

L. Jimenez-Treviño¹
H. Blasco-Fontecilla²
M.D. Braquehais³
A. Ceverino-Dominguez⁴
E. Baca-Garcia²

Endophenotypes and suicide behaviour

¹Área de Psiquiatría
Universidad de Oviedo
Oviedo, España

²Departamento de Psiquiatría
Fundación Jiménez Díaz (Madrid)

³Hospital Universitario Vall d'Hebron
Barcelona

⁴Centro de Salud Mental de Hortaleza
Madrid
Spain

Background. Recent studies have suggested that genetic predisposition to suicidal behavior may be independent of the risk of suicide associated to mental disorders, such as affective disorders, schizophrenia or alcohol dependence. Given the suicidal behavior heterogeneity and its hereditary complexity, the need to find demonstrable intermediate phenotypes that may make it possible to establish links between genes and suicide behaviors (endophenotypes) seems to be necessary. The main objective is to review which are the candidate endophenotypes of suicidal behaviors.

Methods. We carried out a non-systematic review of all published literature in English, French and Spanish in MEDLINE. The search terms were endophenotypes and suicide behaviors.

Conclusions. The main candidate endophenotypes of suicidal behaviors are neuropsychological (decision-making, executive functions), personality traits (impulsivity, aggressiveness, and neuroticism), neurochemistry (5-HIAA in CNS) and neuroimaging (fMRI of cerebral amygdala or PET of prefrontal cortex metabolism).

Key words:

Candidates endophenotypes, suicide behaviour, neuropsychology, personality traits, neurochemistry, neuroimaging.

alcohol. Dada la heterogeneidad de las conductas suicidas y la complejidad de su herencia, parece necesario el uso de fenotipos intermedios demostrables que permitan establecer una ligazón entre los genes y las conductas suicidas (endofenotipos). El principal objetivo es revisar cuales son los endofenotipos candidatos para las conductas suicidas.

Métodos. Se realiza una revisión no sistemática de la bibliografía publicada en MEDLINE en los idiomas inglés, francés y español. Los términos de búsqueda usados fueron endofenotipos y conductas suicidas.

Conclusiones. Los principales endofenotipos candidatos provienen de áreas como la neuropsicología (toma de decisiones, funciones ejecutivas), los rasgos de personalidad (impulsividad, agresividad y neuroticismo), la neuroquímica (5-HIAA en líquido cefalorraquídeo) y los estudios de neuroimagen (el metabolismo de la amígdala cerebral medido a través de Resonancia Magnética Funcional y el metabolismo de la corteza pre-frontal medido a través de Tomografía por Emisión de Positrones).

Palabras claves:

Endofenotipos candidatos, conducta suicida, neuropsicología, rasgos de personalidad, neuroquímica, neuroimagen.

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Endofenotipos y conductas suicidas

Introducción. Estudios recientes sugieren que las conductas suicidas tendrían una predisposición genética independiente del aumento de riesgo suicida asociado al diagnóstico de enfermedades mentales como los trastornos afectivos, la esquizofrenia, o la dependencia de

INTRODUCTION

In recent years, there have been genetic molecular studies on suicidal behaviors. Some of these works suggest that genetic predisposition to suicidal behaviors is independent of the genetic predisposition to other mental diseases that increase the risk of suicidal behaviors such as affective disorders, schizophrenia, or alcohol dependence.¹ In fact, mention is made of heritability in approximately 55% of serious suicide attempts.²

Among the candidate genes proposed in the different association studies are genes that codify proteins involved in

Correspondence:

Hilario Blasco-Fontecilla
Avenida Reyes Católicos 2
28040, Madrid (España)
E-mail: hmbiasco@yahoo.es

Table 1		Studies on genetic association and suicidal behaviors [modified of Savitz, 2006 ²⁰		
Gene	OMIM	Locus	Association Studies	
Serotonin transporter (5-HTT)	182138	17q11.2	7+ vs 7- (2+meta-analysis)	
Tryptophan hydroxylase (TPH)	191060	11p15-14	5+ vs 7- (2+meta-analysis vs 1- meta-analysis)	
Monoamine oxidase A (MAO-A)	309850	Xp11.23	3+ vs 2-	
Serotonin 1A receptor 1A (5-HT1A)	109760	5q11.2-q13	1+ vs 2-	
Serotonin 1B receptor 1B (5-HT1B)	182131	6q13	1+ vs 5-	
Serotonin 2A receptor 2A (5-HT2A)	182135	13q14.2	3+ vs 9- (1- meta-analysis)	
Catechol-O-methyltransferase (COMT)	116790	22q11.21	3+ vs 2-	
Dopamine 2 receptor (DRD2)	126450	11q23	1+ vs 1-	
Dopamine 4 receptor (DRD4)	126452	11p15.5	2 -	
GABA-A Receptor (GABRA3)	305660	Xq28	1 -	

+ γ - indicate the positive or negative result of the association studies

the metabolism of serotonin such as tryptophan-hydroxylase (TPH), serotonin transporter (5-HTT), monoaminooxidase (MAO-A), serotonin receptors (5HT1A, 5HT1B, 5HT2A), as well as other genes that are related with the dopaminergic receptors (DRD2 and DRD4), or Catechol-O-methyltransferase (COMT).³⁻¹⁹

Although the search for genes that predispose to suicidal behaviors has led to more than 100 studies published up to date, success has been partial, it becoming stagnant at the point in which a series of candidate genes have been identified. These genes, in practice, are not conclusive when explaining the complex inheritance that this type of behavior implies.²⁰ Table 1 shows the genetic association studies in suicidal behaviors. (Table 1)

In Psychiatry, it is difficult to identify phenotypes because of the heterogeneity of the mental disorders, which often correspond to clinical syndromes. One approach consists in an attempt to define clinical subgroups with common characteristics (intermediate phenotypes) of importance for diagnosis, treatment and prognosis.

Already in the first years of genetic research on suicidal behaviors, Mann stated that the future of genetic research on suicide was related to the study of intermediate phenotypes such as impulsiveness, aggressiveness, changes in psychomotricity, alterations in sleep architecture, and other biological markers.²¹

Gottesman and Shields defined endophenotypes as

internal phenotypes demonstrable by means of a biochemical test or through microscopic observation.²² Endophenotypes are a product of the expression of certain genes involved in a more complex pathophysiological process, which constitutes mental disease.

This concept is not synonymous of intermediate phenotype, biological marker, subclinical trait, or vulnerability marker, concepts in which there can be no participation of genetic factors.

The study of endophenotypes has been proposed as a good strategy to overcome the methodological difficulties derived from the nosology in psychiatry, up to the point that it has now been demonstrated to be effective in genetic research of complex psychiatric diseases such as schizophrenia.²³ In the writing of the present work, the concept of endophenotypes has been used according to the model proposed by Gottesman and Gould,²³ who established five criteria that should be fulfilled by the endophenotypes in genetic psychiatry:

1. the endophenotype is associated with the disease in the general population
2. the endophenotype is inheritable
3. the endophenotype is a marker of stable trait, independent of the disease status
4. the endophenotype and the disease co-segregate in the family
5. the endophenotype is manifested in unaffected relatives with greater frequency than in the general population.

REVIEW

Candidate endophenotypes in suicidal behaviors

Different authors have already proposed a series of candidate endophenotypes for suicidal behaviors that are being investigated. Most of them come from etiopathogenic models for suicidal behavior that are already known as the stress-diathesis model proposed by Mann²² or the four-way clinical-biochemical model proposed by Fawcett et al.²⁴ The candidate endophenotypes come from such diverse fields as neuropsychology, personality traits, neurochemistry, or neuroimaging studies.

Personality traits

Certain personality traits such as impulsiveness, aggressiveness, or neuroticism have been proposed as candidates to endophenotypes in the suicidal behaviors.

In the specific case of the impulsiveness-aggressiveness binomium, we would be speaking of an endophenotype for the suicidal behaviors that reflects an underlying serotonergic dysfunction.²⁵ It has been demonstrated that this association between impulsiveness-aggressiveness and the serotonergic function remains stable over time. This, combined with the results of the longitudinal studies in which these personality dimensions are associated with the risk of committing a suicide attempt,²⁶ support the idea that it would be a marker of the trait involved in the vulnerability to suicidal behaviors. In fact, there are many publications in which impulsiveness and aggressiveness are related, not only with suicidal behavior^{4, 21, 27, 28} but also with serotonergic genes known for their relationship with the suicidal behaviors: 5-HTT²⁹ MAO-A,³⁰ 5-HT2A^{31, 32} or 5HT1B.³³

Along this line of investigation, Turecki et. al. have proposed Impulsive-Aggressive Behaviors (IABs) as endophenotypes, using the Buss-Durkee Hostility Inventory (BDHI) as a measurement instrument. In two works of the same group, it has been stated that the IABs are associated with a greater risk of suicide, especially in the young population,³⁴ and as a variation in A-161T locus of the promoter gene of the 5HT1B receptor, it affects both the IAB levels and the presence of suicidal behaviors.³³

In addition to the impulsiveness measured with the BDHI Inventory, there is a second candidate endophenotype related with the impulsiveness whose results suggest its utility in the study through endophenotypes of the suicidal behaviors. In this case, it is the impulsiveness measured with the Barratt Impulsivity Scale, since its association with suicidal risk^{9, 27} and its relationship with the genetics of

impulsiveness, specifically with the 5-HTT gene have been demonstrated.^{8, 29}

Another personality trait that has been used as a possible endophenotype is neuroticism. This has been related with suicidal behaviors in many studies.^{2, 26, 35-37} In this case, it would be an endophenotype for the suicidal behaviors that reflects an underlying dysfunction of the serotonergic^{38, 39} and/or gabaergic system.^{40, 41} This is suggested by the results of genetic association studies between genes related with suicidal behaviors such as 5-HTT(42-45) and GABRA6.⁴⁰

On the contrary to what occurs with the aggressiveness-impulsiveness binomium, the works that have used neuroticism as an endophenotype in suicide do not provide clear results. This is largely due to the use of different instruments to measure the neuroticism dimension so that the results are not comparable.

Thus, an analysis was made of studies that use similar measurement instruments, observing how when neuroticism is measured with the Eysenck Personality Questionnaire, an association is found with the presence of personal and familial backgrounds of suicidal behaviors.³⁵ On the contrary, a study on the influence of the 5-HTTLPR genotype in the neuroticism dimension on the EPQ questionnaire indicates that the different allelic variants of the genotype are not associated with different scorers in neuroticism⁴⁶ (Table 2).

Psychological-cognitive characteristics

As occurs in mental diseases such as schizophrenia, it has been demonstrated that patients who have suicidal behaviors have alterations in psychological-cognitive processes such as decision-making or executive functioning.

In the first case, the suicidal patients obtain worse results than the healthy controls on neuropsychological tests that evaluate decision-making process, the difference being greater in patients who have had a violent suicide attempt.⁴⁷ Decision making would constitute an endophenotype for suicidal behaviors that reflects an underlying serotonergic dysfunction since it has been described that the serotonergic system modulates decision-making,^{48, 49} or, from an anatomical-clinical perspective, between suicide and alterations in the brain cortex on the ventromedial or dorsolateral prefrontal level.⁵⁰⁻⁵⁴

On the other hand, variations in the decision-making process have been related with already known polymorphisms in genetic studies and suicidal behaviors such as 5-HTTLPR, TPH1, TPH2, or MAO-A.^{55, 56}

Table 2		
Personality traits, risk of suicide and genetics		
Personality traits	Trait studies of personality/suicide (measurement instrument)	Trait studies of personality/genetics (measurement instrument)
Impulsiveness/aggressiveness	Fergusson et al. 2000 (TCI)	5-HTT [2+] (BIS,BIS)
	Oquendo et al. 2004 (BIS)	MAO-A [1+] (BIS,)
	Turecki 2005 (BDHI)	5-HT2A [2+] (BIS,STAXI)
	Baca-García et al. 2005 (BIS)	5-HT1B [1+] (BDHI)
Neuroticism	Statham et al. 1998 (EPQ)	5-HTT [4+ vs 2-] (NEO-PI-R, NEO, STAI,TPQ vs NEO-FFI, NEO-PI-R)
	Beautrais et al. 1999 (EPQ)	GABRA6 [1+] (NEO-PI)
	Fergusson et al. 2000 (EPQ, TPQ)	5-HT1A [1+] (NEO-PI-R)
	Roy 2002 (EPQ)	

+ y - indicate the number of positive or negative association studies
 TCI=Temperament and Character Inventory; BIS=Barratt Impulsivity Scale; EPQ=Eysenck Personality Questionnaire; BDHI=Buss-Durkee Hostility Inventory; STAXI=State Trait Anger Expression Inventory; STAI=Spielberger State-Trait Anxiety Inventory; NEO-PI (R)=NEO personality inventory (revised); TPQ=Tridimensional Personality Questionnaire

Following this line of investigation, the Jollant and Courtet group successfully used the decision-making endophenotypes (using the *Iowa Gambling Task* test as a measurement instrument) in suicidal behaviors. In their first work, they demonstrated how suicidal patients obtained worse results on the Iowa Gambling Task compared with healthy subjects, and in the case of suicides with violent methods, the results of the test were worse than those obtained by patients with affective disorders but without suicidal behaviors.⁴⁷

In a subsequent work of the same group, they studied four polymorphisms that modulate the serotonergic function (5-HTTLPR, TPH1, TPH2, or MAO-A) in a sample of suicidal patients. The patients who were carriers of the genotypes that previously had been associated to a greater risk of suicidal behaviors, greater vulnerability to stressful events or greater tendency to negative feelings, obtained worse results on the Iowa Gambling Task. Thus, the authors concluded that the influence on suicidal behavior of the genetic polymorphisms studied would be mediated partially by the modulation carried out on the decision-making process and, specifically, on the learning of them.⁵⁶

The executive function is another cognitive process that has been demonstrated to be altered in suicidal patients, both in euthymic patients as well as in patients with depression and emotional personality instability.⁵⁷⁻⁵⁹

The alteration in executive functioning would constitute an endophenotype for suicidal behaviors that reflects a dysfunction of the underlying dopaminergic system,⁶⁰ or,

from an anatomic-clinical perspective, alterations in the cerebral cortex on the dorsolateral, prefrontal level.^{57, 59}

The genetic polymorphisms that modulate executive functioning include some of those studied in suicidal behaviors such as TPH2, COMT, or DRD4.⁶¹⁻⁶⁴

In spite of the fact that executive functioning is a promising candidate endophenotype for suicidal behaviors, up to date, there are no works on suicidal samples in which the alteration in the executive functioning is related with the suggested candidate polymorphisms. Furthermore, the neuropsychological studies conducted in suicides and genetic studies conducted with the candidate polymorphisms have not been carried out using the same measurement instrument (in the Keilp et al. study with suicidal patients, the Trail Making Test was used while in the genetic studies by Reuter and de Frias, the Attention Network Test and Verbal Fluency Test were used, respectively). Thus, mention can still not be made of a specific endophenotypes in regards to executive functioning in patients with suicidal behaviors (Table 3).

Neurochemistry

Neurochemical findings obtained in the biological research of suicidal behaviors can also be used as possible endophenotypes. One of the neurochemical findings most replicated in suicidal patients is low levels of 5-HIAA cerebrospinal fluid (CSF) compared with healthy controls and non-suicidal patients.⁶⁵⁻⁶⁸ This finding is more

Table 3 Psychological-cognitive, suicide and genetics characteristics		
Psychological-cognitive characteristics	Study of psychological/suicide characteristics (measurement instrument)	Studies psychological/genetic characteristics (measurement instrument)
Decision making	Jollant et al. 2005 (IGT)	5-HTTLPR [1+] (IGT) TPH-1 [1+] (IGT) TPH-2 [1+] (IGT) MAO-A [1+] (IGT)
Executive functioning	Keilp et al. 2001 (TMT) LeGris Et van Reekum 2006 (Trails, Stroop) Raust et al. 2007 (N-back, Hayling, Stroop,Go-noGo)	COMT [3+] (VFT, Torre de Hanoi) APOE [1+] (Digit Span Backward) TPH-2 [1+] (ANT) ADRA2A [1+] (TMT, Stroop) DRD4 [1+] (VFT)
+ indicates the number of positive association studies IGT=Iowa Gambling Task; VFT=Verbal Fluency Test; TMT=Trail Making Test, ANT=Attention Network Test		

Table 4 Neurochemistry studies, associated risk of suicide and genetics		
Neurochemical studies	Neurochemical/suicide study	Neurochemical/genetic studies
Levels of 5-HIAA in CSF	Asberg et al, 1986 Roy et al, 1989 Nordström et al, 1994	TPH-2 [1+]
+ γ - indicate the number of positive or negative association studies CSF = cerebrospinal fluid		

consistent when dealing with impulsive suicidal attempts.⁶⁹ In two recent works of Mann et al., mention is even made of the predictive power of suicidal behaviors of the 5-HIAA levels in CSF, specifically odds ratio of 4.48 for the prediction of suicide. They have proposed a biological model of suicide prediction that includes the 5-HIAA levels in CSF combined with the dexamethasone suppression test that obtains a sensitivity for the positive results of 37.5%, specificity of 88% and a positive predictive value of 23%.⁷⁰

The 5-HIAA levels in CSF would therefore constitute an endophenotype for suicidal behaviors that reflects a central serotonergic dysfunction.⁶⁸

In addition, it has been seen how 5-HIAA levels in CSF are affected by polymorphic variations of genes associated with suicidal behaviors such as 5-HTTLPR, TPH2, or MAO-A.^{71,72}

Following this line of investigation, Zhou et al. used the 5-HIAA levels in CSF as endophenotype in suicidal behaviors to study the effect of the TPH2 polymorphism. In this work, it was indicated that one of the haplotypes (212121 *yii*) is more frequently present in suicidal patients but, on the contrary to that expected, it is associated to lower concentrations of 5-HIAA in CSF in the controls than in the cases⁷¹ (Table 4).

Neuroimaging

Modern functional neuroimaging techniques have constituted an important advance in investigation in neuroscience and may be a source of endophenotypes as they provide quantifiable data on cerebral metabolism.

Although there are many published works, both regarding the association between genetics and cerebral

Table 5		
Functional neuroimaging studies, associated risk of suicide in genetics		
Functional neuroimaging	Neuroimaging/suicide studies	Neuroimaging/genetic studies
fMRI-amygdala	NA	5-HTTLPR [4+]
Prefrontal cortex PET	Oquendo et al, 2003	5-HTTLPR [1+]
+ γ - indicate the number of positive or negative association studies NA= no studies available		

metabolism and between cerebral metabolism and suicidal behaviors, as occurs in the case of neuropsychological tests, the different techniques used in the works published make it difficult to establish a functional genetic-neuroimaging suicidal-behavior sequence in most of the cases.

Even so, and even though there are no works using the endophenotype neuroimaging techniques, we do have sufficient data to indicate promising candidate endophenotypes.

Specifically, metabolism of the cerebral amygdala is measured by Functional Magnetic Resonance Imaging (fMRI) and metabolism of the prefrontal cortex is measured by Positron Emission Tomography (PET).

The metabolism of the cerebral amygdala measured with the Functional Magnetic Resonance Imaging (fMRI) has been related in different works with the serotonin transporter gene,⁷³⁻⁷⁶ one of the genes studied the most in suicidal behaviors.⁷⁷

In this case, cerebral metabolism measured with the fMRI would constitute an endophenotype for the suicidal behaviors that reflect an underlying serotonergic alteration.

The data in favor of this line of investigation comes from the Hariri et al. group, who demonstrated how the allele S of the 5-HTTLPR polymorphism is associated with greater neuronal activity of the amygdala (measured by fMRI) when there are threatening stimuli.⁷³⁻⁷⁵ These data were subsequently replicated in a work at the University of Berlin.⁷⁶ We bring to mind that the allele S of the 5-HTTLPR polymorphism is associated with suicidal behaviors in psychiatric patients, especially with violent suicides.⁷⁷

Although these data point to the metabolism of the cerebral amygdala measured by fMRI as a good candidate endophenotype, up to now there have been no published works using the same technique on the possible alterations of metabolism of the amygdala in suicidal patients. It has been verified how depressive suicidal patients have greater volume of the right amygdala (measured by structural

Nuclear Magnetic Resonance) compared with the non-suicidal depressive subjects. This suggests an alteration in this structure which, in turn, would have a metabolic correlate in the functional neuroimaging tests.⁷⁸

Metabolism of the prefrontal cortex measured by PET would once again be an endophenotype for suicidal behaviors that reflects an underlying serotonergic alteration.

The data in favor of this thesis come from a study by Oquendo et al. In that study, it was observed how lower metabolism (measured by PET) in prefrontal cortical regions (superior frontal gyrus, anterior cingulate gyrus and inferior cingulate gyrus) is associated with greater suicidal ideation and greater lethality in suicide attempts in depressive patients.⁷⁹

On the other hand, the metabolism of the prefrontal cortex has also been related with the serotonin transporter gene. However, in this case, mention is made of higher metabolism (measured by PET) in limbic regions (anterior, posterior cingulate and amygdala) and cortical structures (fusiform gyrus, dorsolateral prefrontal and superior temporal cortex) in the group with **homozygosis** for the allele S of the 5-HTTLPR polymorphism. These structures are also associated with greater response to the presence of visual stimuli with emotional characteristics.²²

Even though these results are contradictory, the fact that these are two works conducted by research groups and in different samples, the already mentioned endophenotype cannot be ruled out since the data of the neuropsychological studies in suicidal patients are also in favor of an alteration on the level of the prefrontal cortical structures,^{50-54, 57, 59} which should have a quantifiable functional correlate with the current neuroimaging techniques (Table 5).

CONCLUSIONS

The concept of *endophenotype* provides an advantage for the study of genetically complex diseases, but it is not exempt of complications.

Research in suicidal behaviors using endophenotypes entails important methodological problems, both in regards to the definition of the endophenotype as well as to the heterogeneity of the measurements used, even in regards to the concept per se of suicidal behavior, whose definition and nomenclature are undergoing continuous revision.⁸⁰

This fact has contributed to the fact that the results obtained up to date have not met the expectations generated.

In spite of the problems mentioned, the use of endophenotypes in research on suicide is providing promising results to the obtaining of a more precise definition of the complex interaction between genetics and this type of behaviors.

Therefore, it is necessary to have a larger volume of research and the search for endophenotypes for suicidal behaviors, using the maximum methodological rigor and homogenizing the measurement instruments, so that comparison and replication of the results would be facilitated.

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