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Review

Implications for families of advances in understanding the genetic basis of epilepsy

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ABSTRACT

Investigations into families with a large number of individuals with epilepsy have led to the discovery of epilepsy-causing (or epilepsy associated) gene mutations. These discoveries offer advantages and insights for the patient, family, healthcare professionals and biomedical scientists. Despite these benefits, there is little evidence about the impact of participation in genetic research for families with epilepsy. Here we report on the reflections of individuals who have participated in epilepsy genetic research through the Wales Epilepsy Research Network (WERN). Undergoing genetic investigation for inherited epilepsy has extensive emotive impact, both positive and negative, on individuals and families. Recognising these impacts is imperative to researchers working with families; having implications for study design, research consent and the provision of appropriate support.

1. Introduction

Epilepsy as an inherited condition is not a new concept. Two and a half thousand years ago, Hippocrates recognised and documented the genetic basis for epilepsy.[1] "I am about to discuss the disease called "sacred". It is not, in my opinion, any more divine or more sacred than any other diseases, but has a natural cause ... Its origin, like that of other diseases, lies in heredity".[2] However, it is only recently that we have begun to identify and understand the gene mutations responsible for epilepsy onset and their biological context.[3,4] Investigations into families with a large number of individuals with epilepsy have been at the forefront of these advances in our understanding of the genetic basis of epilepsy.

2. Implications for families

Those conducting genetic investigation for inherited epilepsy have an obligation, as part of the consent process, to acknowledge the psychological risks associated with participation in genetic research.[5] Despite this requirement, there is a paucity of research describing the impact of participation in genetic research for families with epilepsy.[6] In this paper we discuss the reflections of individuals who have participated in epilepsy genetic research through the Wales Epilepsy Research Network (WERN). Areas discussed are illustrated by comments derived from a qualitative case study of one of these families. First, the members of the case family are introduced in the context of their involvement in genetic investigation and their experience of epilepsy. Individual names have been altered in all accounts of the case family that appear in this paper and quotations are verbatim.

Caroline

Caroline is deeply embarrassed by her epilepsy. She equates seizures in public to 'freak shows' for passers by. She is terrified that her children will inherit her epilepsy.

> "I think I worry more about the kids, the children, because I feel like I'm the one that's let them down"

The fear for her daughter runs the deepest as she associates seizures not just with epilepsy but with problems conceiving, problems in pregnancy and repeated miscarriages. This fear is so overwhelming she is unable to engage with her children on any level about the potential risk of them developing epilepsy.

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"She hasn't got a clue, I haven't mentioned nothing to her, nothing at all, and I wouldn't. Not yet. She hasn't got a clue"

"No, we wouldn't talk about it, I wouldn't talk about it to the children, Max hasn't got a clue, I don't talk to him at all about it, he doesn't... he's very scared"

Jack

Jack, Caroline's husband, considers it his responsibility to protect his wife from the negative experiences he witnesses when she has a seizure in public. This impacts upon every aspect of their life together. Jack will go to any lengths to help his family and to protect them from harm.

"A lot of people don't understand and a lot of people, like, we've been out together and Caroline's been bad and then someone will walk past and say, 'oh look she's pissed' and it's horrible [...], and then like, people walk past and say, 'what the bloody hell's the matter with her'"

Genetic investigation has become a double-edged sword for Jack. He understands that results may help by providing a better understanding of Caroline's epilepsy. At the same time he knows he will be unable to protect his family if results confirm his worst fears; that their children are at-risk of developing epilepsy.

Angela

Angela is taking part in genetic investigation to help Caroline; this is an extension to her role as Caroline's aunt and carer. Historically, Angela has had no epilepsy concerns for herself or for her sons. However, recognising a genetic basis for the epilepsy in her family has thrown up doubts, making her reassess the perceived risk to herself and her family.

"So there is a little thought right deep, deep in the back to think it could after this research, it has brought that to the front that, you know, if it is hereditary, perhaps it's not my time yet to get it and something's going to trigger mine off"

Margo

For Margo, also Caroline's aunt, the time between her own seizure onset and subsequent diagnosis of epilepsy was traumatic. A diagnosis of epilepsy proved a relief following this period of uncertainty, emotional turmoil, perceived medical dismissal and questioning of her mental health. Margo is determined that future generations of her family should not suffer the same fate. Taking part in genetic investigation has been a great relief for Margo. There is comfort that her family history is finally being taken seriously and investigated.

"As I said, it wasn't just giving a blood test because we realised that there was going to be a follow-up, and it was relief in a way to think that somebody is interested and somebody could perhaps try and find the reason for it in the family"

Joanna

Joanna, Margo's daughter, is appalled by her experience of the circumstances surrounding her mum's diagnosis of epilepsy. She takes comfort in the genetic investigation because she views it as a way of preventing other family members being treated in the same way.

"Dreadful, it was absolutely horrific for her and ... it shouldn't have been. It's bad enough having epilepsy anyway you know, and seeing her and seeing the way she was and having to transfer her from one hospital to another because they wouldn't treat her for it ... it was, you know we look back on it now and it was dreadful and I don't want that for anybody"

The investigation will document a genetic basis for the epilepsy in her family which can be used as evidence in all future interactions with healthcare professionals.

Pam

Pam, Caroline's half-aunt, entered the investigative process expecting nothing from it. She was willing to help the wider family while feeling personally removed from the process and from her family.

"I've always felt a little bit like a cuckoo in the nest"

She believes her epilepsy is in the past, and has a different cause to that of other family members. Genetic investigation has led her to reconsider this belief.

The reflections of these individuals provide valuable insights into the implications for families of involvement in genetic epilepsy research. These reflections are discussed below.

2.1. "It puts everything in focus" (Caroline)

Genetic investigation can be considered a magnifying glass, with each contact with the research team bringing existing worries and concerns to the forefront. This does cause worry and anxiety, but is described as acceptable by those involved in the research. Genetic investigation puts the spotlight on concerns about the epilepsy risk to future generations, thoughts and preoccupations about epilepsy, and the reality of an individual's circumstance and experience of epilepsy. This focus on an individual's reality is important because for some individuals with epilepsy, the way they feel is overwhelmingly governed by the fact that epilepsy is something which is socially very difficult and awkward.

"You're obviously going to feel embarrassed, there's no person out there that got it that doesn't feel embarrassed" (Caroline)

2.2. "We've had a fabulous life together, but the epilepsy has impacted a lot on that" (Jack)

The impact of undergoing genetic investigation ripples beyond the 'genetic family'. For partners of those undergoing genetic investigation the process has the potential to have significant impact, both immediate and long term. There is an immediate impact as the investigation process brings into focus their existing worries and concerns, magnifying the reality of living in the shadow of a stigmatising condition. There is then a potential long term impact because the process of genetic investigation may reveal information about the risk of their children, grandchildren and future generations developing epilepsy.

"If I had ten thousand pound and I had to give it to guarantee that I would, I would sign this house over, I would give it just to guarantee that they wouldn't have it" (Jack)

2.3. "It sort of sharpened our thirst for knowledge about everything" (Jack)

Genetic investigation can spark a heightened need for knowledge about everything to do with epilepsy, not necessarily limited to a potential genetic aetiology.

> "Well ... the what's? the ifs? the whys? What is it, why me, that's most of it. Like people ... it's just ... everybody wants answers to it, is it going to go away? Go away leave us alone" (Caroline)

This may include re-examining triggers, looking for new patterns of seizures or asking to be re-referred to a specialist. It may provoke an interest in attending support groups or knowing more from epilepsy charities.

2.4. "Perhaps it's not my time yet to get it" (Angela)

Taking part in genetic investigation for inherited epilepsy has the potential to make people reassess their own risk of developing epilepsy, people who may have previously decided that they had escaped the family illness.

> "So there is a little thought right deep, deep in the back [...], if it is hereditary, perhaps it's not my time yet to get it and something's going to trigger mine off"(Angela)

This may be because, as described above, taking part in genetic investigation magnifies thoughts and preoccupations about epilepsy, or because participants have come to realise the likelihood that the epilepsy in their family is hereditary.

2.5. "A quicker diagnosis, quicker medication" (Margo)

Involvement in genetic investigation brings with it an expectation for future generations of the family. The expectation is that confirmation of a genetic basis for their epilepsy will help future family members receive a quicker diagnosis, benefiting from appropriate treatment sooner.

> Its not going to help me, it's not going to help my mother but it's going to help my daughter and my granddaughter and her family and that's quite a relief" (Margo)

2.6. "It does look more hereditary now doesn't it" (Angela)

Inviting a family to take part in genetic investigation will have consequences. In issuing such an invitation the family are immediately receiving an acknowledgment that the epilepsy in their family is likely to have a genetic basis. This can have both positive and negative consequences. This acknowledgment can support those family members who already strongly hold this belief, but for years have felt that this has been ignored or dismissed by health professionals.

> "I don't want them dismissing it - I want them to say, 'look epilepsy in the family is being looked into, they've found a connection in the blood'. Listen to me, that's what I want" (Joanna)

At the same time, this acknowledgment has the potential to cause distress; reinforcing that their explicit fears about loved-ones developing epilepsy, especially younger generations, could be well founded.

2.7. "I didn't realise how many of you had it" (Margo)

The process of undergoing genetic investigation for inherited epilepsy can be seen as putting together a jigsaw puzzle. At the start of the process, information about how epilepsy affects individual members is fragmented across the whole family. Each family member or family unit has their own knowledge. Genetic investigation is a way of bringing all of the information together. One consequence of providing the family with a better understanding of the epilepsy is that genetic investigation can shift the focus and concern away from individual cases to an appreciation that the impact is a holistic family issue. The assembly of the jigsaw puzzle pieces can also highlight the number of people in the family with epilepsy. This knowledge may have significant consequences for family members who are currently removed and distant from the family. It has the potential to provide them with a new identity, as part of an 'epilepsy family'.

> "I think it's worried them a bit because you know as I said it has brought it home to them that this is close to home" (Margo)

2.8. "It hasn't affected the relationship at all with anybody, no" (Jack)

Little attention has been given to what impact genetic investigation for epilepsy may have on intra-family dynamics, the exception being Shostak and Ottman, who consider that "identifying genetic aetiologies for epilepsy may have consequences for familial relations".[7] Importantly, genetic investigation can have a positive impact upon intra-family dynamics. The most noticeable effect is that genetic investigation initiates discussion between partners, family members with epilepsy, parents and children, and family members more generally.

> "But it keeps a line open, you know, that otherwise I think even that line would close because of that bit, that line might close down. So it keeps a line open that we can keep in contact about something" (Margo)

However, experience demonstrates that involvement in genetic investigation can and does have negative consequences for some families. The following e-mail was received following one family's recruitment into the WERN family study (Fig. 1).

3. Implications for researchers

3.1. "When it's your own home, it is much better" (Margo)

Home visits are considered essential in the genetic investigation of inherited epilepsy for a number of reasons. They allow people to relax and help alleviate nerves, giving family members time to consider their responses. Home visits also reduce the burden on participant's time, and ensure that everyone feels equally involved in the process.

> "Yes, if you think that my conversation, my participation is important or of any importance then that's fine but I probably wouldn't think that it would be if I had to go to you, I would probably think, 'oh they're only doing that because my name is on the family list, you don't really want to speak to me'" (Angela)

I'm sorry I haven't got back to you earlier but the research has caused some fuss in my family. [...].

One of my sisters ( ) is objecting to me revealing family information but believe me this is no surprise to me as she objects to most things I do. She is married to a specialist and likes to be in control. She has been given information about your research and may contact you privately. Because of her reaction I should be grateful if you would not reveal my conversation with you should she make contact. I'm not sure what you wish to do with information about my Mother and Grandmother. My sister and I are sure she told us. Because of my mothers frailty at present I have not told her that I have spoken with you about what she said because it would cause too much distress.

I'm really sorry about all this. My family can be a blessing and a trial at times but I would like to stay out of trouble with them. I wonder if I would have all this fuss if I had been discussing asthma in my family. I suspect not! There is still such a stigma about epilepsy even within a family with medical professionals in it. Hope I haven't frightened you off.

Fig. 1. E-mail discussing the impact upon intra-family dynamics as a consequence of undergoing genetic investigation for inherited epilepsy (reproduced with permission).

3.2. "At the moment other families are just numbers, they don't exist" (Margo)

Some individuals may benefit from hearing about the experiences of, and having an opportunity to meet other families with epilepsy.

> "Yes, especially if you had an evening that they could meet in neutral surroundings, just a very casual evening that you could talk to each other casually and just discuss things with different families and just have a talk to them and perhaps relax with them, just find out how they are feeling, it would be interesting" (Margo)

The relationship a research team develops with a family during genetic investigation would allow them to arrange meetings between suitable families, using the investigator's institution as a safe contact point. Alternatively it may be that improved links with local epilepsy support groups would be a more appropriate means of offering families access to peer-support.

4. Methods

This paper has reported on the implications of genetic investigation for individuals, family and intra-family dynamics. To describe how this information was collected, the final section defines the data capture and analysis methods. Case study methodology was adopted,[8,9] underpinned by qualitative methods. Eight family members from the case family gave their consent to take part in multiple, extended interviews, discussing their experience of undergoing genetic investigation for inherited epilepsy. Textual data were analysed using Summative Analysis, an innovative qualitative research method which employs group work activities to develop a very clear interpretation of the data.[10]

5. Conclusion

The identification of genetic factors in the epilepsies has the potential to improve the quality of life of people in families affected by epilepsy, offering new means of diagnosing, preventing, controlling and even curing epilepsy.[5,7] It can be argued that identifying a gene mutation in a person with epilepsy will not currently alter their disease outcome. However, knowledge that a gene mutation is responsible for the epilepsy can offer relief to individuals and their family. Uncertainty about whether their epilepsy is a result of something they did, or failed to do, leads many individuals to seek the underlying reason for their epilepsy.

While the inheritance of epilepsy is a very complicated issue, this knowledge can provide some relief, as it offers proof that the epilepsy is not their fault. Identification of a gene mutation also makes available all accumulated knowledge about the condition. Without that knowledge, it is often difficult, or impossible, to establish a likely prognosis, resulting in unanswered questions. Identifying a gene mutation provides the individual not only with a cause, but also with answers. Even when faced with a diagnosis for which there is no immediate answer or cure, we would emphasise that knowledge is almost always preferable to uncertainty.

Genetic testing, made available through progress in human genetic research, may also lead to an earlier diagnosis for a person with epilepsy and their family.[5] Molecular diagnosis in symptomatic individuals is already available for several of the epilepsies. In some epilepsies, early control of seizures might limit cognitive decline; therefore, early confirmation of diagnosis by genetic testing can be helpful.[11] Genetic testing may also be used for family planning, including the prediction of risk to future children and predictive testing in presymptomatic individuals. However, these pose ethical questions which need to be addressed before being introduced into clinical practice.

Consequently, if at present the definite health advantages of being a research participant in a genetic project are mixed—it is important to measure what impact family involvement has on individuals and their families. Even under the mini-revolution of genome-wide association studies and next generation sequencing, families are still essential and are being recruited to help us understand more about hereditary conditions. Epilepsy is different from many chronic conditions with greater perceived stigma and social exclusions than other disorders, but the principles described in this report could be transferable to other health challenges and their impact on families consented into research.

Conflict of interest statement

Dr. Carrie Hammond received a post-graduate bursary from Epilepsy Action in support of her Ph.D. studies.

All other authors: No conflicts declared.

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References

1. Turnbull J, Lohi H, Kearney JA, Rouleau GA, Delgado-Escueta AV, Meisler MH, et al. Sacred disease secrets revealed: the genetics of human epilepsy. *Hum Mol Genet* 2005;**14**(17):2491–500.
2. Riggs AJ, Riggs JE. Epilepsy's role in the historical differentiation of religion, magic, and science. *Epilepsia* 2005;**46**(3):452–3.
3. Helbig I, Scheffer IE, Mulley JC, Berkovic SF. Navigating the channels and beyond: unravelling the genetics of the epilepsies. *Lancet Neurol* 2008;**7**(3): 231–45.
4. Rees MI. Advances in understanding the genetic basis of epilepsy. *Seizure*; this issue.
5. Godard B, Cardinal G. Ethical implications in genetic counseling and family studies of the epilepsies. *Epilepsy Behav* 2004;**5**(5):621–6.
6. Pal DK, Pong AW, Chung WK. Genetic evaluation and counseling for epilepsy. *Nat Rev Neurol* 2010;**6**(8):445–53.
7. Shostak S, Ottman R. Ethical, legal, and social dimensions of epilepsy genetics. *Epilepsia* 2006;**47**(10):1595–602.
8. Stake RE. *The art of case study research*. Sage Publications; 1995.
9. Yin RK, *Case Study Research; Design and Methods*, third ed., Thousand Oaks, California, Sage Publication, 2003.
10. Rapport F, Summative Analysis:. A new qualitative research method. *Int J Qual Methods* 2010;**9**(3):270–90.
11. Gourfinkel-An I, Baulac S, Nabbout R, Ruberg M, Baulac M, Brice A, et al. Monogenic idiopathic epilepsies. *Lancet Neurol* 2004;**3**(4):209–18.