

The Molecular Genetics of Suicide

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Abstract The increasing number of suicidal victims all over the world is a major concern. There are three neurobiological systems involved in the pathophysiology of suicidal behavior: dysfunction of the serotonergic system, hyperactivity of the noradrenergic system, and increased activity of the hypothalamic–pituitary–adrenal (HPA) axis appear to be involved. Increasing evidence points to an overlap between neurobiological and cognitive psychological approaches to understanding suicidal behavior. The authors reviewed the molecular genetics of suicidal behavior. A better understanding of the neurobiology of suicide can help detect at-risk populations and help develop better treatment interventions. Because suicide continues to be a major public health problem, further studies are necessary, including research on the effects of combined medical and psychosocial approaches.

Keywords Dopamine • Molecular genetics • Neurobiology • Noradrenalin • Serotonin • Suicide

Introduction

The number of suicide victims in Japan in the recent 11 years (1998–2008) is more than 30,000 a year, and in the year 2009 this number is 32,753. The suicide rate (number of suicide victims per 100,000 population) in Japan is about 25, and

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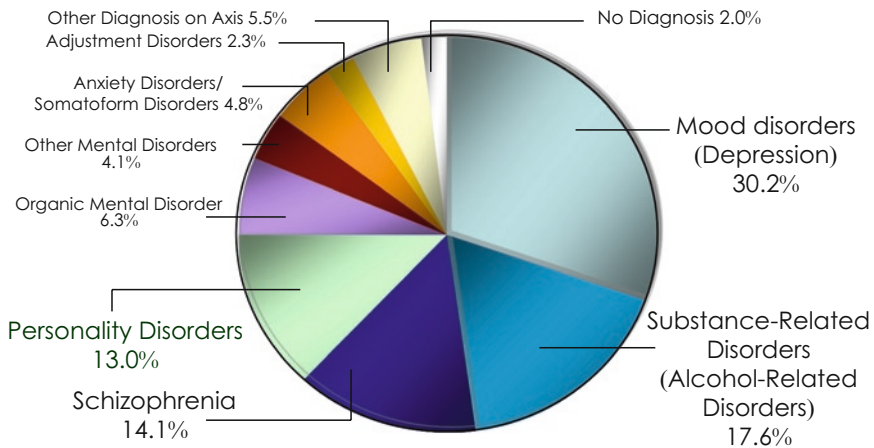
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this number is the fourth highest in the world. Suicide is one of the most important public concerns and a major cause of death among young people throughout the world. No remarkable reduction in the number of suicide victims has yet been achieved, although there has been recent progress in the treatment and management of psychiatric disorders. During the past two decades, there has been a considerable accumulation of findings in the neurobiology of suicide [1].

Although many factors such as biological, psychological, and social factors are involved in suicide behavior, the presence of mental disorder is thought to play an important role in suicide [2]. More than 90% of suicide victims or suicide attempters are diagnosed having mental disorders such as depression, schizophrenia, or alcohol dependence (Fig. 1). However, the underlying mental disorders are diverse, and the severity of the mental disorders does not necessarily correlate with increased risk of suicide.

Even in the psychiatric groups at the highest risk, most patients never attempt suicide. These findings indicate the importance of a diathesis or predisposition to suicidal behavior that is independent of the main psychiatric disorder.

[Suicide and Mental Disorders (n=15,629)]



Preventing Suicide; A Resource for General Physicians.
WHO/WNH/MBD/00.1, World Health Organization, Geneva, 2000.

Fig. 1 Mental disorders in suicide. In completed suicide, about 30% of all suicide victims occur in relation to mood disorders, and the rest are related to various other psychiatric disorders, including substance-related disorders, such as substance abuse and alcoholism, schizophrenia and personality disorders. Source: World Health Organization: preventing suicide; a resource for general physicians. WHO/WNH/MBD/00.1, World Health Organization, Geneva, 2000

Molecular Genetics of Suicide

Numerous studies on neurochemical abnormalities have been done; the results obtained from those studies are summarized in Table 1. Recently, studies on the biological aspect of suicide have been shifting from neurochemical to molecular genetic approaches. Genetic studies on suicidal behavior have suggested that the heritability of such behavior is independent of psychiatric diagnosis. Adoption studies have shown a higher rate of suicide in the biological parents of adoptees who commit suicide compared with biological relatives of control adoptees, even after controlling for rates of psychosis and mood disorders (Table 2). Concordance rates for suicide and suicide attempts are higher in monozygotic than dizygotic twins, and the heritability of suicidal behavior was estimated to be approximately 55% based on twin studies in people with serious suicide attempts [3]. People who commit suicide or make suicide attempts are those with a higher rate of familial suicidal acts. These findings suggest the presence of hereditary and biological factors that determine the threshold to commit suicide and which are independent of specific psychiatric disorders. Thus, genetic factors in suicide have been a recent focus, and recognition has been growing that suicide and suicidal behaviors are highly familial and that genetics contributes to suicide and suicidal behaviors (Table 3). In addition, completed suicides are thought to be more homogeneous than suicide attempters in terms of inheritance of suicidal behavior [4].

Table 1 Risk factors for suicide: bio-psycho-social

Biological factors
Mental disorders
Physical disorders
Family history of mental disorders or suicide
Age, sex, race, etc.
Psychological factors
Temperament/character
Coping skills/problem solving skills
Social factors
Economic and livelihood issues
Family problems

Table 2 Genetic studies on suicidal behavior

<ul style="list-style-type: none"> • Adoption studies: ~sixfold increased risk • Twin studies: 38–55% heritability 		
No. of twins (%)	Concordant for suicidal behavior	
MZ	DZ	<i>P</i>
40/172 (23.0)	2/294 (0.7)	<0.0001
<ul style="list-style-type: none"> • Family studies: 2- to 12-fold increased risk 		

Roy A, Segal NL (2001) [3]

Table 3 Exploration of susceptible genetic variants for completed suicide

Serotonergic system
Suicide-associated personality and cognitive dysfunction (aggressiveness, impulsiveness)
Noradrenergic and hypothalamic–pituitary–adrenal (HPA) system
Stress vulnerability (anxiety/agitation, hopelessness)
The sites of action of mood stabilizers
Antisuicidal effects of lithium
Gene expression analysis in postmortem brains of suicide victims

Table 4 Results of association between polymorphisms of serotonin-related genes and completed suicide

Gene	Polymorphism	Suicide		Control		OR	95% CI	P value
		Allele wt	Allele vt	Allele wt	Allele vt			
5-HT1A	Pro16Leu	320	6	322	4	0.66	0.19–2.37	0.524
	Gly272Asp	309	17	311	15	0.88	0.43–1.79	0.717
5-HT1B	G861C	161	165	165	161	0.95	0.70–1.29	0.754
5-HT2A	–1438A/G	157	145	157	169	1.17	0.85–1.59	0.338
5-HT6	u (GCC)2/3	239	87	237	95	1.1	0.78–1.55	0.581
	267C/T	213	113	213	119	1.05	0.76–1.45	0.751
TPH	–6526A/G	220	44	216	48	1.11	0.71–1.74	0.646
	Int 218C/A	138	126	141	123	0.96	0.68–1.34	0.794
5-HTT	Ins/del	148	44	205	61	1	0.64–1.56	0.997
	Int VNTR	331	41	331	29	0.71	0.43–1.17	0.173
MAO-A	u VNTR	107	92	116	98	0.98	0.67–1.48	0.929

On the basis of these findings, we have conducted genetic association analysis of completed suicides to explore the susceptible genetic variants for suicide. Up to the present date, we have found a number of associations for genetic variations with completed suicide. We have been focusing attention on several neurobiological factors including the serotonergic system, noradrenergic and hypothalamic–pituitary–adrenal (HPA) system, and the sites of action of mood stabilizers, especially the antisuicidal effects of lithium.

In addition, for the purpose of identifying new candidate systems and gaining new insight into biological mechanisms mediating suicide, we have conducted gene expression analysis in the postmortem brains of suicide victims [5–11, 13–18]. Recently, molecular genetic studies have been performed intensively to confirm disturbance of serotonergic neurotransmission in suicide. We have performed association studies of polymorphisms and mutations of genes encoding synthesizing and metabolic enzymes, receptors, and transporters involved in serotonergic neurotransmission in suicide [5–11]. However, in our studies, we have not observed any significant association between these polymorphisms and suicide (Table 4).

In addition, many other studies performed to date have not provided strong evidence supporting such an association. The relative risk was small even when association was detected by meta-analysis (Table 5).

Table 5 Summary of meta-analysis of association between serotonergic genes and suicidal behavior

Gene	Polymorphism	No. of studies	Subject origin	OR	95% CI
<i>TPH</i>	Intron 7	16	Inc. Asian	1.14	0.97–1.34
<i>TPH</i>	Intron 7 A218C	7	Caucasian	1.33	1.17–1.50
<i>5-HTT</i>	Ins/del	12	Inc. Asian	1.17	1.04–1.32
<i>5-HT2A</i>	102T/C	9	Inc. Asian	1.09	0.93–1.27

Anguelova M, Benkelfat C, Turecki G (2003) [12]

It has been suggested that noradrenergic system abnormalities are involved in suicide [13, 14]. Recently, we have found that one promoter genetic variant (C-1291G SNP) of the α_{2A} -adrenergic receptor (ADRA2A) gene was significantly associated with suicide in Japanese females ($P=0.043$ and 0.013 for genotypic and allelic comparisons, respectively). One of the common haplotypes, CC of this polymorphism and another variant of the ADRA2A gene (rs3750625C/A), was also associated with suicide in females ($P=0.015$). These associations were also significant in the female violent suicide victims ($P=0.009$ and 0.009 for allelic and CC haplotypic comparisons, respectively; Table 6) [13]. In contrast, neither of these two SNPs showed any association with violent and/or nonviolent suicide in males. The noradrenergic system regulates activation of the HPA axis, dysregulation of which might be involved in the pathogenesis of suicide. Therefore, this promoter variant in the ADRA2A gene might be involved in the pathogenesis of suicide as a result of the noradrenergic dysfunction that destabilizes the HPA system.

The catechol-*O*-methyltransferase (COMT) gene, the catecholamine-degrading enzyme, exhibits a functional common polymorphism (158Met/Val), and this variant is considered to affect the HPA system. Individuals who are homozygous for the low-activity form of COMT (A/A, Met/Met) would exhibit greater HPA-axis activation than those who are either homozygous or heterozygous for the high-activity form of the enzyme. We found that the genotype distribution of the COMT 158Val/Met polymorphism was significantly different between male suicide completers and male controls ($P=0.036$), whereas the frequency of the Val/Val genotype, a high-activity form of the enzyme, was significantly less in male suicide completers than in male controls [odds ratio (OR)=0.52; 95% confidence interval (CI)=0.31–0.89; $P=0.016$] [14]. These findings were not the case in females. We found that this polymorphism was associated with suicide in males, and that high COMT activity could exhibit a protective effect for suicide in males (Table 7) [15].

Table 8 shows the distributions of the four polymorphisms in the μ -opioid receptor (OPRM1) gene. The OPRM1 gene is implicated in stress responses through the HPA system [16]. The substitution of A118G polymorphism in the OPRM1 gene, which results in an Asn to Asp change at amino acid 40, is suggested to influence the HPA axis response in an inhibitory manner and, possibly, decrease the HPA axis response to a social stressor. Therefore, the suicide-protective G allele would be expected to inhibit the HPA axis responses. We genotyped four single-nucleotide polymorphisms, including a

Table 6 Distribution of polymorphisms in the ADRA2A gene

Marker	Controls		Minor allele frequency		Suicide victims		Minor allele frequency	Statistics genotype		Statistics allele		
	CC	CG	GG	C	CC	CG		GG	C	P value	χ^2	P value
Male and female												
C-1291G	CC	CG	GG	C	CC	CG	GG	C				
(n=185)	0.086	0.422	0.492	0.297	(n=171)	0.117	0.474	0.409	0.354	0.264	2.589	0.108 (0.226)
rs3750625	CC	CA	AA	A	CC	CA	AA	A				
(n=183)	0.536	0.404	0.06	0.262	(n=181)	0.607	0.343	0.05	0.221	0.397	1.693	0.196 (0.376)
Male												
C-1291G	CC	CG	GG	C	CC	CG	GG	C				
(n=112)	0.089	0.446	0.465	0.312	(n=118)	0.093	0.458	0.449	0.322	0.98	0.048	0.826 (0.979)
rs3750625	CC	CA	AA	A	CC	CA	AA	A				
(n=120)	0.55	0.392	0.058	0.254	(n=122)	0.631	0.328	0.041	0.205	0.426	1.66	0.198 (0.386)
Female												
C-1291G	CC	CG	GG	C	CC	CG	GG	C				
(n=73)	0.082	0.384	0.534	0.274	(n=53)	0.17	0.509	0.321	0.425	0.043	6.228	0.013 (0.027)
rs3750625	CC	CA	AA	A	CC	CA	AA	A				
(n=63)	0.508	0.429	0.063	0.278	(n=59)	0.559	0.373	0.068	0.254	0.844	0.173	0.678 (0.977)

Fukutake M, Hishimoto A, Nishiguchi N et al. (2008) [14]

Table 7 Genotype and allele frequencies of the COMT 158Val/Met polymorphism

	Genotype			Allele	
	AA (%)	AG (%)	GG (%)	A (%)	G (%)
Suicides (<i>n</i> = 163)	16 (10)	79 (48)	68 (42)	111 (34)	215 (66)
Controls (<i>n</i> = 169)	18 (11)	61 (36)	90 (53)	97 (29)	241 (71)
Male suicides (<i>n</i> = 112)	9 (8)	60 (54)	43 (38)	78 (35)	146 (65)
Male controls (<i>n</i> = 114)	10 (9)	42 (37)	62 (54)	62 (27)	166 (73)
Female suicides (<i>n</i> = 51)	7 (14)	19 (37)	25 (49)	33 (32)	69 (68)
Female controls (<i>n</i> = 55)	8 (15)	19 (35)	28 (50)	35 (32)	75 (68)

Total: genotype $\chi^2=5.4$, $df=2$, $P=0.068$; allele $\chi^2=2.2$, $df=1$, $P=0.14$

Male: genotype $\chi^2=6.7$, $df=2$, $P=0.036$; allele $\chi^2=3.1$, $df=1$, $p=0.080$

Female: genotype $\chi^2=0.86$, $df=2$, $P=0.96$; allele $\chi^2=0.07$, $df=2$, $P=0.93$

Ono H, Shirakawa O, Nishiguchi N et al. (2004) [15]

common A118G SNP. The genotypic and allelic distributions of the A118G SNP were significantly different between the completed suicide and control groups ($P=0.014$ and 0.039 , respectively; Table 9). Moreover, the dominant model of genotype (AA vs. AG + GG) analysis showed an enhanced association with suicide ($P=0.0041$, $OR=0.575$). This finding means that individuals with one or two copies of the G allele of the A118G SNP of the OPRM1 gene are less vulnerable to suicide. These results raise the possibility that the A118G SNP of the OPRM1 gene is associated with suicide.

We have conducted another association study examining the functional gene polymorphisms of angiotensin-converting enzyme (insertion/deletion), prostaglandin E receptor subtype EP1 [17], and neuronal nitric oxide synthase (nNOS or NOS1), which affect the HPA system, and demonstrated significant associations with suicide. These findings have suggested that the disturbance of the HPA system plays an important role in suicide (Table 9).

Recently, we found an association between regulators of G-protein signaling (RGS) 2 gene polymorphisms and suicide and observed increased RGS2 immunoreactivity in the postmortem brains of suicide victims (Tables 10, and 11) [18]. RGSs are a family of proteins that negatively regulate intracellular signaling of G protein-coupled receptors (GPCRs), such as the serotonin receptor. RGS2 is thought to play an important role in anxiety and/or aggressive behavior.

To explore the involvement of the RGS2 gene in vulnerability to suicide, we screened Japanese suicide victims for sequence variations in the RGS2 gene and carried out an association study of RGS2 gene polymorphisms with suicide victims. In the eight identified polymorphisms that were identified by mutation screening, we genotyped four common single-nucleotide polymorphisms in the RGS2 gene and found significant differences in the distribution of the SNP2 and SNP3 genotypes and alleles of the SNP2 and the SNP3 between completed suicides and the controls. The distribution of the haplotype was also significantly different between the two groups (Table 11; $global < 0.0001$). Furthermore, RGS2 immunoreactivity significantly increased in the amygdala and the prefrontal cortex [Brodmann area 9] of the postmortem brain of the suicide subjects (Fig. 2). These findings suggest that RGS2 is genetically involved in the biological susceptibility to suicide in the Japanese population.

Table 8 Distribution of the single-nucleotide polymorphisms (SNPs) in the *OPRM1* gene

Marker	Controls		Minor allele frequency		Completed suicides		Minor allele frequency		Statistics		
	AA	AG	GG	Minor allele frequency	AA	AG	GG	Minor allele frequency	genotype P value	χ^2 P value	
rs1074287 (n=373)	74.8%	23.9%	1.3%	0.132	71.5%	26.8%	1.7%	0.151	0.706	0.666	0.414 (0.927)
rs12205732 (n=372)	GG	GA	AA	0.114	GG	GA	AA	0.106	0.403	0.127	0.722 (0.998)
A118G (n=367)	AA	AG	GG	0.452	AA	AG	GG	0.387	0.014	4.252	0.039 (0.198)*
IVS2 +G691C (n=370)	GG	GC	CC	0.227	GG	GC	CC	0.251	0.471	0.762	0.383 (0.840)
	4.1%	37.3%	58.6%		6.4%	37.4%	56.2%				

Hishimoto A, Cui H, Mouri K et al. (2008) [16]

* $P < 0.05$

Table 9 Susceptible polymorphisms for suicide associated with HPA system

Functional variants associated with suicide

COMT Val158Met SNP
 OPRM1 Asn40Asp SNP
 ACE insertion/deletion polymorphism
 ADRA2A promoter C-1291G SNP
 Prostaglandin E receptor EP1 gene SNPs
 Neuronal nitric oxide synthase SNP

Functional polymorphisms *not associated* with completed suicide

FKBP5 rs1360780 T/C polymorphism
 Peripheral benzodiazepine receptor gene polymorphism
 Glucocorticoid receptor (*Bc/IRFLP*, N363S, ER22/23EK) polymorphism

Hishimoto A, Shirakawas O, Nishiguchi N et al. (2006) [17]

Table 10 Genotype distributions and allele frequencies of RGS2 gene polymorphisms

SNPs	Genotype frequency			<i>P</i> value	Allele frequency			<i>P</i> value
	Genotype	Control	Suicide		Allele	Control	Suicide	
SNP 1	A/A	64 (0.30)	39 (0.21)	0.068	A	228 (0.54)	176 (0.47)	0.0293*
	A/G	100 (0.48)	98 (0.52)	<i>df</i> =2				<i>df</i> =1
	G/G	46 (0.22)	52 (0.27)	$\chi^2=5.365$	G	192 (0.46)	202 (0.53)	$\chi^2=4.749$
SNP 2	G/G	85 (0.40)	52 (0.28)	0.0383*	G	260 (0.62)	197 (0.53)	0.0175*
	C/G	90 (0.43)	93 (0.51)	<i>df</i> =2				<i>df</i> =1
	C/C	35 (0.17)	39 (0.21)	$\chi^2=6.527$	C	160 (0.38)	171 (0.47)	$\chi^2=5.644$
SNP 3	C/C	68 (0.32)	37 (0.20)	0.0105*	C	243 (0.58)	179 (0.48)	0.0048**
	C/G	107 (0.51)	105 (0.56)	<i>df</i> =2				<i>df</i> =1
	G/G	35 (0.17)	45 (0.24)	$\chi^2=9.119$	G	177 (0.42)	195 (0.52)	$\chi^2=7.939$
SNP 4	T/T	80 (0.38)	47 (0.26)	0.0528	T	257 (0.61)	189 (0.53)	0.0287*
	C/T	97 (0.46)	95 (0.54)	<i>df</i> =2				<i>df</i> =1
	C/C	33 (0.16)	35 (0.20)	$\chi^2=5.883$	C	163 (0.39)	165 (0.47)	$\chi^2=4.787$

SNP1: -638 A/G (rs2746071); SNP2: -395 C/G (rs2746072); SNP3: 2,971 C/G (rs4606); SNP4: 3,438 C/T (rs3767488) (db SNP ID)

Cui H, Nishiguchi N, Ivleva E et al. (2008) [18]

* *P* < 0.05, ***P* < 0.01**Table 11** Haplotype analysis of RGS2 gene SNP 1–4

Haplotype of SNP 1–2–3–4	Frequency		Global <i>P</i> value = 0.000046	
	Control	Suicide	χ^2	<i>P</i> value
1 A-G-C-T	0.5183	0.4382	4.8671	0.0274*
2 G-C-G-C	0.3479	0.427	5.0199	0.0251*
3 G-G-G-T	0.0565	0.0285	3.5473	0.0596
4 G-G-C-T	0.0201	0.0266	0.3563	0.5506
5 G-G-G-C	<0.01	0.0295	12.5573	<0.01**
6 G-C-G-T	<0.01	0.0144	1.9983	0.1575
7 G-C-C-C	0.0161	<0.01	5.6202	0.0178*
8 A-C-C-T	<0.01	0.0121	1.2136	0.2706
9 A-G-G-T	<0.01	0.012	1.1609	0.2813
10 G-G-C-C	0.0119	<0.01	4.1444	0.0418*
...	<0.01	<0.01

SNP1: -638 A/G (rs2746071); SNP2: -395 C/G (rs2746072); SNP3: 2,971 C/G (rs4606); SNP4: 3,438 C/T (rs3767488)

* *P* < 0.05, ***P* < 0.01

Cui H, Nishiguchi N, Ivleva E et al. (2008) [18]

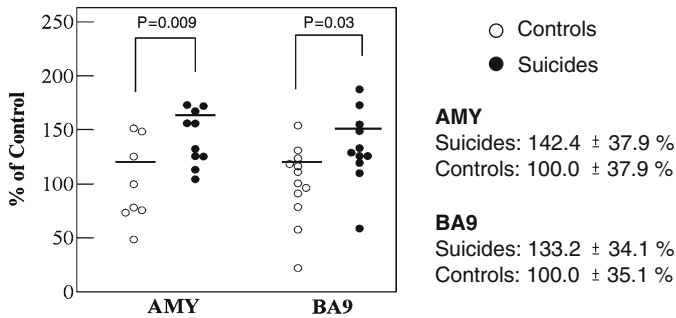


Fig. 2 Increased RGS2 immunoreactivity in suicides. RGS2 immunoreactivity significantly increased in the amygdala and the prefrontal cortex [Brodmann area 9] of the postmortem brain of the suicide subjects. These findings suggest that RGS2 is genetically involved in the biological susceptibility to suicide in the Japanese population. Cui H, Nishiguchi N, Ivleva E et al. (2008) [18]

Conclusion

Taking into consideration the presence of mental disorders as underlying suicide, it is natural that the recent trend tends to link early screening of depression to suicide prevention as a medical approach. It is inadvisable to interpret suicide solely as a symptom or outcome of disease. Expansion of the disease concept and subsequent additional medical intervention may be inappropriate. However, the biological and medical understanding of suicide, that is, interpretation as a condition that allows or requires medical intervention, may encourage people at high risk for suicide to visit psychological counselors and psychiatrists. In addition, although the processes may be indirect or secondary, medical and biological approaches could have considerable influence on individual views and social consciousness of life and death, which may contribute to the prevention of suicide.

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