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Review

Translation of genetic findings to clinical practice in juvenile myoclonic epilepsy

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ABSTRACT

It has been estimated that JME (juvenile myoclonic epilepsy), when compared to other adult epilepsy syndromes, is most likely to have a genetic cause. However, decades of research have not brought us closer to finding a single 'JME gene' that is important on a population basis. Is this due in part to the genetic complexity of the syndrome, the cryptic nature of the genes of effect, or perhaps because JME is not one condition at all but many? Before we can begin to harness the power of next-generation sequencing techniques, we must first reduce JME down to lacunae of homogeneity — using increasingly more sophisticated phenotyping tools. The current technological advances in gene sequencing have been used to dramatic effect to identify single gene causes in rare syndromes and identify risk variants in malignancies. Filtering the variety of the human exome or genome down into a handful of biologically plausible candidates now relies on a pipeline of biostatistics, software, and functional analyses. It is simply unacceptable to return uncertain findings to the clinical domain and, therefore, it is crucial that pathogenicity is fully determined before families receive genetic counseling and test results.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".

1. Introduction

The importance of genes in the causation of epilepsies could not be more clearly stated than in the most recent ILAE revision of the nomenclature for seizure types and epilepsy syndromes [1]. Idiopathic as a term meaning broadly 'something that occurs spontaneously' is not too poor a synonym for a genetic epilepsy. However, idiopathic also has a co-meaning — 'something with an obscure or unclear origin'; this cannot clearly describe the state of our knowledge regarding the 'idiopathic' epilepsies. Of the generalized genetic epilepsies (GGE previously IGEs), juvenile myoclonic epilepsy (JME) has been estimated to have the highest likelihood of having a genetic cause [2]. Juvenile myoclonic epilepsy can cluster in families (sometimes occurring with other absence epilepsies, sometimes with more heterogeneous family phenotypes such as GEFS+) [[]]. There is a slight preponderance of maternally inherited cases, and an increased chance of developing JME is seen in twin studies [4]. Identifying myoclonic seizures (the ubiquitous in JME) is important as myoclonic seizures in families show a concordance distinct from GGEs with absence seizures alone [5,6]. We therefore have chosen JME as an ideal example of a condition in which to highlight the challenges, and successes, of translational research.

Of course, other potential exemplar epilepsies exist. The catastrophic childhood epilepsies (often associated with learning difficulties) are clearly strong models of a primarily genetic epilepsy syndrome. They are predominantly rare on a population basis, relatively uniform in their presentation, and occur early in life. There is strong evidence that the epileptic encephalopathies are caused by de novo mutations or inheritance from mosaic parents. This is in contrast with JME which is a common epilepsy syndrome (for 5–11% of all epilepsies and up to 26% of the GGEs), where homogeneity of presentation has not been confirmed, seizure onset can be as late as the 20s, and the familial link is strong. Furthermore, twenty years of scrutiny has not identified a single gene that is important on a population level for JME [7,8]. This is not to say that the genes identified have not brought us closer to understanding this complex condition — for example, *EFHC1* (EF-hand domain (C-terminal) containing 1) may disrupt migration of post-mitotic neurons and tantalizingly hints at JME as a disorder of impaired neuronal development. It is simply that candidate gene screening has not identified a convincing high-frequency genetic association. The heterogeneity and the sample size needed have prevented an adequately powered genome-wide association study. Those genes that have been described are restricted to isolated families (so called private mutations) and do not appear to have an effect across unrelated cases. A multinational cohort of JME families did

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identify a major susceptibility locus at 15q13–14 via linkage analysis [9–11]; however, despite the efforts of large collaborations, we are currently many years away from routine gene testing for JME in clinical practice. The candidate gene approach has been likened to searching for a 'needle in a haystack'; if the majority of cases are answered by private mutations, then maybe we are searching for many needles. It is therefore from two complementary directions that we are working towards better understanding JME, and through this understanding we make a valuable translation of scientific findings into clinical practice. The first of these is a critical clinical analysis of what we call JME to enable stringent case identification and disease of JME; the second is harnessing the power of cutting edge genetic tools which enable small number of patients to be studied in great depth.

2. Juvenile myoclonic epilepsy

Clinically, JME is recognized as an electroclinical syndrome under the IGE/GGE umbrella mainly characterized by seizure types, age of seizure onset, EEG pattern, and response to medication. One would also expect unremarkable standard neuroimaging, predominantly early morning myoclonus with a benign progression, a lifelong liability for seizures, and seizures triggered by photo-stimulation, sleep deprivation, and illness or stress. Some authors will only make a diagnosis of JME in the context of a normal IQ. However, there is a remarkable degree of variability between individuals — so much so that some authors have made the case that there may be a spectrum of 'juvenile myoclonic epilepsies'. An attempt by seizure type alone to subclassify these epilepsies – for example, by the age of onset of absence seizures (discussed below) – is fraught with difficulty as absence seizures are not an essential seizure type for a diagnosis of JME.

Age of onset and seizure type. There is a significant variation in the age of onset of absence seizures particularly – with many individuals seemingly having a true childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE) phenotype before evolving into JME – whereupon others have their first absence seizures after their myoclonus begins (typically in the teenage years). Furthermore, epileptic myoclonus is the *sine non qua* of JME but as increasingly more women are advised to avoid sodium valproate, how do we classify myoclonus that appears to be brought on by lamotrigine or carbamazepine therapy? There is also a variation seen within myoclonic seizures experienced. Some have exclusively early morning attacks, while some only ever have upper limb jerking — others have leg and head involvement. When positive and negative jerks are included in the equation, it is no wonder that facial injury is reported so much more frequently in JME compared to other epilepsies [12]. If the age of absence onset is crucial in defining subtypes [13], then we need to pay greater heed to the major gene of effect for early onset CAE (up to 12% of cases) *SLC2A1* and other major genes as they emerge [14,15].

Electroencephalogram pattern. The EEG has the potential to add diagnostic doubt rather than clarity with up to a third of people demonstrating interictal EEG characteristics that would be in keeping with a focal onset of seizures [16,17]. This is more remarkable when you consider that this proportion is very similar to those who report absence seizures at all. Do this third of people have a similar but unrelated disorder or is a mix of focal and generalized activity typical for JME?

Response to medication. The response to sodium valproate, although generally excellent, is by no means uniform (up to 80% become seizure free), and the degree by which myoclonus is exacerbated by lamotrigine or carbamazepine depends on the individual. Although valproate is uncontroversially the treatment of choice for young men with JME, the best agent is not clear for women of child bearing age [18]. This heterogeneity in drug response to second line agents goes against the homogeneity of JME.

Unremarkable imaging. Although standard clinical magnetic resonance imaging does not reveal an abnormality on visual inspection, we can no longer say that imaging is normal in JME [19]. A range of advanced techniques including PET, structural MRI, diffusion tensor imaging (DTI), and magnetic resonance spectroscopy reveal evidence of predominantly frontal lobe and thalamic changes at the group level. Changes in microstructure connectivity in the mesial frontal region (measured using functional MRI and DTI) are postulated to be the crux for triggering motor seizures [20].

Neuronal development disorder? Some authors ask whether cortical developmental abnormalities could underpin JME [21]. Specifically, this is proposed after identifying a role for the *EFHC1* gene — a gene linked to JME phenotypes. EFHC1 is a microtubule-associated protein involved in the regulation of cell division. *EFHC1* impairment in the rat developing neocortex causes a marked disruption of radial migration, with defects in the radial glia scaffold organization and in the locomotion of post-mitotic neurons.

Benign epilepsies. Not only have cognitive deficits in JME been long established (below) but they also have been correlated with the imaging abnormalities mentioned previously. A recent DTI study of 25 people with JME (versus matched controls) demonstrated widespread disturbance of microstructural white matter integrity in the frontal lobe and corpus callosum that interconnects frontal cortices [22]. This was taken as further support of the theory of thalamofrontal network disconnection syndrome in JME.

Life-long seizures. Even the dictum that JME is a lifelong condition and that seizure recurrence should be expected following drug withdrawal has been challenged with long-term studies. For example, Delgado-Escueta and colleagues [23] noted that only 12/43 relapsed at two years following valproate withdrawal. This was corroborated by a study of 23 people (17 females) from Canada where 11 discontinued treatment, six remained seizure free, 3 had myoclonus only, and two had infrequent seizures [24]. Juvenile myoclonic epilepsy is thought to be an epilepsy syndrome with little in the way of serious complications, but the Camfield paper added further clinical heterogeneity as eight of the 23 had an episode of convulsive status epilepticus. This pattern of a varied long-term outcome was further described recently in a review of 31 people [25]. Here, only two thirds achieved true seizure freedom. Nine patients attempted to discontinue drug treatment — six of these were successful (mean duration of seizure free follow up was 19 years). This study concludes (and we would agree) that this is once more very strong evidence against the homogeneity of JME.

2.1. Are there true neuropsychological traits in JME?

If the above clinical features are variable and cannot be relied upon to identify a 'true JME', is there a role for neuropsychological or cognitive trait analysis? In Janz and Christian's seminal paper of 1957 [26], personality was a key part of the description, alongside information on the following: characteristics of minor seizures, rhythmicity, age of onset, prevalence, etiology, heredity, course, triggering factors, nosology, EEG, treatment, prognosis, differential diagnosis, pathophysiology, and constitution of the patients. From the onset, a JME personality was proposed "*characterized by unsteadiness, lack of discipline, hedonism and an indifference to their disease… most were of average intellectual ability, none was extraordinarily gifted…. They often appear self-assured and bragging, the girls and women coquettish and seducing, but can also act decidedly mistrustfully and be, timid frightened and inhibited. … Their mood changes rapidly and frequently. This makes their contact both charming and difficult. … They are easy to encourage and discourage, they are gullible and unreliable.*" Allowing for the change in use of language since 1957, this description still seems stark. Clearly, if thalamofrontal circuitry disconnection is an important feature of JME pathogenesis then the above quote could be describing executive function impairment — but the concept of an 'epileptic personality' let alone a JME personality remains highly controversial.

The GGEs have not been as aggressively investigated by psychological researchers as temporal lobe epilepsy, where surgical treatment has focused attention. The first studies into JME, which were