J Genet Counsel (2008) 17:261–273
DOI 10.1007/s10897-007-9145-9

ORIGINAL RESEARCH

Impact of a Genetic Diagnosis of a Mitochondrial Disorder 5–17 Years After the Death of an Affected Child

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Received: 18 September 2007 / Accepted: 5 December 2007 / Published online: 12 February 2008

Abstract This study used in-depth interviews to explore the experiences of parents who were re-contacted with new genetic results many years after the death of a child with a mitochondrial disorder. At the time of their child's illness, parents had consented to a tissue sample being taken to help with diagnosis of a suspected mitochondrial disorder, and subsequently further DNA testing identified the genetic cause. Parents did not express negative feelings about being re-contacted with new information, and hoped that continuing research might help other families. Positive aspects included relief from feelings of guilt over the cause of the child's disorder, and having accurate genetic information available for surviving children. Difficult emotional and psychosocial implications included contradictions to previous beliefs about inheritance, deciding how and when to communicate information to surviving children, and coping with new fears for the mother's health if a gene located in the mitochondrial DNA was identified. In half of the families the new results significantly altered the parents' understanding of the inheritance pattern. This study highlights the impact of new genetic information offered after a delay of several years, which has the potential to re-open feelings of grief and uncertainty and can present a new inheritance scenario for which research participants or their families are unprepared. Health professionals involved in conveying genetic research results can help to support families through this process.

Keywords Mitochondrial · Genetic counseling · Re-contact · Narrative · Delayed diagnosis

Names used in the manuscript are pseudonyms.

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Introduction

Continuing research on stored tissue or DNA that could potentially result in a genetic diagnosis has raised recent ethical debate about returning genetic research results to participants (Knoppers *et al.* 2006; Ravitsky and Wilfond 2006). Ethical dilemmas arise around issues such as whether there is a duty to recontact participants, taking into account principles of autonomy, the 'right not to know', potential benefits versus harms, and the clinical significance of the results. If there is an obligation to recontact research participants, then dilemmas arise about how and when this should be done. The complexity of the situation is further increased when the participant dies before the research results are completed, and even more so when the results pertain to a paediatric patient. Guidelines in this area are lacking. Despite the theoretical debate, there have been few reports on the impact of genetic research

results from the perspective of participants and their families. Possible harms include increased anxiety and stress, guilt or regret about past decisions, intrusion of privacy, strain on family relationships, and concerns regarding health and life insurance. Alternately, potential benefits include improved health care through follow-up, more accurate risk information, reduced uncertainty, greater hope for the future, and resolution of emotional burdens such as guilt (Fitzpatrick *et al.* 1999; Hunter *et al.* 2001). A recent study by Ormondroyd *et al.* (2007) investigated the impact on relatives who received results of *BRCA2* mutation testing pertaining to a deceased adult male relative. Receiving genetic results led to increased anxiety and distress for some relatives, while others perceived benefits in the availability of cancer surveillance programs. To our knowledge there are no qualitative analyses in the literature on the impact of receiving genetic results many years after the death of a child, and this is the focus our study.

Mitochondrial disorders of infancy are an important situation where genetic diagnoses are often made through on-going research, sometimes many years after the death of an affected child. These disorders affecting children are incurable, neurodegenerative diseases caused by defects in energy production (oxidative phosphorylation) which occurs in the mitochondria, small compartments within each cell of the body. Mitochondrial function is controlled by many nuclear genes, inherited from mother and father, and also by genes on DNA located only in mitochondria (mtDNA), inherited through the mitochondria of the egg (maternal inheritance). Thus, a disorder such as Leigh syndrome could be caused by a mutation in one of many different genes and so has more than one possible inheritance pattern. The estimated prevalence of all mitochondrial disorders is up to 1 in 5000 births (Skladal *et al.* 2003). The initial diagnosis can be difficult, requiring many enzymatic, biochemical and neurological tests (Bernier *et al.* 2002; Thorburn *et al.* 2004). Furthermore, in over 50% of suspected cases mutational analysis is not successful in identifying a causal gene, as more than 50 nuclear and 30 mitochondrial (mtDNA) genes are known to cause oxidative phosphorylation defects. Many of these genes have only been discovered in the last 10 years (Fig. 1) and it is estimated that future research will identify at least 30 additional genes (Thorburn 2004). The first autosomal recessive mutation causing Leigh syndrome was found as recently as 1995 (Bourgeron *et al.* 1995) and there are currently 11 genes associated with autosomal recessive Leigh syndrome, 11 mitochondrial DNA genes and one X-linked gene (Thorburn and Rahman 2006). Clinical diagnosis and genetic inheritance of Alpers syndrome was very unclear until the 1990s, and mutations in the *POLG* gene were only identified in 2004 (Harding 1990; Naviaux and Nguyen 2004). A timeline of the major changes in knowledge about two mitochondrial diseases, Leigh syndrome and Alpers syndrome is shown in Fig. 2.

The identification of a mutation therefore has potential clinical relevance by enabling more accurate genetic counseling for risk estimates, by providing the ability to offer genetic testing to at-risk relatives, and by providing specific information on reproductive options (Brown *et al.* 2006; Thorburn and Dahl 2001). The Mitochondrial Diagnostic Group at Victorian Clinical Genetics Services (VCGS) Pathology acts as the main Australasian referral centre for children with suspected mitochondrial disease. The centre has diagnosed nearly 400 children with mitochondrial disease and pathogenic mutations were identified in children from 127 families. In 54 of these families, the child (or children) had died prior to the molecular diagnosis. Currently, genetic research is performed as an extended part of the diagnostic process on stored samples.

When many years have elapsed since the death of a child, sometimes this information is no longer clinically beneficial to parents in terms of health and genetics, although there may be psychological benefits to knowing the genetic cause of the illness. For autosomal recessive inheritance, there are no known health risks to carriers, and reproductive information may not be relevant if the couple are not planning to have more children, although in consanguineous families there may still be other family members at risk. The discovery of a mtDNA mutation may have clinical relevance to the health

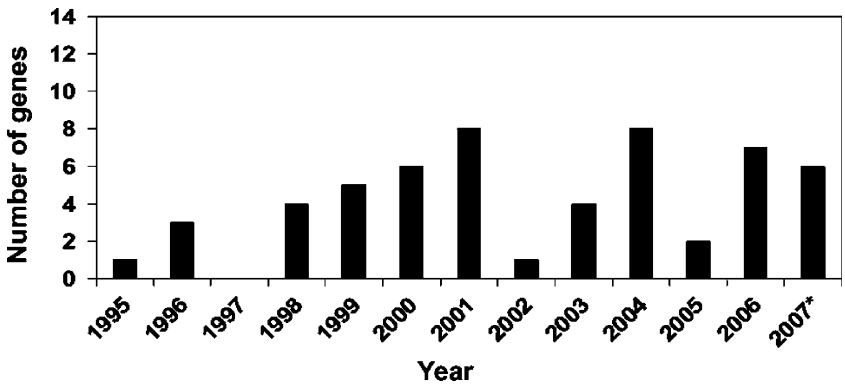

Fig. 1 Annual numbers of novel nuclear oxidative phosphorylation "disease" genes reported between 1995 and mid-2007

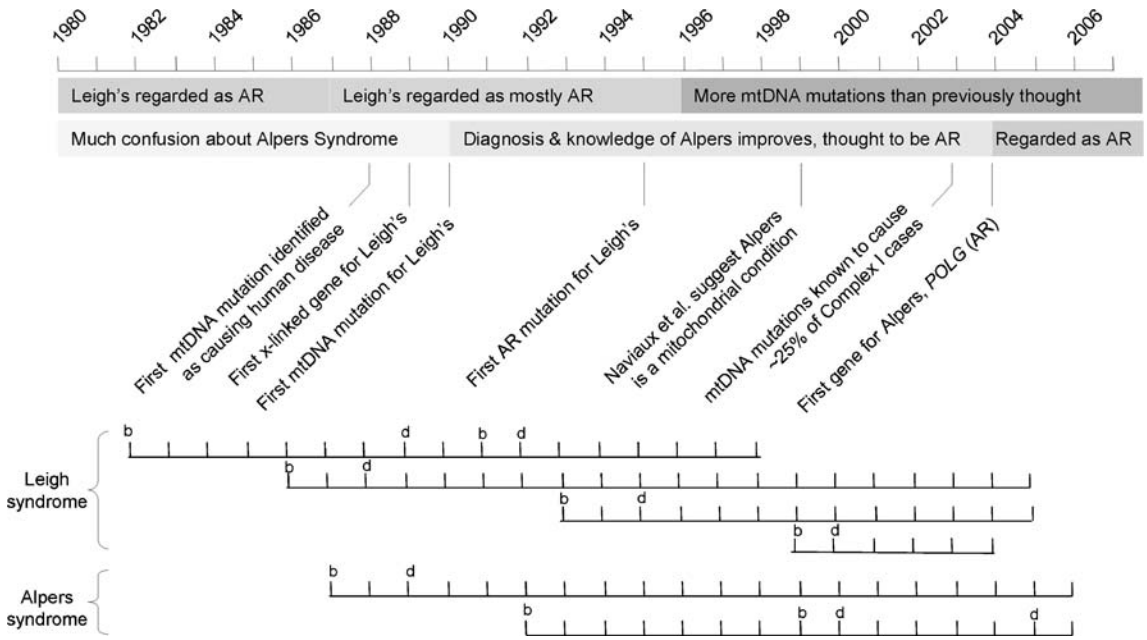

Fig. 2 Changes in knowledge of the genetic basis of Leigh syndrome and Alpers syndrome from 1980 to the present. *Lines below* represent families participating in this study, spanning from the birth of the first child in the family who developed Leigh syndrome or Alpers syndrome to the re-contact about research results identifying the causal gene. *AR* autosomal recessive, *b* birth, *d* death, *Leigh's* Leigh syndrome, *Alpers* Alpers syndrome

of mothers of affected children, but the risk of developing symptoms, such as eye problems or migraine headaches, and the severity of the symptoms are uncertain. This uncertainty is because symptoms depend on the number of mitochondria carrying the mtDNA mutation in different tissues, which can be highly variable. In some families although the genetic diagnosis may not be relevant to the health and reproductive options of parents, it may be relevant to surviving siblings or other at-risk family members. The aim of this study was to learn of the experiences and opinions of families who were re-contacted with new genetic results years after the death of an affected child. In-depth (open-ended) interviews were conducted to gain a qualitative understanding of the impact of a delayed genetic diagnosis from the perspective of bereaved parents. Narrative analysis was used, aiming to understand each storied account of experiences as a whole within the context of time and the world-view of each participant, and to identify important events and relationships influencing the outcomes and meanings from participants' perspectives.

Materials and Methods

Background Information on Re-contacting Parents to Offer New Genetic Results

Parents had originally consented to the samples being taken from their child for diagnosis of a suspected mitochondrial disorder. They were informed that this may involve multiple tests including enzyme, biochemical and genetic studies. If mutation testing was available at the time, they were told that when the initial genetic testing did not find a mutation, then further testing might be done in the future, depending on new advances in knowledge and laboratory techniques. However, for some families, at the time when these samples were obtained, no genes had been identified, and therefore they may have remained unaware that genetic testing might be conducted in future, raising the question of informed consent. However, after careful consideration by researchers and the hospital's Human Research Ethics Committee, the research was viewed as a continuation of the originally consented diagnostic process. The decision was not to seek renewed consent, in light of the potential psychological harms of contacting parents before any new information became available, as there would be no guarantee that results would be obtained or how long the research would take. Re-contact with parents had only been sought after a genetic diagnosis was confirmed. Parents were contacted via a telephone call from a physician experienced in consulting families about mitochondrial diseases, and were offered a clinic appointment to discuss the new genetic information. In some cases where the families had not had contact with hospital staff for many years, or due to subsequent marriages and changed surnames, tracing parents to a current address has been unsuccessful. Of ten Victoria and Tasmanian families for whom adequate records of re-contact were available, one

family declined, explaining that they did not wish to re-open those issues. It is unclear how many of the remaining 44 families were re-contacted with new results for the following reasons: records were incomplete or not found; genetic file was available but there was no record of contact about genetic results (contact may have occurred many years ago, or via a clinician not directly associated with the genetic service); it appeared that a general practitioner gave the family the genetic diagnosis (one family); records indicated that the parents' address for re-contact could not be found; and 30 families lived outside the states of Victoria and Tasmania.

Identifying Participants for Interviews About Experiences of Receiving Genetic Results

For this study, we then approached parents who had received new genetic information after a delay of 2 years or more since their child's death. Additional criteria for the interview study were documented contact with the genetic service within the last 10 years, and English speaking and reading sufficient to enable fully informed consent. All participants were over the age of 18 years. Records of re-contact were available for ten families living in Victoria and Tasmania, Australia, where the parents were potentially available for interview. Eight families met the criteria and parents were approached via a cover letter from an expert clinician introducing a letter from the researchers about the interview-based study and providing researcher contact details for willing participants.

Interviews

Parents participated in in-depth interviews of between 35 min and 2 h, conducted by a researcher (AS) who is independent of the clinical genetics team. The interviews involved open-ended questions and prompts about how parents felt about the initial clinical diagnosis of the disorder, the impact of receiving the genetic information after many years, and whether or not the information was useful to themselves and/or their families. Interviews were held at a venue of the participants' choice. Couples were interviewed together. Prior to and following each interview, participants were given the details of how to contact the researcher or either of two genetic counselors independent of the research team, should any questions or issues arise following participation in the study. Participants were offered a summary of results to be sent by mail at the conclusion of the study. Interviews were audio-taped and transcribed verbatim.

Narrative Analysis

Transcribed interview data were analyzed using narrative analysis facilitated by use of *NVIVO* software (NVivo qualitative data analysis software 2006). A hermeneutic approach was used, which aims to understand storied accounts of experiences from the perspective of the participant, and how these stories are influenced by pre-existing interpretations and the changing world-view of that person (Gilbert 2002; Liamputtong and Ezzy 2005). These stories, or narratives, are analyzed by searching for plot lines, turning points or important relationships or interactions within each story. Narrative analysis has advantages when compared to thematic analysis, as it views participants' stories as a whole, avoiding fragmentation, and retaining context by providing coherence over time. This fine-detail in-depth analysis style is suited to small numbers of participants as it does not attempt to define general rules or trends, but rather serves to identify important aspects or events that influenced the narratives (Liamputtong and Ezzy 2005). Narrative analysis is particularly relevant to counseling research due to its focus on individual experiences and meaning-making processes. It does not focus on whether remembered events described in the narrative account are completely accurate, but seeks to uncover the responses and meanings of life events experienced by people, from their own perspective. To minimize issues of validity, such as reluctance to reveal extra levels of complexity and meanings in the stories, the effect of the interviewer on the participant's responses, and the filtering of descriptions to project a more positive self-image, it is the role of the interviewer to adopt an open and unobtrusive, non-judgmental manner, to actively listen with prompts to encourage further reflection or exploration of events and meanings, and to ensure that the narrative reflects the participant's own voice with minimal influence from the interviewer (Polkinghorne 2007).

Each interview was analyzed in detail by coding each transcript to obtain a list of topics and narrative sections, based on important periods of time, events or interactions in the stories. Coding analysis was repeated independently by three researchers to ensure validity and consistency of the interpretations. After all interviews had been individually analyzed, topics were re-analyzed from the perspective of organizing sub-topics into overall groupings. To obtain an overview of each participant's experiences, summary narratives were reconstructed, using participants' original words where possible, to put events in chronological order, including the main feelings or meaning that the participants described for each event or period of time. Participant quotes were carefully selected to provide a balanced contextual representation of the data and to illustrate the major findings of the study. As narrative analysis aims to avoid fragmentation of the data, lengthy quotes are sometimes necessary. All names were replaced with pseudonyms.

Results

Nine parents from six families responded, were contacted by telephone and were mailed full information on the study. Subsequently they all (three couples and three mothers) agreed to participate. No response was received from the remaining two families. Two mothers chose to meet the researcher at a hospital, one couple at the male partner's workplace, and the others at their homes. In these families, the time between death of the first affected child in each family and the genetic diagnosis was 5–17 years. To protect parents' privacy, specific dates and times are not provided for individual families. At the time of the interview, participants were aged between 28 and 58 years old, and all had surviving children, aged between four and 35 years. The mitochondrial disorders affecting children who had died were Leigh syndrome (four families) and Alpers syndrome (two families). Children in these families died aged between 6 months and 7 years old. In two families there were two siblings affected by the same illness. Narrative analysis revealed three main phases in parents' experiences: (1) experiences leading up to the initial diagnosis of the disorder, (2) coping with their child's illness and dealing with loss and grief in the family, and (3) experiences of receiving new genetic information several or many years later; here we focus on the impact of receiving genetic information years after the death of an affected child.

Opinions About Being Re-contacted with Research Results

None of the parents interviewed objected to being re-contacted with the offer of new information, even when this was unexpected and many years had passed since the death of their child. One mother who was contacted more than 15 years after her daughter's death felt that if the re-contact had been initiated via a letter, she may not have responded, preferring a phone call so that she could speak to the clinician. All parents in this study were pleased that research was continuing on the mitochondrial disorder, as they hoped it would help other children. Colin and Debbie wanted to help research, and provided blood samples after being contacted about the new results. When asked if they objected to being re-contacted, Colin explained:

> …as I said, we don't mind. I mean if it helps somebody one day down the track—that's why we let them take a piece of Sam's leg.

Several parents had in fact been seeking further information on research findings in the intervening years, and had contacted genetic services themselves. Gina said:

> I found [Researcher's] email, and I actually emailed to him and asked him about it, because we hadn't heard anything back, and I knew that they—, we'd been told that they had the material and they'd continue to do tests. So I actually, […] initiated that and just expressed interest in knowing if they did find out. So in that sense I wasn't surprised. Oh he responded immediately as well, saying we're continuing to […] revisit and learning more. And, and then, oh I don't know how long, it was a couple years later [that I got the results]…so in that sense it wasn't surprising, because I had already made that contact.

Leanne spoke of her need to know further information before having more children:

> About two years after he died, I was desperate for another one and I wrote him [clinician] a letter saying 'is there anything you can tell us' and that's when they came up with, you know, we went down to the Children's [Hospital] and spoke to him and a couple of others, and […] that's when they told us that [the gene had been found]…
>
> Later she also said "I personally would like to [have had more contact/news from the hospital] because like I said his tests were still going three years after. I guess, even if they had of done it on a yearly basis, just written a letter saying 'we're still testing, no results yet'… that sort of stuff. I mean, even today, it'd be nice — I don't know if they're still testing, or not, I have no idea, and would love to know if they are. If they are, fine, we don't have a problem with it. […] If it's helping them in their research, and that sort of stuff. I personally would like that."

For Patricia, more than 15 years had passed since her last contact with the hospital, and she had since changed her surname. The genetic service had tried unsuccessfully to contact her with new results. Then she telephoned the hospital on an unrelated matter, and at the same time decided to ask if there was any more information on the mitochondrial disorder. When asked whether she would have minded being contacted if that had been possible, she said:

> Absolutely. Look, to me, she died, she was beautiful, there was nothing anyone could do, there was nothing I could do, and if having her tissue, or whatever they had of hers was going to help one child be diagnosed quicker than what she was…You know, to save the parents that terrible anguish of not knowing, or to, you know, to find out more about it, I was happy for that to happen. Yep. And see, it's come back as a blessing to me anyway, because now [my son] has been tested, so we know where he's at, and that's another great thing.

Thus for some families, the letter or call offering new genetic results was the first re-contact with the hospital and

genetic service since the death of their child, and came as a surprise, although none of the families described this surprise as undesirable. Other families, who had re-initiated contact in the hope of finding more information, may have been more aware that research was occurring, and were pleased to be offered new results.

However, two families described finding it emotionally difficult to return to the hospital for the appointment about the new results. Most families had spent weeks or months on end in hospital at the time of their child's illness, and had vivid memories associated with their child being critically ill, enduring many tests while waiting to find out what was wrong and the shock of diagnosis of a fatal illness. In several cases, parents had experienced poor staff attitudes and care towards their severely disabled child. Leanne said:

> It was hard for us, the first time we went down to the Children's [Hospital] because we hadn't been back since he'd died. So for us it was hard in that aspect. But […] my recollection of the actual, of the meeting […] was really quite good. […] Yeah and I think that's what made it harder for us because it was such a long drive, and we had time to dwell on things going home.

Although a meeting with health professionals to learn of the new results was desired, this was accompanied by difficult emotions associated with returning to the hospital for the first time since their child's death.

Responses to New Genetic Research Results After a Delay of Many Years Since the Death of an Affected Child

Parents' reactions to the new genetic information appeared to depend on their previous understanding and beliefs about the inheritance of the disorder, and the perceived relevance of the information to themselves and their family. When the information did not change parents' existing knowledge about the inheritance pattern, some parents attributed little importance to knowing the specific gene change in their family. Colin and Debbie had limited recollection of what the new genetic information was about, and had responded to the re-contact with the main aim of helping research. The new results did not have a big impact for Sarah, who never believed that she carried a gene change, confirmed by testing after discovery of the gene change in her daughter, but she was pleased that research was continuing:

> I talked to my sisters and my friends. I told them that they still have Anna's blood and Anna's skin, so part of Anna is still here, and that they're still doing research and I'm happy about it. I didn't want them to take any skin when she was alive. Because I didn't want her to get, to get hurt. That's the only reason. But they took some when she passed away, and […] I'm happy that they are still doing research. I hope that from that they will find a cure for the other kids. I hope, I really hope.

Patricia saw the new information as helpful for her son and for other families, although details about the particular gene did not have a high impact for her:

> Patricia: "It's great to know that they've found the gene, but for me it was more important to know that, you know, [my son] could be checked, perhaps like myself or [his father], so that […] that might help towards research. I mean, they were my primary interests, certainly not interested in POLG gene! [laughs]"
>
> Interviewer: "Would you say that there were any negatives in finding out about the gene change, or for you?"
>
> Patricia: "No negatives, no. It's all positive, good"

In other families, the new genetic results changed previous beliefs about the mitochondrial disorder, and thus the impact on parents was significant. For Leanne and Robert, who had believed that the disorder was most probably maternally inherited, the new information provided psychological benefits. Leanne talked about how the discovery of an autosomal recessive gene change relieved some of the self-blame she had been struggling with:

> I guess because I always blamed myself in the beginning. I guess once we got more information and found out […] well for me it was a huge relief.

Discovery of a mtDNA mutation may not only be a shock if the family previously believed it to be an autosomal recessive disorder, based on the information provided at the time that the child was initially diagnosed, but can also create fears that the mother's own health may be affected in the future. Two families believed the disorder was autosomal recessive, discovering 9 or 10 years later that the causal mutation was identified in mitochondrial DNA and was therefore maternally inherited. This was difficult for mothers Gina and Hannah to come to terms with, after many years believing that the disorder was inherited from both parents, and they experienced feelings of guilt. Gina's words highlight this:

> You feel responsible for everything that goes wrong and every bunion that appears, or every other genetic sort of weakness that might show up [laughs]. Without it being something as terrible as Leigh syndrome […] I mean I have heard of relationships where [...] parents have blamed each other, or, or maybe one in particular has blamed the other. And being told early on that it was autosomal recessive perhaps helped [small laugh], perhaps helped to avoid that. […] Yeah well we both had a hand, it's coming from both sides so we both

> equally…yeah there's no way round it. But then finding out, oh it is actually all me, that's …[pause] […] And then it's not known, was it my mother? Was it my grandmother? Did it start with me? You know, is there something in my life that I have done wrong and yes other of those questions that go on, obviously, it's not something that's gone wrong during conception because it's been found in me, so, you know, is there something that I have done? […] And they said "No" to that, […] but I still don't know. I don't know whether I can believe it or…I don't know. It's possibly an irrational thing. But there's that sense that there's always that question "maybe it was me".

For these mothers the new genetic information required a reassessment of health beliefs, and adjusting to further uncertainty about their own health and whether their daughters may be affected in future. Hannah had already altered her health practices after the diagnosis of her first son, changing the family's diet to try to avoid food allergies, and taking vitamin supplements. Finding out that the disorder was caused by a mitochondrial gene led to concerns about her future health:

> Yes it might affect Kylie as well. Yeah, so, I would, I would definitely like, you know, to be informed, although it was a bit of a shock, to find out that it only comes through the mother and not through the father, and that I might have symptoms. Remember they said to me if you, you know, have any unusual symptoms like anything to do with the eyes, it could be related.

Both Hannah and Gina had fears about whether there would be an impact on their daughters, although they both maintained that despite the difficult implications of the new findings, they would rather know the information than not. Gina said:

> …what I thought had been laid to rest, at least in that department, has been reopened, by further knowledge. […] Yeah, which is important to have, but difficult to deal with.

Usefulness of the Genetic Information to Families

Information about a specific gene change for a mitochondrial disorder was useful to families in various ways, depending on whether the parents were thinking of having more children, the ages of surviving children, and the parents' understanding of the genetic information in relation to testing options and the implications for other family members. When the genetic diagnosis was identified at a stage when parents were considering having more children, the new information provided much more accurate risk figures for future pregnancies, and options for prenatal testing. However for mtDNA mutations, prenatal diagnosis and risk figures are still difficult to predict (Brown *et al.* 2006). When Leanne and Robert found out that testing was now possible, Leanne was pregnant and the option of having a CVS (chorionic villus sampling) test was unexpected, requiring a quick decision due to time constraints of performing the test. Leanne said:

> We don't feel that we were prepared for it properly, and that's really our own fault because we said "yes go ahead and test".[..] We would have waited a week just to get our head around the fact that there was testing and what the test involved.

Other parents, who were not planning to have more children, described how knowledge of the specific gene change in their family would have been an important factor in past decisions, had it been available at the time. This emphasizes the high potential importance of research aimed at finding these gene changes. One couple considered the possibility of using IVF with donor eggs, before finding out whether it was an autosomal recessive or maternally inherited gene. This would not have been necessary if the gene change had been found to be autosomal recessive, as donor sperm or prenatal testing would have been alternative options. Another participant was pregnant when her young daughter became seriously ill, and sadly, they had a second child with the same disorder. It took many months for their daughters' illness to be diagnosed, and the father said that if they had known that it was a fatal illness, they would have considered terminating the second pregnancy. Another mother, Patricia, talked about the options for genetic counseling and testing that were unavailable to her but now will potentially benefit the next generation following the discovery of a family-specific gene change:

> Oh for [my son] it's just great. And I mean, I know his chances of having a child with [this mitochondrial disorder] are as much as mine were. It's 1 in 100,000, so the chances of it happening are very slim. But it did happen, to me. You know, and it does happen, so um…there was no form of coun[seling], of anything, when I had Rebecca. It was, no we couldn't be tested beforehand, we couldn't be tested while in vitro, there was just nothing. So at least now we've got all those, all that knowledge, for him. Which is wonderful yeah,

Discovering the specific gene change in the family sometimes raised the issue of when and how to inform other family members. Often the gene mutation information was relevant to the health and reproductive risks and options for sibling of affected children. Parents were concerned about the timing of telling their children about

genetic information, and the balance between not causing them too much worry versus the responsibility of letting them know. Sarah said:

> "I didn't want my daughter to know because she was pregnant. I told the other daughter what we are going to do [find out about the new results]."…Later she told her first daughter: "I mean she told me, it's in the back of her mind all the time. That can happen to anyone. Which I hope it doesn't, but who can, […]. And then I told her that I am not a carrier so my kids are not carriers."

Gina was able to tell her son that he was not at risk:

> My older son at that point was in a relationship, and he really had the question then about what did it mean for him, and should they go for genetic counseling. And I was able to say to him that, at that point, because they, they, that was the information they were talking about, the maternal […]inheritance, so I said well "you're clear".

But she was concerned about how and when to discuss it with her daughters and thinks that genetic health professionals may be able to help with this:

> Possibly I do need to talk to them [Genetic Health Service] and ah just say "look I haven't talked to Melanie about this yet, I want to get her through VCE [final school year]," but…yeah, it's awkward. They were good in the way they talked us through that whole thing and getting the balance right there, you know, we want to get those girls before they actually start launching into something as dramatic as having babies.

Colin did not think that the information was relevant to extended family, but thought it might be useful for his daughter when she reaches adulthood.

Extended family members sometimes benefited from the new genetic information. Robert described telling Leanne's sister, who had been delaying starting a family, that the new results had shown that it was an autosomal recessive gene:

> Because there was a while there when Leanne's sister [name] and her husband wanted to have kids of their own, but they were just, they didn't know what to do, because they thought it was maternal, so they just waited for the test, and as soon as we found out that it was ok, they just went 'oh right'.

Hannah told of an incident where the genetic information was useful to a niece. When asked whether the new genetic information was useful to her family, Hannah said:

> No, because I haven't got any sisters or anything like that […]. Only in terms of my own health. Yeah. As I said I'm always pleased to be informed. […] [To Ian:] What about when your niece's son was in hospital, you know when he was 10 months old? They thought it might have been a neurological condition […] I went down to the hospital […] It was after we'd heard this latest information eight years ago, and because if I hadn't have heard that, I would've thought…You know, I did, I did tell our niece then, you know, she knew about Ben's condition but, I was actually able to update and say "well it can't be anything to do with your side of the family, sort of thing, because um it's just coming through me, and not, not through Ian and his side now." So that was important yeah, in terms of extended family situations. Otherwise they may have thought that it was a similar thing.

These stories suggest that for these parents, the most important implication of the gene identification was for their surviving children. Extended family members were sometimes informed, depending on whether the parents perceived any relevance to that relative. No participants spoke of instances where any family members other than surviving children had pursued genetic counseling/testing.

Renewed Contact with Clinicians as a Result of the Research Interview

Participation in this research provided the opportunity for renewed contact with the genetic service. Several participants inquired about the disorder and genetic testing issues pertaining to their family during the interview. The researchers facilitated the requests by contacting an appropriate clinician on the participants' behalf. The clinician then wrote or telephoned the participant, depending on the participants' preferences as discussed during the interview. After one interview held at the hospital in which the genetic service is located, a clinician was available to speak with the participant following the research interview. One couple wanted further information about reproductive risks and the options for prenatal genetic testing, and two mothers asked about testing and health risk information for their children.

Discussion

Qualitative analyses of experiences of illness and loss can be important in providing health professionals with a deeper understanding and ability to support families, as shown by previous studies on illnesses such as cancer (Frank 1995; Woodgate 2006). Furthermore, narrative research is particularly suited to ethically challenging areas

of genetics and health research in "a society that will continue to work out its moral dilemmas in story form" (Frank 2002). A significant feature of this type of research is that it allows researchers the opportunity to recognize and respect participants' stories through the research interaction, without restricting participants to answering a multitude of specific questions. This type of analysis avoids fragmentation of the qualitative data and retains context by providing coherence over time. The results presented here add to the limited literature currently available on participants' experiences of receiving genetic research results, and to our knowledge this is the first research to address this in the situation of a paediatric patient who died before results were available. Mitochondrial conditions present complicated issues for genetic counseling due to the large number of possible causal genes (known and unknown), the consequent range of possible inheritance patterns, and difficulty in providing accurate risk information. These interviews provided valuable insights from the perspectives of parents of children who have died due to a mitochondrial illness.

Parents who participated in our study did not express any negative feelings about being re-contacted with new genetic information, despite the complexity, often unexpectedness, and in some cases difficulties experienced adjusting to implications of the genetic diagnosis years after the death of a child. There is a limited number of previous reports on research participants' views of being contacted with new results, and these involved adult participants rather than children. Ormondroyd and colleagues (2007) conducted interviews with people who had received a letter about research results on the breast cancer gene *BRCA2* from stored material belonging to an adult male relative who had since died. They found that although re-contact was sometimes a surprise, the letter itself did not have a big impact. All interviewees approved of being informed, as the results were clinically significant and provided a basis for decisions about cancer surveillance (Ormondroyd *et al.* 2007). Bernard *et al.* (1999) used a questionnaire to survey the attitudes of people with a family history of fragile X syndrome who had been re-contacted when DNA testing for the condition became available. Two of 28 participants were unhappy about being re-contacted. One of these seemed to be struggling with accepting the diagnosis and implications of fragile X syndrome in the family, and the other said that they had no wish to raise the issues surrounding fragile X syndrome again as they had finished dealing with those issues in the past (Bernard *et al.* 1999).

In our interviews, parents were pleased that research on their child's illness was continuing, they wanted to know information relevant to their own families, and they wanted to assist researchers in the hope of ultimately helping other families. Altruism is a common motive for research participation and has been noted in other studies about illness, genetics, and research involving bereaved people (Dyregrov 2004; Kaphingst *et al.* 2006; Scott *et al.* 2002). However the acceptability of research relating to a deceased family member may vary among bereaved people of different cultural backgrounds.

Several parents expressed a strong desire to be informed about generalized new research developments about the mitochondrial condition and had been actively seeking more information prior to the genetic diagnosis. This raises the issue of how to support parents who may be finding an absence of further information difficult. What method of contact could be used to provide up-to-date information on a particular disorder, and what is feasible and practical for clinicians and/or researchers to achieve? There is some consensus among ethical guidelines that new information should come from clinicians rather than researchers, as they have the necessary expertise in explaining the clinical relevance and providing appropriate support (Knoppers *et al.* 2006). A personalized newsletter could be an option for maintaining contact with parents and providing updated information on research for parents who may be trying to seek out more information on their own. Similarly, Griffin and colleagues (2007) surveyed patients and research participants regarding re-contact by cancer genetics clinicians, and found that a personalized letter was the preferred method of re-contact about advances in medical genetics. However, in our research, mothers from two families said that they would not have wanted to be re-contacted within a year or so of their child's death as new genetic information would have been too much of an added burden at that time. This raises issues about when to offer new information, as parents may be at different stages in the grieving process. Furthermore, individual preferences differ about the benefits of more information when there is no impact on treatment or disease progression. Kaphingst *et al.* (2006) found that most breast cancer patients who had donated blood or tissue for research did not want results of uncertain clinical significance. However, in our study, even though there are still no effective clinical treatments or cure for the diseases, the family-specific genetic information sometimes had relevance in terms of psychological issues over the cause of the illness, and in providing reproductive risk information for future pregnancies or other family members. To some degree a personalized letter addresses these individual preferences about what type of information is wanted and when, as it does not require the parent to take any action or respond in any way if they do not want to. Referral to a social worker as part of the multidisciplinary team may be warranted, as social workers have contact throughout the grieving process following the death of a child and are well placed to know when families will be receptive to new information, and what is appropriate.

Despite a positive response to the offer of new information, the delayed genetic diagnosis was sometimes far more of a shock than anticipated. Difficult emotional and psychosocial implications that were experienced included sad and traumatic memories brought up by returning to the hospital for the first time since their child's illness and death, contradictions to previous beliefs about inheritance, deciding if, how and when to communicate the information to teenage and adult children, and coping with new fears for the mother's health in the case of a mtDNA gene. The discovery of a maternally inherited gene sometimes resulted in mothers experiencing a burden of guilt and responsibility. This has parallels with findings on X-linked maternally inherited conditions suggesting that mothers of children with X-linked conditions are more likely to feel guilty and blame themselves than those carrying a gene for an autosomal recessive disorder (James *et al.* 2006). The impacts of a delayed genetic diagnosis on parents of children with mitochondrial disorders highlights that new genetic information offered after a delay of several years has the potential to re-open feelings of grief and uncertainty, and may present a new inheritance scenario for which research participants or their families are unprepared. The contradictions about inheritance may be due to the initial information provided at the time of the child's illness being incomplete or outdated and changed in the intervening years, and/or recalled incompletely by parents. For example, in the past, mtDNA mutations were thought only to be a rare cause of mitochondrial disorders in children, a myth that has since been dispelled (Rahman *et al.* 1996; Thorburn 2004).

It is possible that Parkes' Theory of Psychosocial Transition (Parkes 2006) may be helpful in understanding and providing support for parents' responses to both the initial diagnosis of their child's illness and a later genetic diagnosis which may contradict parents' previous beliefs about the condition. Psychosocial Transition Theory relates to major life events that suddenly challenge the 'assumptive world', and the subsequent transition during which people are required to revise their view of the world. For example, this theory has been applied to the impact of newly diagnosed childhood diabetes, where parents experienced a sudden change in their world, creating insecurity and uncertainty about the future (Lowes *et al.* 2005). Those authors made suggestions for professional support based on the diagnosis as a psychosocial transition, such as acknowledging and being sensitive to reactions of grief, loss and fear, understanding why information may be difficult to retain, and providing repeated opportunities for discussing new information. This seems applicable in the situation of a delayed diagnosis of a mitochondrial disorder which has unexpected implications for parents and their family.

Positive aspects of learning of new genetic results included relief at discovering the cause of their child's illness, accurate information about inheritance risks and options for prenatal testing, and benefits of the new knowledge for other relatives. As mentioned above, simply knowing that research on the disorder was continuing was a positive aspect for most parents. The major way in which parents used the information was for providing reproductive risk information to surviving children, or for prenatal testing and risk information for themselves if planning for future pregnancies. Occasionally they had informed other relatives, when the relevance of the genetic diagnosis to that family members' situation was apparent. Studies on family communication about genetic risks, mostly in relation to cancer, have shown that this is a highly complex process dependent on many factors such as individual communication styles, family hierarchies, and perceived benefits and risks (Forrest *et al.* 2003; Gaff *et al.* 2005). This indicates a role for the genetic service team in helping families think through the complexities of giving genetic information to other family members, by "warning" them of some possible reactions, and suggesting ways of explaining complex genetic information simply and accurately.

Limitations of this Research

There are several potential limitations of this research. Firstly, the number of participants was necessarily small. Although the genetic research to identify a causal gene change in children with mitochondrial diseases was done by the major referral centre in Australasia, the difficulties involved in obtaining a genetic diagnosis means that the number of families eligible to be re-contacted with new results was low. The response rate for this follow-up research was high, with six of eight families who were sent a recruitment letter agreeing to participate. The two non-responding families may have different attitudes to being offered the information or may have regretted electing to learn of the genetic diagnosis. The narrative analysis presented here is intended to explore the experiences of the nine participating parents, in order to raise important issues surrounding re-contact with delayed genetic information obtained through research. It is not intended that the results should be generalized, rather that these families' perspectives can help identify aspects of the process that are important to consider for future genetic counseling research. As we note above, perspectives of parents from diverse cultural backgrounds may differ. A second limitation is that in two interviews the presence of children at times may have affected the discussion, perhaps creating reservations for both parents and interviewer about how much to continue discussing sensitive topics. Thirdly, participants may have viewed the researcher as a representative of the hospital (as the research institution is located there) and this may have affected the disclosure of negative

experiences. However, this seems unlikely to have been a major factor, as several participants openly discussed negative interactions with health professionals which had occurred during their child's illness.

Summary

In summary, the impact of genetic information obtained many years after tissue or blood samples were provided varied from negligible to far-reaching on an individual basis. None of the parents in this small study expressed negative feelings about being re-contacted with the offer of new information, even though the genetic diagnosis sometimes had difficult implications for the family. All parents were pleased that research had been continuing, with a unanimous hope that it might help other families. However, it is important for health professionals to be aware of the contrasting reactions that parents may have to the genetic diagnosis. For some parents the genetic diagnosis provided welcome information and relief from feelings of guilt, whereas for others the information produced new fears for the mother's health, increased feelings of uncertainty about the reliability of medical knowledge, and dilemmas about informing surviving children about reproductive risks.

Implications for Research and Practice

Clearly some individuals may benefit from psychological support and on-going assistance with understanding and adjusting to a delayed genetic diagnosis. Acknowledging and being sensitive to reactions of grief, loss, uncertainty and fear, and understanding why information may be difficult to retain, may help parents through a resulting psychosocial transition phase. Further research is warranted on the impact and assistance needed for bereaved parents who are re-contacted about a delayed genetic diagnosis, not only in the situation of mitochondrial conditions, but also for other genetic conditions for which this situation occurs. Ideally, this would be a prospective study that would begin at the time of consent for the original samples, and follow through to the re-contact and impact on the family. Clearly, this type of study would need to occur over many years. A multi-centre study would enable various conditions to be included, and would facilitate comparisons of different initial consent procedures as well as a number of options for keeping parents informed about on-going research and/or re-contacting them when results are obtained. For the time being, it would be beneficial to involve social workers in assessing when it is appropriate to offer new genetic information to bereaved parents, through understanding of the needs of the family at the time. Follow-up would provide important opportunities for parents to discuss the implications of the new information, particularly in relation to other family members, and to ask further questions. Assistance from professionals about how to best communicate this information to siblings and extended family is indicated. Future research into the value of follow-up consultations after a delayed genetic diagnosis will help to determine the issues that may arise for both immediate and extended family members, and to discover how genetic health professionals can best meet the needs of these families.

Some preparation is indicated for the health professional. As discussed, the nature of the contact may provoke strong emotional reactions in families, resulting in counter-transference issues for the health professional (Evans 2006). This can result in feeling challenged, upset, stressed and emotionally drained. These feelings need to be recognized and acknowledged, to avoid burn out stress or "compassion fatigue" (Benoit *et al.* 2007). In anticipation, health professionals should ensure that they have adequate supervision organized. Those who are part of a multidisciplinary team can benefit from the advice and supervision of other team members such as social workers who understand the emotional challenges involved.

Acknowledgments We are very grateful to the parents who so generously shared their experiences. We thank Dr. Avihu Boneh for providing the introductory letters for recruitment and for very helpful advice during this research. We thank Dr. Clara Gaff for helpful comments on the manuscript. This work was supported by grants and a Principal Research Fellowship (DRT) from the Australian National Health and Medical Research Council.

Appendix: Guide for Open-ended Interviews

These were general topics to be covered and were not intended to be used as exact wording for each interview. Example questions to be asked by the interviewer are italicized.

Questions for Semi-structured Interviews

Introduction

- Explain what the research is about, what it will be used for, and essential things covered in consent form/Participant Information statement
- *Could you tell me a bit about yourself?* Family composition etc.

Open questions about:
Illness and initial diagnosis

- *I imagine that [name of child]'s illness was a very difficult time for you. Would you be able to tell me a bit*

about the time when you were finding out about what was causing them to be sick?

- *What information did you have about the condition at the time? How do you feel now you know the extra information about the gene change?*

Being re-contacted with genetic information after several/many years

- *Some people are surprised to be contacted after many years about genetic information in their family. Could you tell me what it was like for you?*
- *Could you tell me about when you went to talk with the doctors or counsellors about it?*
- *Was there anything about the way you were told that could have been done differently?*
- *Did you talk to friends or family about the results? How did they respond?*

After receiving the diagnosis—meaning/impact

- *Have you thought about how this information could be useful to you or your family?*
- *How does this fit into what else is happening at the moment in your life?*

Any other issues

- *Is there anything else that you think is important about your experiences that we have not discussed?*
- *Overall how important is it to you to know about the gene change?*[1]

After interview

- Thanking participants, discussing other issues that arose during interviews (e.g., Facilitating contact with genetic health professionals for more information), emphasising options for follow-up if participants wish to contact researchers or genetic counsellors following interview.

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[1] This question was an addition after reflecting on the first three interviews and therefore was not asked of all participants.

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