a existence of a genetic vulnerability to suicidal behaviour. Even though the results of individual studies are difficult to compare, genetic influences could explain up to half of the variance of the occurrence of suicide.

Conclusion. Genetic vulnerability could be a distal risk factor for suicide, which helps us to understand the occurrence of suicide among vulnerable people. Ethical implications of such vulnerability are highlighted.

Keywords:
suicide, suicidal behaviour, genetics, vulnerability, families, probands, offsprings, review, ethical considerations

IZVLEČEK

***Uvod**. Samomor je večrazsežnostni problem. S študijami družinskih anamnez samomorilnega vedenja je bilo ugotovljeno, da bi genetska komponenta lahko vplivala na občutljivost za samomorilno vedenje.*

***Namen**. Članek skozi zgodovinski vidik proučuje današnje poznavanje genetske ranljivosti za samomorilno vedenje, ki se razlikuje od genetske ranljivosti za psihiatrične motnje v kliničnih in populacijskih študijah ter prikazuje ugotovitve zadnjih študij molekularno genetskih raziskav.*

***Metoda**. Strokovni pregled vključuje raziskovalne članke in poročila iz strokovne literature v angleškem jeziku, pridobljene iz PubMed/Medine in PsycINFO.*

***Rezultati**. Pregled obstoječe strokovne literature kaže na prisotnost genetske komponente kot dejavnika tveganja za samomorilno vedenje. Čeprav je rezultate posameznih študij težko primerjati, pa lahko genetski vplivi pojasnijo tudi do polovico različnih pojavov samomorilnega vedenja.*

***Zaključek**. Genetska ranljivost bi lahko bila distalni dejavnik tveganja za samomor, kar nam pomaga razumeti pojav samomora med osebami s tveganjem za samomorilno vedenje. S tega pogleda so zajeta tudi etična vprašanja.*

Ključne besede:
samomor, samomorilno vedenje, genetika, ranljivost, družine, preiskovanci, potomci, pregledni članki, etična vprašanja

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1 INTRODUCTION

Suicide is a multidimensional event. It is the result of a process with risk and protective factors in the cultural, social, psychological, psychiatric and biological fields. A risk factor is represented by a measurable characteristic that precedes an outcome in time, and it increases the probability of the outcome. Moscicki suggested distinguishing between proximal and distal risk factors. Distal risk factors represent a 'foundation,' they are 'necessary but not sufficient' for suicide, while proximal risk factors (precipitating events) are neither necessary nor sufficient (1). Suicide is not a result of the effect of one single risk factor, but rather of an interaction of factors that lead to the necessary and sufficient conditions for suicide (1). Genetic vulnerability for suicidal behaviour could be considered as a distal risk factor.

1.1 A Historical Perspective

Motto argued that 'history can provide a valuable perspective on contemporary questions' (2). 'The prevalent attitude of a society to suicide is shaped and fashioned from time to time by the beliefs of its people in the different periods of its history' (3). As such, nowadays experts are the heirs of the 19th century psychosocial tradition (4). In addition to centuries of philosophical and moral writings, Fedden noticed new perspectives emerging in the 19th century (5).

Indeed, observations suggested that there could be a genetic heredity of suicide (6- 8). Falret, a student of Pinel and Esquirol, who became the head of the clinic 'la Salpêtrière' in Paris, was amongst the first to apply statistical data. In his book 'De l'hypochondrie et du suicide,' he pointed at the interaction of causal risk factors, which he grouped into four categories, namely: predisposing factors including heredity; accidental direct factors, such as passions; accidental indirect factors, such as pain or illness; and civilization including religious fanaticism (9-10). Winslow stressed the impact of heredity further on: 'It is not necessary that the disposition to suicide should manifest itself in every generation; it often passes over one, and appears in the next, like insanity unattended with this propensity.' And: 'the suicidal tendency descending from one generation to another […] has been observed much more among insane persons, who have committed self-destruction, than among the sane' (11), thus Bucknill & Tuke who also discussed the heredity of mental illnesses (12). Masaryk completed a sociological monograph on suicide.[1] Taking into consideration social factors and mental illnesses regarding suicidal heredity, he concluded: 'Obviously, psychical inheritance occurs indirectly in a physiological, morphological and pathological way, but how we are to conceive of this no one yet perceives' (13). Almost simultaneously, Morselli reflected further on the complex and interacting causality of suicide, incorporating both environmental and heritable aspects: '[I]f it were possible to know exactly the physiological temperament of all self-destroyers, and, above all, the hereditary transmission, direct or indirect, of the morbid germs, we should be able to trace back the fatal determination of their last act to its true and efficient cause' (14).

The historical perspective of the question of heredity of suicidal behaviour could be expanded by many more, such as Moore, Burrows, Westcott, Tuke and Savage, Durkheim, as presented by Goldney and Schioldann (8). In addition, Motto's review of the 19th century editions of the American Journal of Insanity (later renamed as the American Journal of Psychiatry) (2) and the presentations by Berrios and Mohanna (15) and Berrios are interesting windows to that period (16).

However, early contemporary research, such as the observation of Ringel, saw that suicidal behaviour was transmitted at least partly independent from psychiatric disorders (17). The psychological autopsy study by Farberow and Simon conducted on two samples of fifty suicides in two cities, found three parental suicides in each group – a rate 88 times higher than the expected rate (18). More sceptical regarding a genetic influence was Baechler: 'It is clear that one does not inherit a solution [suicide] but at most a disposition to consider a solution of this nature' (19). Exploring causal pathways to suicide, Maris compared a sample of 266 suicides with suicide attempts and natural deaths by means of psychological autopsies. He found that suicides were distinguished from natural deaths by increased levels of a wish to die, seeing death as an escape from pain, not wanting to change things regarding the past life, hopelessness, no social participation, dissatisfaction with life, and suicide in the history of first-degree relatives (0% for the natural deaths vs. 11% for the suicides) (20). Murphy and Wetzel interviewed 127 patients who were hospitalised after a suicide attempt. A family history of suicide, attempted suicide, and suicide threats was found in 14%, 24% and 6% of the patients, respectively. Suicidal behaviour was found in 36% of the study group, with the highest rates in the subgroups with personality disorders (including addictions) and primary affective disorders. As an explanation, the authors stated that they were 'not bound to a genetic, or even to a familial, hypothesis.' They rather adhered to the hypothesis of 'assortative association' and 'shared deviance' (21). Mitterauer presented results from five studies (two population and three clinical studies) focusing on suicide of one specific

[1] But with due impediments, he was appointed as a lecturer at the Viennese Faculty of Philosophy (Austria), since sociology was not yet recognised as a scientific discipline. Masaryk would became the founder, and from 1918, the first president of Czechoslovakia.

area, Salzburg in Austria. At the population level, 49.6% of the suicides had a family history of suicide, compared with as much as 69.7% of the suicidal mental health patients. These high figures resulted from gathering the information from general practitioners, elders, clergy, etc. Indeed, only 39% of the suicide positive families had been reported by the relatives. Findings from the two studies, on bipolar mood disorder and suicide, and on psychosis and suicide, indicated the existence of an independent vulnerability to suicide. However, he was cautious, contending that 'not every case of suicide must have a genetic disposition.' Rather, it is 'a matter of finding the appropriate role that each of the three factors - the genetic disposition, the life history and the socio-cultural situation – plays in suicide' (22), a statement that could be equal to the current 'interplay between genes and environment' (23-24).

1.2 The Clinical Perspective versus the Population Perspective

Suicide prevention strategies can be developed from the health-care / clinical perspective focused on high risk groups, and the public health perspective focused on the general population (25). The same distinction can be made regarding the research on genetic vulnerability.

The reviews of Bondy et al. (26), Brent and Mann (27), Pedersen and Fiske (28), Roy (29), Roy et al. (30) and Rujescu et al. (31) looked at clinical, twin, adoption and genetic studies, and concluded that there is a genetic aspect that manifests itself when a person experiences major stress or a psychiatric disorder. In the same line, the reviews of Träskman-Bendz and Mann (32), Mann et al. (33) and Van Heeringen (34) on the biological processes in suicidal behaviour concluded that there probably exists a genetic influence on suicide risk independent of the genetic risk of psychiatric disorders. Wasserman stated that genetic inheritance does not equal 'predestination.' The biological vulnerability will be activated through life conditions and experiences, which may lead to stress, hopelessness and psychiatric conditions (25).

When investigating genetic contributions to suicidal behavior, one should not overlook family studies. In these, the risk for suicidal behaviour among family members of those who have already expressed suicidal behaviour is compared with the same risks among relatives of those who have not expressed suicidal behaviour. Many studies have been reported in reviews so far, but Baldessarini and Hennen aggregated the risk estimates from almost all these family-study reports, and reported the overall risk ratio of almost 3 (35). So-called natural experiments of natural clones (monozygotic twins who share 100% of their genes) and adoption studies have the potential to disentangle genetic familial contribution from environmental familial contributions (e.g., raising children, role models, etc.). These have already been extensively and profoundly reviewed by the above mentioned authors, as well as in a recent systematic review (36) and a meta-analysis (37).

2 AIM

Starting with a historical perspective, this paper reviews current knowledge of a genetic vulnerability to suicidal behaviour, distinct from the genetic vulnerability to psychiatric disorders, with the focus on clinical and population-based studies, and recent findings from molecular genetics association studies.

3 METHOD

Databases PubMed/Medline and PsycINFO were searched with the following search words: gene, meta-analysis, offspring, proband, suicide, and suicidal behavi*, to retrieve peer-reviewed research articles and review papers from the professional literature in English language. With no restriction for publication dates, the search identified 208 papers. Studies not related to genetic aspects of suicide were excluded. The references of relevant papers were checked.

4 RESULTS

4.1 Genetic Studies Based on Clinical Samples

Looking for biological markers of depression, Åsberg and colleagues focused on the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in cerebrospinal fluid (CSF). Almost by coincidence, they found that forty percent of the subgroup with low 5-HIAA had attempted suicide compared to fifteen percent in the subgroup without suicide attempt. Since their first publication in 1976, the serotonergic system has been studied extensively across psychiatric disorders both with living subjects and post mortem (32-34, 42-43).

The research that led to the formulation of the stress-diathesis model confirmed the genetic transmission of aggression. According to this model, certain people are more vulnerable to suicidal behaviour due to a predisposition for strong feelings and cognitions of hopelessness and suicidal ideation on the one hand (state), and aggression and impulsivity on the other hand (trait), when they suffer from stress and adverse life conditions (38).

The cognitive and behavioural components of the diathesis are related with neurochemistry, more specifically with the serotonergic and noradrenergic neurotransmitter systems (34, 38- 42, 44-45). The potential role of the dopaminergic system is not clear, since this has received only little research attention (25, 41). The neurobiology

is mostly genetically determined, but early childhood experiences and head injuries may alter this (25, 33, 40-41).

It was proposed that impulsivity and aggression correlate with a dysfunction of the serotonergic system, and that hopelessness correlates with a dysfunction of the noradrenergic system (40, 41). Further, it was found that the biological correlates of suicidal behaviour differ from the biological correlates of major psychiatric disorders (24, 32-33, 39, 41, 43, 45-47).

Clinical studies are summarized in Table 1.

Table 1. Clinical studies of suicidal probands: the risk of offspring suicidal behaviour.

Author	Year	Proband	Risk	Co-transmission
Brent et al. (48)	2002	Mood-disordered suicide attempters (n=81) vs. mood disordered non-attempters (n=55).	Offspring of attempters had a 6-fold increased risk for suicide attempt vs. offspring of non-attempters: 12% vs. 2% (p = 0.008).	Mood disorders; Sexual abuse and impulsive aggression.
Brent et al. (49)	2003	Mood-disordered suicide attempters: - group 1 - with siblings who attempted suicide (n=19), - group 2 - with non-attempted suicide siblings (n=73). Non-suicide attempters with non-suicide attempting siblings (group 3, n=73).	Attempted suicide risk: - in group 1: 18.8%, - in group 2: 8.5%, - in group 3: 4.2%. (p = 0.0005)	Impulsive aggression (and not mood disorder) predicted an earlier age of the onset of suicidal behaviour in the offspring of group 1, compared with the offspring of groups 2 and 3.
Burke et al. (50)	2010	Parents (n=255) with lifetime history of mood disorder (major depression, depression not otherwise specified, dysthymic disorder, or bipolar disorder) vs. offspring (n=449) over the age of 10.	Offspring (n=212) exposed to suicide attempt were 4 times more likely to report a lifetime suicide attempt compared with unexposed offspring (n=237).	Increased odds of suicide attempt.
Cheng et al. (51)	2000	Suicides (n=113) vs. living community controls (n=226).	Independent risk factors: - major depressive episode (p < 0.001), - substance use disorder (p = 0.05), - emotionally unstable disorder (p = 0.034), - loss events (p = 0.001), - suicidal behaviour in first-degree relatives (p = 0.022)	Depressive disorders.
Farmer et al. (52)	2001	Depressed subjects (n=108) with suicidal ideation (without attempts) and nearest age siblings, and healthy controls (n=105) and nearest-age siblings.	The study did not find a family risk for suicidal ideation.	Suicidal ideation was associated with life events, and with levels of neuroticism and psychoticism.
Klimes-Dougan et al. (53)	2008	Probands with mood disorders aged 17 years and older (n=457). 51.9% of probands had attempted suicide.	Significant predictors of suicide attempt in first-degree relatives of mood disordered probands: - mood disorder in first-degree relative ($p < 0.0001$); - proband history of abuse ($p < 0.02$).	Early onset of depression. Aggressive/impulsive traits may be related to childhood abuse.
Roy (55)	2000	Alcohol-dependent subjects (n=333) with and without suicide attempts.	Family loading of suicidal behaviour among suicide attempters vs. non-suicide attempters: 15.3% vs. 4.3% ($p < 0.001$).	Not reported.

Author	Year	Proband	Risk	Co-transmission
Stenager & Qin (56)	2008	Suicide victims under 35 years of age (n=4,142) vs. matched living controls (n=82,840)	Personal history of psychiatric hospitalization (OR (males) = 13.5, OR (females) = 38.9); risk for suicide with peak immediately after admission or discharge. Parental history of admission to a psychiatric hospital. Risk increased progressively with numbers of psychiatric admission. The highest risk for schizophrenia spectrum disorders, affective disorders or substance abuse.	Parental psychiatric history.
Trémeau et al. (57)	2005	Three psychiatric populations with: unipolar depression (n=160), schizophrenia (n=160), and opioid- dependence (n=160).	Family history of suicide increased the risk of attempted suicide: OR= 2.4 (p = 0.001), with no significant differences between the three groups.	Early onset: 60% of the suicide attempts occurred before the age of 25.

Brent and co-workers studied mood disordered suicide attempters in two relatively small samples (48-49). The first study found a statistically significant elevated risk for attempted suicide in the offspring of people with a mood disorder who had attempted suicide, when compared with offspring of people with mood disorders who had not attempted suicide. The majority of the attempts occurred in the context of a mood disorder; and the transmission of suicidal behaviour was related to the trans-generational transmission of sexual abuse (an original finding), and to increased aggression. On the other hand, there was no evidence of time clustering between parent and child suicide attempts, counter speaking the hypothesis of transmission through the role models in the family (48). The second study (49) compared the offspring of three groups of adults with mood disorders: 1) suicide attempters with siblings concordant for suicidal behaviour, 2) suicide attempters with siblings discordant for suicidal behaviour and 3) suicide attempters with siblings concordant for no suicidal behaviour. The study found that suicide attempts in the parents not only increased the risk of suicide attempts and impulsive aggression in the offspring, but also lowered the age of the first suicidal behaviour (49). The strongest predictor of attempted suicide in parents and offspring, and early first attempt in offspring, was impulsive aggression, thus confirming other studies that had identified this trait as being part of a diathesis for suicidal behaviour. Family loading of mood disorders was not related with early first attempt, contrary to the history of physical and sexual abuse of offspring.

The third study of the same researchers (54) looked at a large sample of mood-disordered probands, and focussed on suicidal behaviour and mood disorders among their first-degree relatives. They found that 23.2% of the attempted suicide probands had a first-degree relative who had attempted suicide, compared with 13.2% of the probands without an attempt. 30.8% of the relatives with mood disorders had developed suicidal behaviour, compared with 6.6% of the relatives without mood disorders. But the incidence of mood disorders in first-degree relatives was similar in probands with and without the history of suicide attempt, 50.6% vs. 48.1%, respectively. Childhood abuse and aggression (26.1% vs. 14.1%) were higher in probands with suicide attempts and with family loading of suicidal behaviour. And early age of onset of proband mood disorders was associated with aggression, childhood abuse, mood disorders and suicidal behaviour in relatives. The authors concluded that mood disorders only do not explain the occurrence of suicidal behaviour, and that genetic vulnerability as described in the stress-diathesis model should be considered. In addition, as in the previous studies (48-49), childhood abuse and sexual abuse seem to be independent risk factors for suicidal behaviour. The interaction between abuse, aggression (as a cause and as a result of abuse), mood disorders and suicidal behaviour needs to be studied. The prevention of abuse and treatment of victims had the potential to prevent suicidal behaviour. Common limitations for all three studies were that they involved an inpatient population, mostly females with mood disorders, and studies focused on attempted suicide, not on suicide.

Farmer et al. (52), Burke et al. (50), and Klimes-Dougan et al. (53) specifically studied depressed probands. Farmer et al. found that 66% of the depressed probands reported to have experienced suicidal ideation in the previous week, while the control probands and their siblings reported 5% and 7%, respectively. The occurrence of suicidal ideation was related to personality measures of neuroticism and psychoticism, and to having experienced severe threatening life events (the article did not specify what events were involved). The authors concluded that ideation probably is a state, rather than a partly genetic determined trait related to suicide (52). However, the study did not include the link between ideation and, for instance, impulsivity and aggression. In the study of Burke et al., almost half (47%) of the offspring were exposed to suicidal behaviour, and the proband diagnosis was not related to offspring exposure or suicidal attempt. The exposed offspring were more likely to report lifetime suicide attempt than the unexposed offspring, and neither timing, degree nor the number of exposures were associated with the risk for suicide attempt. The results of their study therefore do not support the causal pathway of imitation or modelling explanation (exposure prior to suicide attempt), but they suggest that individuals with a higher risk of suicidal behaviour may show a tendency for aggregation (51).

Klimes-Dougan et al. in a longitudinal study, from childhood through adolescence, followed depressed mothers, and compared their offspring to the offspring of mothers without psychiatric diagnosis. The study demonstrated that the offspring of mothers with a major depressive disorder had an earlier onset and a more persistent suicidality than the offspring of mothers with bipolar disorder and mothers without psychiatric diagnosis (53). Therefore, this offspring represents an important vulnerable group for preventive interventions.

Trémeau et al. studied the family history (up to third-degree relatives) of suicide and attempted suicide in three different groups of psychiatric disorders, namely: inpatients with depression, schizophrenia, and opioid dependent patients. Family history of suicidal behaviour significantly increased the risk of suicide attempt. Family history was also a risk factor for multiple suicide attempts and for the use of highly lethal methods (1 in 4 of the depressed group, and in more than half of the two other groups). Almost 60% of the suicide attempts in this population occurred before the age of 25. On the other hand, there were no relations with the age of the first attempt, with receiving mental health care in the period before the first attempt, or with the diagnostic group (57). However, the findings point to a need to better detect, treat, and assess suicide risk at an early age.

Studying family history of suicidal behaviour and alcohol dependence, Roy determined that both, suicide and suicide attempt in the family history, were significantly more often present in subjects who attempted suicide than among those who did not attempt suicide (29.8% and 11.5%, respectively) (55).

By means of psychological autopsies, Cheng et al. examined psychosocial and psychiatric risk factors in suicides and community controls in Taiwan. The suicides had higher rates of previous suicide attempts, more early parental deprivation, and more first-degree relatives with suicide, attempted suicide, depression, and emotionally unstable personality disorder, but not more substance abuse. The latter could be explained by high alcohol consumption in general in Taiwan. The effect of family history of suicidal behaviour was independent of demographic, psychosocial and psychiatric factors, and of environmental factors, such as parental deprivation or family history of psychopathology. Other independent factors were depression, substance abuse, unstable personality disorder, and loss events. The authors concluded that the independent factors influence or cause psychosocial factors, and that genetic vulnerability could increase due to these factors. Effective intervention should focus on loss events and major depression among emotionally unstable people with a family history of suicidal behaviour and substance abuse (51).

A nested-case control study on suicide victims and their psychiatric history was performed by Stenager and Qin. They investigated psychiatric hospitalisation as a risk factor for completed suicide in adolescents and young adults under 35 years of age in Denmark between 1981 and 1997. They demonstrated that a diagnosis of schizophrenia was a strong risk factor for completed suicide, which peaked immediately after admission to, or discharge from, psychiatric hospital. In addition, paternal history of admission to a psychiatric hospital represented a strong predictor for suicide, being more pronounced for mothers than fathers and female than male group of suicide victims (56).

4.2 Population-Based Studies

Table 2. Population-based studies of suicidal probands: the risk of offspring suicidal behaviour.

Author	Year	Proband	Risk	Co-transmission
Agerbo et al. (58)	2002	Young people (<21 years old) suicides (n=496) vs. community controls (n=24,800).	Percentage-attributable risk (PAR) of father suicide (1.1) and admission for mental disorders (3.9). PAR of mother suicide (1.4) and mental hospital admission (6.4). PAR subject individual admission: 15.0.	Psychiatric disorders
Brent et al. (59)	1998	Adolescent suicides (n=58) vs. community controls (n=55)	Increased rates of suicide attempts and completions (and not of suicidal ideation) in first-degree relatives of suicide probands vs. controls after controlling for psychiatric disorders (OR = 4.3).	Aggression
Goodwin et al. (60)	2004	National US representative sample (n=8,098), aged 15-54 years.	After controlling for psychiatric disorders, parental suicidal ideation was related with offspring ideation (OR = 1.7), and parental suicide attempt was associated with offspring ideation (OR = 2.0) and offspring attempt (OR = 2.2.). All: $p < 0.05$.	Not reported
Kim et al. (61)	2005	Male suicides (n=25) and their relatives (n=247) vs. community controls (n=25) and their relatives (n=171).	After controlling for psychopathology, relatives of male suicides were more likely to complete or attempt suicide: OR = 10.62 ($p < 0.05$). Past or present suicide ideation did not differ in the two groups of relatives, but the level of suicidal ideation was higher among the relatives who committed suicide ($p = 0.008$).	Not reported
Lieb et al. (62)	2005	933 adolescents whose biological mothers had participated in the parent survey.	Increased suicidal ideation in the offspring of mothers with suicide attempts vs. mothers without suicidality: OR = 5.1. Increased suicide attempts in this offspring: OR = 9.0 ($p > 0.05$). Differences remained significant after controlling for socio-demographic factors, and psychopathology.	Earlier onset of suicidal behaviour. Impulsivity and aggression. Irritabilities in families directed inward or outward, stable over time and generations.
Mittendorfer-Rutz et al. (63)	2008	Hospitalised suicide attempters (n=14,440) vs. community controls (n=144,400).	The strongest independent familial risk factor for youth suicide attempt were siblings' (OR = 3.4), maternal (OR = 2.7) and paternal (OR = 1.9) suicide attempts, and paternal (OR = 1.9) and maternal (OR = 1.8) suicide completion.	Familial personality and substance abuse disorders.
Qin et al. (64)	2002	Suicides between the ages of 9 and 45 (n=4,262) vs. community controls (n=80,238).	Family history of suicide (OR = 2.58) and family history of psychiatric disorder (OR = 1.31) independently increased suicide risk in relatives ($p < 0.01$). A suicide risk was increased after a suicide death of a mother, father and sibling, but not after non-suicide deaths.	Not reported.

Author	Year	Proband	Risk	Co-transmission
Qin et al. (65)	2003	Suicides between the ages of 9 and 103 (n=21,169) vs. population controls (n=423,128).	Psychiatric admission increased the suicide risk in males: OR = 28.23, and in females: OR = 77.77 ($p < 0.01$). A suicide risk was highest soon after discharge (<8 days) in males: OR=137.48, and in females: OR = 493.45 ($p < 0.01$). The history of first-degree relative suicide in male subjects: OR = 1.90, and in female subjects: OR = 2.95 ($p < 0.01$).	Protective effect of parenthood for fathers with a child < 2 years old, and for mothers with a child up to 6 years old.
Runeson (66)	1998	58 consecutive suicides, between the ages of 15 and 29.	An early onset (< 20 years old) for males in families with a history of mental disorders vs. families without such a history (p = 0.03). Longer duration of the suicidal process (> 2 years), and several suicide attempts.	Possibly: - mental disorders, - substance abuse, - personality traits.
Runeson & Åsberg (67)	2003	First-degree relatives (n=33,173) of suicide victims (n=8,396) vs. controls who died from other causes (n=7,568) and their first-degree relatives (n=28,945).	The history of psychiatric care and of suicide was higher among the relatives sof suicide victims vs. relatives of controls ($p < 0.001$).	Possibly: - aggressive/impulsive behaviour, - social learning.
Tidemalm et al. (68)	2011	Suicide among family members of suicides (n=83,951) vs. suicides among relatives in population controls	Patterns of familial aggregation of suicide among relatives to suicide decedents suggested genetic influences on suicide risk; the risk among full siblings (OR = 3.1, 95% CI 2.8-3.5,), maternal half-siblings (OR = 1.7, 95% CI 1.1-2.7), despite similar environmental exposure. Shared (familial) environmental influences were also indicated; siblings to suicide decedents had a higher risk than offspring (OR = 3.1, 95% CI 2.8-3.5 vs. OR = 2.0, 95% CI 1.9-2.2.	Not reported
Waern (69)	2005	Elderly suicide victims (> 65 years old) with (n=13) and without (n=72) family member suicide.	Elderly with family member suicide had more previous suicidal behaviour: 100% vs. 65% ($p < 0.01$).	All elderly suicides with offspring suicide had a substance use disorder (correlation).

Goodwin et al. studied associations between parental and offspring suicidal ideation and suicide attempts among adult offspring in community samples. All participants were examined for psychiatric disorders, suicidal ideation and suicide attempt, as well as for family history of suicidal ideation and suicide behaviour. The lifetime prevalence of suicidal ideation in the cohort was 13.5% and the history of suicide attempt was 4.6%. The results showed that parental suicidal ideation and attempt was associated with a significantly increased likelihood of suicidal ideation and suicide attempt among offspring. Co-morbid mental disorders contributed to the strength of associations, but the significance remained after adjustment. In this study, suicidal ideation and behaviour were assessed each with only one question. As such, as authors proposed, a more extensive evaluation of suicide ideation and suicidal behaviour would be needed (60).

Mittendorfer-Rutz et al. focussed on suicide attempts. They analysed a large record-linkage database with the data from hospitalized youth suicide attempters, and matched community controls for gender, month of birth and county. Among the cases, 12% had a history of suicide attempt in the family and 2% of suicide in the family. The strongest independent familial risk factors for youth suicide attempt were siblings', maternal and paternal suicide attempt, and paternal and maternal suicide completion. The boys were more prone to attempting suicide when having a family member who died by suicide than girls. Although the study avoided common research limitations, like recall and selection bias, the study was not able to include suicide attempts when individuals were not hospitalised (63).

Runeson and Åsberg compared suicide rates of people bereaved by suicide with those bereaved after other

causes of death. The data was collected from the Swedish death register. The authors found 9.4% and 4.6% suicides in both groups of relatives, respectively. Previous psychiatric treatment and family history of suicide had the strongest predictive value for suicide, with the latter as an independent factor. No gender difference was found. The study showed that the bereaved by suicide are a risk group for suicide (67). The finding was extended by results of the first total population study that provided estimates for familial suicide risk in relatives with varying genetic and environmental backgrounds (68). Tidemalm et al. compared relatives of suicides (from 1952 to 2003) with relatives of community controls. They revealed patterns of familial aggregation of suicide: the risk for suicide was higher in the population of first-degree relatives of suicide probands, which was also higher in the group of maternal siblings. Furthermore, they determined that siblings and offspring of suicide victims had a high risk for suicide, but it was more pronounced in the first group (68).

Qin et al. studied suicides between 1981 and 1997, and matched living controls, regarding family history of suicide and psychiatric illness, and socioeconomic, demographic, and psychiatric data (64, 65). Major findings were that both, family history of suicide and psychiatric disorder, significantly and independently increased the suicide risk (64, 65). Furthermore, a history of psychiatric hospitalisation was the strongest risk factor for suicide, and more in females than in males. Suicide risk was highest shortly after discharging from hospital. Single marital status and being an age pensioner were the two next important factors. Economic stressors, such as unemployment and low income, increased suicide risk in males more than in females. Being a parent of a young child was a protective factor. The authors reported the finding of family clustering of suicidal behaviour which would not be explained by familial loading of mental disorders. Lastly, living in urban areas decreased the suicide risk for males, but increased the risk for females (65). This finding was replicated in the study on suicide risk in relation to the level of urbanicity by Qin (70).

Agerbo et al. retrieved data from several population and hospital registers of young people who had died by suicide between 1981 and 1997. They found that mental disorders of a young person (measured by psychiatric admission, 15% of suicide cases), and suicide or mental disorder of a parent were the most important risk factor for youth suicide. After controlling for these factors, the importance of socioeconomic factors, such as unemployment, low income, poor schooling, etc., decreased. As such, the authors recommended early recognition and treatment of mental disorders in young people as an important prevention strategy. The study confirmed clinical findings of the importance of mental disorders and suicidal behaviour in first degree relatives as risk factors (58).

Strengths of these studies (58, 64, 65) were a case-control study design based on a huge database, and focused on suicide as the outcome. Important findings were the gender differences regarding risk and protective factors. A shortcoming was that the data on previous suicide attempts as a major risk factor for suicide was not available in the databases. However, as mentioned by Goldney, the population attributable risk (PAR) assessment allows us to weight different risk factors, and may thus help us to target prevention efforts (71).

Lieb and co-workers performed a four-year follow-up study on maternal transmission of suicidality on the adolescents and young adults born from 1970 to 1981 (62). About one-third of the mothers reported lifetime suicidal ideation and 2.3% reported suicide attempts. In comparison, about one-third of the study subjects reported suicidal ideation in their lifetimes and 5% reported suicide attempts. Suicidal ideation and suicide attempts were more common in female offspring than in male (OR = 1.7 and OR = 2.5, respectively). The odds for suicidal ideation and the odds for suicide attempts were higher in the offspring of the mothers who had ever attempted suicide compared to the offspring of the mothers without any suicidality. The results remained after control for psychopathology of the mothers. The authors concluded that familial risk acts similarly in females and males, but that an earlier onset of the first suicide attempt in the offspring tends to be predicted by maternal history of suicide attempts. However, the manifestation of suicidality has to be understood as a complex interplay of multiple factors, with maternal suicidality being just one of the risk factors (62).

In the family study by Kim et al., the majority (80%) of the suicide completers was diagnosed with a major axis I disorder (alcohol or drug abuse or dependence, depressive disorder) and 56% was diagnosed with an axis II personality disorder, while 4% of the control subjects was diagnosed with the latter. The study found a significant difference in the presence of aggressive behaviour in first-degree relatives of suicide completers (OR = 3.97). Moreover, the relatives of suicide victims were more likely to attempt or complete suicide than the relatives of comparison subjects after controlling for psychopathology. The study findings confirmed the existence of a strong familial component of suicidal behaviour, and that aggressive behaviour with severe suicidal ideation might be implicated in familial transmission of suicidal behaviour (61).

Waern conducted a pioneer study regarding the family history of suicide among elderly suicides, by means of psychological autopsies and data from health care facilities. The subgroup of elderly suicides with offspring suicide had more substance abuse, and contrary to sibling/parent suicide, offspring suicide could have played a role in the elderly suicide (69). This study highlighted

a few interesting questions, such as the specificity of offspring suicide, the role of bereavement, and the role of substance abuse in a diathesis for suicidal behaviour. Limitations of the study were the use of a small sample size and non-consideration of attempted suicide in the family history.

A quite different approach to the study on population level was provided by Marušič and Farmer (72) and Marušič (73). They observed a geographical area in a 'J-shaped curve' from Finland in the north of Europe, to Austria and Slovenia in the south. These were the European countries with suicide rates above 20/100,000. A shared genetic background/history would at least partly account for the shared high suicide rates, in interaction with environmental aspects. The authors concluded that prevention in vulnerable populations would require a combination of medical, psychosocial and environmental strategies.

4.3 Molecular Genetic Association Studies

More straightforward information on the role of a genetic background of suicidal behaviour could be found in studies of different candidate genes that were proposed to be involved in various behavioural disorders.

So far, the most comprehensive study has been performed by Schild et al., who analysed all meta-analyses in the field of single nucleotide polymorphisms (SNPs) and suicidal behaviour published by May 2012 (74). Based on their results and on even more recently published meta-analyses the study findings point at several genes that show association with suicidal behaviour and are involved in the serotonergic neurotransmission. Also other genes, whose protein products, like the brain-derived neurothropic factor (BDNF), are closely linked to the serotonergic function. The first and probably the most extensively studied gene in the field of psychiatric genetics is the serotonin transporter gene (*SLC6A4*). Clayden et al. (75) conducted the largest meta-analysis of 44-base pairs long insertion (L) or deletion (S) polymorphism in the promoter region of *SCL6A4* (5-HTTLPR), and found an association with attempted suicide (OR = 1.13, 95% CI 1.05-1.21). When studies on completed suicide were analysed, there was no statistically significant association. Another gene, also often studied, is the gene coding for tryptophan hydroxylase 1 (*TPH1*). The protein, TPH1, namely, plays a very important role in the serotonin synthesis, since it catalyses the first and the rate-limiting step. Positive association was, again, determined by Clayden et al. (75) for the polymorphism A218C and attempted suicide, but not for completed suicide. In an even more recent study of González-Castro et al. (76), the locus A218C/A779C has been associated with suicidal behaviour at a clinical level. The association was confirmed based on fixed effects model, and also separately on Asian and Caucasian populations (76). For the neuronal isoform of TPH, designated as TPH2, there are fewer studies interrogating its polymorphisms in association with suicidal behaviour, and only two meta-analyses conducted by González-Castro et al. (76) and Choong et al. (77). The association of two polymorphisms, rs7305115 and 1386486, with suicidal behaviour has been determined by the latter; however, there was a high heterogeneity among the included studies (77). The genetic polymorphisms of the gene of one of the key enzymes for degradation of catecholamines, catechol-o-methyl transferase (COMT), were investigated in few meta-analyses. First results indicated an association of the substitution of amino acid valine to methionine on the position 158 (78). However, the latest and even more comprehensive meta-analysis of this polymorphism, and also other polymorphisms, by Clayden et al. (75) and Calati et al. (79), failed to confirm the association. Nevertheless, they found an association with particular personality traits, like angry reaction and irritability (79), which are also important when considering suicidal behaviour. So far, there is only one meta-analysis on the polymorphisms of the monoamine oxidase A gene (*MAOA*), whose protein product deaminates neurotransmitters noradrenaline, adrenaline, dopamine and serotonin. It has been previously associated with the pathogenesis of suicidal behaviour, but the results of the meta-analysis on the most extensively studied polymorphism in the promoter region, uVNTR, could not confirm its implication in suicide attempt, either among psychiatric patients or when stratified for psychiatric diagnosis (80).

Beside the relatively large number of studies on genes of serotonergic system, other genes are not as extensively investigated. Currently, only studies of an important protein that regulates neuronal growth, plasticity, and also effects mood, cognition, behaviour, and stress response, the neurotrophin BDNF, seem to offer promising results. For the *BDNF* gene, Zai et al. (81) in their meta-analysis, reported association of methionine allele on position 66 with suicide (OR = 1.16, 95% CI 1.01-1.32), and also with the history of suicide attempt.

The accumulating results of case-control studies of serotonergic as well as of other genes are quite inconclusive, and there are only a few more polymorphisms that were included in meta-analyses. In general, the differences between study designs, particularly in the sample characteristics, contribute substantially to the heterogeneity. It has been determined that suicide attempts and completions should be considered separately, as two phenotypes, and that adjustment for psychiatric comorbidities is necessary (75).

Beside the hypothesis-driven approach of case-control studies of existing candidate genes, the development of technology now offers the possibility of genome screening.

The microarray technology and next generation sequencing are probably the best ways for the determination of SNPs, RNA expression and epigenetic patterns, in order to identify new candidate genes and pathways that may be involved in the suicidal process. One particular way of such hypothesis-generating approach represents genome-wide association studies (GWAS). There are three types of GWAS, namely: SNP-by-SNP, gene-wide GWAS, and pathway/network GWAS, which enable either identification of significant SNP-associations, or selection of most significant SNP(s) that is (are) in the linkage disequilibrium of a gene, or grouping of SNPs that are known to belong to the same pathway and/or protein-protein interaction networks (82). As determined in the review of Sokolowski et al. (82), so far, eight GWAS studies, where suicidal behaviour has been included in the analysis, exist. The results show that there are only a few findings that could be genome-wide significant; however, the replication of results needs further attention. It is of particular importance to stress that none of these studies was initially designed to study suicidal behaviour, but psychiatric disorders. The studies differ among each other also in the sample sizes, study designs and definitions, psychiatric diagnoses, analysis methods, and also in the techniques used for the SNPs interrogation (82). Due to all these differences, it is not possible to conclude that there are any important already discerned findings in the narrow field of suicide research. However, the potential of GWAS studies is big and more studies are needed. With a growing number of genetic/epigenetic studies of suicidal behaviour, and with the development of modern bioinformatic approaches that would enable disentangling the vast spectrum of accumulated data, one could expect the next step in the understanding of biological aspects of suicidal behaviour. However, the translation of the results into suicide prevention and management still seems rather farfetched.

5 ETHICAL CONSEQUENCES

It is very likely that, in the future, evidence will confirm some genetic risk factors for suicidal behaviour, most probably a small, additive effect. In such case, being able to identify people who may be at a higher risk for suicidal ideation and/or behaviour will have several implications. In particular, as argued by Marušič and McGuffin, and Marušič and Swapp, a number of ethical public policy issues will be raised (24, 83).

As with any other research in mental health and in genetics, it must be guaranteed that potential subjects in genetic research are asked to provide informed consent. They have to be informed that their participation is voluntary and that they may withdraw at any time. The risks and benefits of the study must be clearly stated, and alternatives to the study should be made available to the participants. It is also important to protect the confidentiality of the data of individuals, both suicidal cases and their controls, from whom the material for molecular genetics research of suicidal behaviour has been taken (24, 83).

Furthermore, if genetic testing for suicidal behaviour once becomes possible, the question of who (suicidal subjects, their relatives…), when (are results valid enough?), and how (after genetic counselling) to present information will have to be addressed (24, 83). Given the recent developments of genetic research in suicidology and neighbouring fields, the importance of a possible impact should not be underestimated. One needs to plan strategically in advance for the challenges that undoubtedly lie ahead.

Lastly, the bridge between the study of genetics and suicide researchers will have to be built. One way forward would be to improve the awareness and knowledge of genetics among suicidologists, and vice versa. A review as the present one definitively presents an attempt to build such a bridge.

6 CONCLUSION

The overview of the clinical, population and genetic studies clearly shows that there are many differences across the studies, regarding the aims, study groups, methods and outcome measurements. Despite these limitations, there are plausible indications for the existence of a genetic vulnerability to suicidal behaviour that could be transmitted independently from psychiatric or other risk factors. At the aggregate level, surviving relatives, after a suicide, have an increased risk for suicide. The assessment of suicide risk should routinely include the family history of suicidal behaviour. Individual risk increases when there is co-morbidity or interaction with psychiatric problems, environmental stressors, such as sexual abuse, and impulsive aggression. Possibly, there could be also certain gender differences. Currently, it is not yet decided what genes, of the estimated 20,000 that are involved in the functioning of the brain, specifically are involved, but the research tends to focus on the tryptophan hydroxylase, the serotonin transporter and receptor genes (30, 33-34, 46-47). In fact, McGuffin et al. estimated that approximately 43% of the variance of the occurrence of suicide could be attributed to genetic influences (47), a figure almost identical with the 45% found in a major twin study regarding suicidal thoughts and behaviour (84). However, the presence of genetic vulnerability would be one (of many) distal risk factor only.

'Suppose we take Jeff, a lad of 18 years, and suppose his family background is marked with depression [let us add also a genetic vulnerability to suicide]; he is isolated; his pain is unbearable; and he sees no escape from his malaise, but suicide. Suppose that 70% of such young adults, having a similar background, become suicidal. Does that mean that Jeff himself has a 70% chance of killing himself? …The answer is – not at all. Jeff is a unique being' (85).

It's important to keep this in mind for any either aggregate or individual prevention strategy. Morselli, already in 1881, warned against the ecological fallacy, saying that 'statistics cannot presume to learn the true mental state' or the psychic process that precedes suicide (14).

Given the fact that the vulnerability to suicide is multifactorial, future research should integrate biological, clinical and population aspects to better understand the protective and risk factors in the diathesis. As knowledge increases, important ethical questions, as mentioned above, need to be addressed.

CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

Karl Andriessen is supported by a PhD scholarship from the Anika Foundation for Adolescent Depression and Suicide. Alja Videtič Paska is supported by the Slovenian Research Agency Programe Grant no. P1-0104.

ETHICAL APPROVAL

Not applicable.

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