Anticipation with Phenotypic Variation in Three Father-son Pairs with Affective Disorder: a Case Series

三对父子其情感性精神病与呈表型变异的遗传早现：病例系列

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Abstract

Anticipation is a phenomenon in which successive generations within a family experience an earlier age of onset and a more severe form of a given illness. It has been observed in various neurological and psychiatric conditions, including bipolar disorder. The molecular basis of anticipation involves trinucleotide repeat expansions in genes, but this has not been conclusively demonstrated in bipolar disorder. The histories of 3 father-son pairs are presented. In each pair, the son presented with an early-onset bipolar disorder, and the father developed severe depression after the age of 50 years. No female relatives were affected. The implications of these observations are discussed. Genetic, epigenetic, and environmental mechanisms that may have contributed to this phenomenon are briefly described. The study of such patients may throw light on the “extended phenotype” of mood disorders, as well as the genetic and epigenetic mechanisms involved in the phenomena of anticipation and phenotypic variation.

Key words: Bipolar disorder; Genetics

Abstract

遺傳早現指某種疾病於連續世代中的發病時間一代早于一代，症狀一代較一代嚴重的现象。這種現象見于各種神經和精神疾病，當中包括躁鬱症。遺傳早現的分子基礎涉及三核苷酸重複擴張的基因，但這還未于躁鬱症中被確切證明。本文報告三對父子的病例，當中兒子皆患上早發躁鬱症，而父親則於50歲後出現嚴重抑鬱症。沒有女性亲属受到影響。本文也討論上述病例的影響，以及簡述導致遺傳早現的遺傳學、表觀遺傳學和環境機制。這個病例系列有助說明引發情緒障礙的「延伸顯型」，以及涉及遺傳早現和顯型變異現象的遺傳和表觀遺傳機制。

關鍵詞：躁鬱症、遺傳學

Introduction

The term “anticipation”, in genetics, refers to a phenomenon in which successive generations within a family have an earlier age of onset and a more severe form of the illness.1 In other words, if a patient’s father is affected with the given disorder, the patient would develop the same disorder at a younger age, and would show more severe clinical manifestations. This concept was first proposed in the 19th century, but was called into question later. It gained a firm scientific footing with the discovery that trinucleotide repeat (TNR) expansions in certain genes provided a molecular basis for anticipation in some diseases, particularly myotonic dystrophy.2 Anticipation has been reported in several neuropsychiatric disorders, including Huntington’s disease3 and familial Parkinson’s disease.4 There is also evidence of anticipation in certain psychiatric disorders including schizophrenia4 and, particularly, bipolar disorder.5-10 The mechanisms underlying this phenomenon are uncertain. A review of anticipation studies in patients with bipolar disorder found significant positive evidence in most of them, and proposed various genetic and environmental explanations for this phenomenon.11

This paper presents 3 father-son pairs in whom there was presumptive clinical evidence of both anticipation and a clear variation in the nature of affective symptoms across generations. The fathers experienced severe depression...
in late life, at the age of 50 years or above, while their sons developed early-onset bipolar disorder. The relevant literature is then reviewed, and the possible mechanisms and implications of this observation are discussed.

**Case Reports**

**Case 1**
A high school student, aged 18 years, presented in September 2003 with symptoms of moderate depression for the past 3 months, which were accompanied by obsessive-compulsive symptoms in the form of sexual and aggressive urges. He had no history of a mood disorder. He was prescribed fluoxetine 20 mg/day, but within a week of starting medication, he developed features of mania and was hospitalised for the same. His symptoms stabilised after discontinuation of fluoxetine and the addition of divalproex 1500 mg/day, with which he was in remission for over a year.

Around this time, his father (aged 52 years), who had no history of mental illness or substance use, was noted to become dull and socially withdrawn. He would frequently brood over past events, and appeared sad most of the day. These symptoms progressed rapidly over the next 2 months, to the point where he stopped going to work and remained at home most of the time. His appetite was markedly reduced, and he lost weight. He frequently expressed death wishes, but his family considered these to be a “normal” response to worry about his son’s illness and did not encourage him to seek treatment for his symptoms. He committed suicide 3 months after the onset of his symptoms. His death triggered a hypomanic relapse in his son, which responded well to the addition of risperidone, followed by supportive therapy to deal with his grief.

**Case 2**
In February 2004, a boy aged 14 years first presented to the hospital with symptoms of pervasive elevated mood, irritability, increased activity, and decreased sleep. He was diagnosed to have a manic episode without psychotic symptoms, and responded well to lithium 900 mg/day. He had a further episode 4 years later, which required hospitalisation and treatment with a combination of lithium and chlorpromazine. He remained stable on these medications for over a year.

About 6 months prior to his second episode, in July 2007, the boy’s father (aged 50 years) presented to the hospital with symptoms of social withdrawal, reduced speech output, forgetfulness, expressing death wishes, and refusal to carry out even basic activities of daily living. He had a history of alcohol dependence, with onset at the age of 25 years, but was abstinent for over 18 months at the time of presentation. He had no history of mood disorder or cognitive impairment. On examination, he reported a sad mood and ideas of worthlessness, and expressed wishes to end his life. Cognitive function assessment revealed global but inconsistent deficits, poor motivation, and frequent “I don’t know” answers suggestive of a depressive pseudodementia. Evaluation for neurological disorders or dementia was negative. He was hospitalised for the above complaints, and treated with citalopram 20 mg/day, with which he showed complete resolution of both his depressive symptoms and cognitive deficits. At follow-up, he was euthymic and had no cognitive impairment.

**Case 3**
A civil servant aged 53 years presented in July 2006 with 3 months’ history of low mood, decreased interest in his work and other activities, and feelings of hopelessness. The patient had no history of medical or psychiatric illness or substance use. He had made a suicide attempt by hanging a week prior to evaluation, and had fallen and sustained a minor head injury during the attempt. Examination revealed a depressed affect, suicidal ideas, and ideas of hopelessness and helplessness. There were no neurological or cognitive deficits, and a computed tomographic scan of the head was normal. He was hospitalised and treated with escitalopram, up to 15 mg/day, along with supportive therapy, and achieved full remission of his symptoms. He was followed up for a year and showed no evidence of recurrence of depression or manic episode. His son, aged 20 years, had been diagnosed with bipolar disorder 2 years earlier, with 2 episodes of mania, and was stable on divalproex 1500 mg/day.

**Discussion**
These 3 pairs of patients all share certain key clinical features. In the first generation, all 3 male patients developed a severe depressive episode for the first time in their lives after the age of 50 years, with a temporal relationship with the stress of their sons’ illness. These episodes were associated with melancholic features and a markedly increased risk of suicide, but in the 2 cases where treatment was possible, they responded rapidly and completely to treatment with selective serotonin reuptake inhibitor antidepressants. None of them developed mania or hypomania at follow-up. In the second generation, all the sons developed bipolar disorder during their adolescence, with prominent episodes of mania, which responded well to conventional mood stabilisers. No female relatives or family members on the maternal side suffered from any similar disorder.

The earlier age at onset, as well as the more varied and severe clinical presentation (bipolar vs. unipolar disorder) in the second generation both suggest that the phenomenon of anticipation was involved. The fact that this involved only male patients suggests a sex-linked genetic phenomenon. Two possible mechanisms for this are: (1) TNR expansions on a sex-linked chromosome, and (2) parental imprinting. However, evidence of clinically relevant TNR expansions in bipolar disorders has not been forthcoming. Other mechanisms to explain anticipation have also been suggested in the literature, such as environmental and sociocultural factors, but have yet to be conclusively established. Given the parent-of-origin effect that was observed in these pairs, an epigenetic mechanism involving parental
imprinting may be involved in these and other patients with early-onset familial bipolar disorder. This possibility has been raised, but not confirmed, in an earlier study, and it is consistent with experimental evidence that gonadal steroids can alter DNA methylation. Alternatively, a lower number of sex-linked TNRs — or an environment-sensitive, gender-dependent epigenetic imprint — could lead to non-expression of the phenotype in the first generation. The psychosocial stress of their sons’ illnesses could then, theoretically, have led to epigenetic changes and the development of a depressive episode. The latter explanation raises the intriguing possibility that a gene/environment interaction can span generations, but this needs experimental verification.

In these patients, the clinical phenotype also varied across generations, from severe unipolar depression in the parents to bipolar I disorder in the offspring. There is a large body of work suggesting that the boundaries between unipolar and bipolar mood disorders are fluid, and that there is a substantial overlap between these 2 categories. Results from 2 studies in genetically different populations have found that anticipation occurs in unipolar as well as in bipolar disorders, while a study from Japan found that anticipation was also present in the bipolar offspring of parents with unipolar disorder. Two studies suggest that gender can affect the age of onset in familial bipolar disorder, but their results were dissimilar: in the earlier study, anticipation was strongly associated with paternal disorder, but their results were dissimilar: in the earlier study, while a study from Japan found that anticipation was also present in the bipolar offspring of parents with unipolar disorder. Two studies suggest that gender can affect the age of onset in familial bipolar disorder, but their results were dissimilar: in the earlier study, anticipation was strongly associated with paternal inheritance, while in the later study, a positive family history affected the age of onset in women, but not in men. Such results suggest a closer relationship between gender-related factors and anticipation in bipolar disorder. Finally, it has been suggested that age at onset alone may not be a valid criterion to ascertain anticipation in a complex condition such as bipolar disorder. If this is true, then phenotypic variants such as the one described here could serve as an additional criterion.

The phenotypic variation between fathers and sons in this series may lead to a natural question: has anticipation truly taken place? Such a question needs to be answered using a larger sample and a more rigorous study design. However, there is fairly strong evidence that unipolar and bipolar depression are genetically correlated, though the overlap is not complete; in fact, some authors have argued for a unitary approach to unipolar and bipolar disorder.

The presentation observed in Case 2, involving both depression and cognitive deficits, is particularly suggestive, as a similar phenotype (bipolar type VI) has been described as a late-onset form of bipolar disorder. Further, it is possible that some of the fathers in these pairs may have developed manic or hypomanic episodes if followed for a longer period, a phenomenon well documented in ‘classical’ bipolar disorder.

Of course, generalising from a small number of clinical cases does have its limitations. It is quite possible that the association found in these patients may be the result of chance, or may reflect purely non-genetic mechanisms, such as the effects of stress — particularly the burden of caring for a child with bipolar disorder — at a vulnerable point in the parents’ life cycle. Further, due to the small number of cases involved and the lack of a clear candidate gene, actual genetic studies to identify possible TNRs could not be carried out. However, the striking similarities between these cases — all drawn from the same population — in terms of age of onset, clinical presentation, and disease severity, all suggest that a genetic mechanism cannot be ruled out. Larger studies of families with patients suffering from both unipolar and bipolar disorders, and studying the effects of gender as well as variations in symptoms and age at onset would serve to confirm or refute this association.

If confirmed, such a finding would have 2-fold significance. Clinically, it would lead to early diagnosis and treatment of potentially severe depression in the parents of young male bipolar patients. From a research point of view, it would further illuminate the ‘extended phenotype’ of affective disorders in humans; the role of genes, epigenes, gender, and environment in determining this phenotype; and the boundaries between unipolar and bipolar forms of affective disorder.

Declaration

The author declared no financial or academic conflict of interest in this study.

References

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