

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/143753/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Mendes, Álvaro, Sequeiros, Jorge and Clarke, Angus J. 2021. Between responsibility and desire: Accounts of reproductive decisions from those at risk for or affected by late-onset neurological diseases. *Journal of Genetic Counseling* 30 (5) , pp. 1480-1490. 10.1002/jgc4.1415

Publishers page: <http://dx.doi.org/10.1002/jgc4.1415>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



**Between responsibility and desire: accounts of reproductive decisions from those at risk
for or affected by late-onset neurological diseases**

Álvaro Mendes^{1*}, Jorge Sequeiros¹, Angus Clarke²

¹ UnIGENE and CGPP – Centre for Predictive and Preventive Genetics, IBMC – Institute for Molecular and Cell Biology, i3S – Instituto de Investigação e Inovação em Saúde; Universidade do Porto; Portugal

² Institute of Medical Genetics, Division of Cancer & Genetics, Cardiff University School of Medicine, Cardiff CF14 4XN; Wales, UK

* Corresponding author:

Álvaro Mendes

alvaro.mendes@ibmc.up.pt

+351 226 074 942

Suggested running head:

Reproductive decisions in late-onset neurological diseases

ABSTRACT

This paper explores ways in which genetic risk foregrounds forms of responsibility while dealing with reproduction. We analyzed individual and family semi-structured interviews ($n=35$) with people at-risk for or affected by transthyretin-related familial amyloid polyneuropathy (TTR-FAP) and Machado-Joseph disease (MJD), which are late-onset neurological diseases. Although generally considered as rare diseases, some areas in Portugal present the world's highest frequency for MJD and TTR-FAP. Thematic analysis of the data revealed that participants drew on various – sometimes ambivalent and competing – understandings of their genetic risk and their wish to have children. Some participants perceived the avoidance of genetic risk to be responsible behavior, while, for others, responsibility entailed accepting risks because they prioritized values such as parenthood, family relationships and the value of life, above any question of genetic disease. Some participants shared accounts that were fraught with ambivalence, repentance and guilt, especially when children were born before participants knew of their own or their partner's risk. Participants' accounts also showed they make continued efforts to see themselves as responsible persons and to appear responsible in the eyes of others. We discuss findings in the context of participants' negotiation between genetic risk and their sense of responsibility towards themselves and others; we conclude that “genetic responsibility” is present not only in accounts of those who chose not to have children but also in those who make an informed decision to have at-risk children.

Keywords: genetics; decision-making; familial amyloid polyneuropathy; hereditary ataxia; Machado-Joseph disease.

What is known about this topic:

Reproductive decision-making is a complex process. Literature on reproductive decisions in the context of late onset neurological diseases is mostly focused on Huntington disease.

What this paper adds to the topic:

This is the first study to report on reproductive decision-making of persons at-risk or already affected by TTR-FAP and MJD, which are late-onset neurological diseases. This paper aims to contribute to filling that gap by examining retrospective accounts of reproductive decisions in people affected by or at risk for these diseases and other family members.

1. INTRODUCTION

People with a family history of hereditary disease commonly face a number of difficult questions about reproduction. They make decisions that entail weighing the risk of passing on their family's genetic condition to offspring, alongside considerations of their responsibilities to themselves and others, including future relatives. The principal reproductive options facing carriers of genetically transmitted diseases include having children without any intervention and accepting the chances, using pre-natal diagnosis with a view to the selective termination of an affected fetus (PND), pre-implantation genetic diagnosis (PGD), or deciding not to have biological children. The last option may include gamete or embryo donation or adoption. The rationale behind reproductive testing technologies lies in the security it provides to prevent the transmission of genetic risks to future generations. This increased control over passing on a genetic disorder raises questions of parental responsibility. While the wish to prevent genetic disease in one's children is often strong and may be seen as "acting responsibly", there are other perspectives from which this would be contested.

In this paper, we report accounts about the reproductive decisions given by individuals at risk for, or affected by, the late-onset neurological diseases (LONDS), transthyretin-related familial amyloid polyneuropathy (TTR-FAP) and Machado-Joseph disease (MJD). We explore the reasoning set out in participants' accounts on the ways in which genetic risk foregrounds different forms of responsibility in the rejection or acceptance of the risk of disease transmission to offspring, and the ambivalence this may entail.

1.1. Genetic risk, reproduction and responsibility

The notion of ‘genetic responsibility’ has been used in the literature with various meanings (Leefman, Shaper, & Schicktanz, 2017). The term was first coined by Lipkin & Rowley (1974) to describe the responsibility towards future generations by means of avoiding the inheritance of diseases. More recently, many authors asserted that genetically at-risk individuals could indeed be considered (by family members or the society at large) to have the moral responsibility to take that knowledge into account when making decisions about their reproduction (Arribas-Ayllon, Sarangi, & Clarke, 2008; Hallowell, 1999; Novas & Rose, 2000; Petersen & Bunton, 2002; Taylor, 2004).

Feelings of responsibility play a major role in decision-making about reproduction for those at-risk for genetic conditions. Reproductive decision-making is a complex psychological process, involving cognitive, emotional, moral and unconscious dimensions. Literature on reproductive decisions in the context of LONs is mostly focused on HD (Decruyenaere et al., 2007; Downing, 2005; Klitzman, Thorne, Williamson, Chung, & Marder, 2007; Quaid et al., 2010; Richards & Rea 2005). These studies highlight the often emotionally-laden decisions of pursuing a prenatal test, and the trade-offs between wanting to avoid testing and hoping not to transmit the disease, as well as to not have children who would have to face the same quandary in their turn as future adults.. They also evidence how the couples’ decisions are sometimes further complicated by their strong wish for a child, which may conflict with their compelling wish to prevent a child from getting HD.

One decision made by some definite or possible pre-symptomatic carriers is not to have children at all. Studies reported they would not want any child of theirs to be brought up by a parent who is likely to become unwell during their offspring’s childhood, irrespective of **whether** the child **would** also **be** at risk (Downing, 2005; Klitzman, Thorne, Williamson, Chung, &

Marder, 2007; Quaid et al., 2010). The study by Decruyenaere and colleagues (2007) also identified personal experiences of growing up in a family with HD, and ethical **concerns** about PND and PGD, as factors in the decision not to have children. Avoidance of **the suffering of** offspring and the ability to raise a healthy child were the main reasons stated in favor of PGD among Portuguese TTR-FAP mutation carriers (Valdrez, Silva, Coelho, & Alves, 2014). This wish for the disease not to impact on a child's experience is often strong and **is often voiced** in genetic counseling, but is much less often mentioned in the context of non-neurological diseases, even those that can also lead to the death of a parent (e.g. familial cancer syndromes). The family's experience with the disease being tested is thus often used in decision-making about reproduction to assess the level of suffering in future offspring and in those around them. There is good research that highlights the wealth of experiential knowledge gained by having the disease or by having lived with affected family members, demonstrating its role as an important mediator of decisions in reproductive contexts (Boardman, 2014a; b). Taken together, these studies suggest that the responsibility **for** decisions about reproduction **is perceived to go** beyond a strict biomedical assessment, extending to lived experiences and personal and family values.

Notions of "genetic responsibility" also raise the spectre of broader societal forces, especially eugenics, and force us to address the shape this perennial force may come to adopt in the 21st century. Duster argued that decisions made about reproduction in the consumerist society of the USA would in effect be eugenic, as they would arise from individual decisions taken under pressure of social conformity and raw market forces, without the application of direct state intervention (Duster, 1990). If health insurance is not a collective social good but is seen as a commodity, or if most families need both parents to work full-time, then the pressure to

avoid a child with additional costs or challenges becomes stronger. Equally, choosing to have a child who will grow up to become an adult at risk of a serious neurodegenerative disorder may be seen as placing an unfair financial burden on them because of the social structure of health care provision, in addition to the burden of the risk of disease. Previously, the term "eugenics" implied centralised direction from the state. This is now being superseded by the cumulative effect of many individuals making their own personal decisions but subject to their social environment and by their (limited) access to healthcare. In spite of the commonly accepted practice of non-directive genetic counseling, external circumstances can be powerful influences. This is indeed a post-modern form of internalized social control, a biological self-discipline, as understood by Novas & Rose (2000).

1.2. The medical context: MJD and TTR-FAP

MJD and TTR-FAP are autosomal dominant and highly-penetrant LONDS. They are progressive and very incapacitating, and no effective cure is yet available. Individuals at risk – the offspring of those who come to be affected or of known presymptomatic gene carriers – have a 50% *a priori* chance of developing it and, thus, their children will be at a 25% risk. Both diseases may be clinically heterogeneous, but lead to severe motor impairment, dependency and premature death (Coelho et al., 2012; Sequeiros & Coutinho, 1993). In TTR-FAP, some therapeutic measures are now available, including liver transplantation and, more recently, tafamidis, a drug that may slow down disease progression. However, these treatments are not available and effective for all patients, as they need to be undertaken at an early stage in the disease and not all patients respond to tafamidis. In MJD, no medical intervention is currently established as safe and effective; pre-symptomatic testing (PST) thus provides information

without leading to any *direct* neurological benefit. Both are typically disorders of adulthood; age at onset for FAP is mainly between 25 and 35 years (Coutinho et al., 2013), while for MJD mean age at onset is around 40 years, although with a very wide range, with infantile and juvenile cases known (Donis et al., 2016; Sequeiros & Coutinho, 1993).

The European prevalence of amyloidosis is estimated at 47/100,000, of which TTR-FAP is the most common form (Parman et al., 2016). The region of Póvoa de Varzim/Vila do Conde, in the Northwestern coast, is the largest cluster of TTR-FAP patients worldwide, with an estimated crude prevalence of 163.1/100,000 (Inês et al., 2018; Sousa, Coelho, Barros, & Sequeiros, 1995). MJD is also generally considered to be rare, although Portugal has a relatively high incidence. MJD (also known as spinocerebellar ataxia type 3, SCA3) is the most common SCA worldwide; estimated prevalence is of 1–5/100,000, with significant geographical and ethnic variations (Martins et al., 2007). Some areas in Portugal present the world's highest frequency for MJD: such is the case for the Tagus valley, in central mainland, and the Azorean islands of Flores and São Miguel, with prevalence rates of 14.4/100,000, and 835.2/100,000 and 27.1/100,000, respectively (Sequeiros, Martins, & Silveira, 2012).

A national programme of PST was established in the mid 1990's, offering comprehensive genetic counseling and psychosocial support for MJD and later extended to all other LONDS, including TTR-FAP and HD (Sequeiros, 1996). PST identifies whether an at-risk person is likely to become ill later in life, and the risk for their current or future offspring, giving them the opportunity to consider important life decisions, including reproductive choices. However, despite efforts by the health services, knowledge of genetic risks may not be readily available to the whole at-risk population and access to appropriate genetic counseling is limited, especially in more isolated areas.

How persons consider and deal with genetic risks in decisions about reproduction is of great public health interest, particularly in regions of high prevalence. To our knowledge, there are no published studies addressing reproductive decisions for these diseases, despite the clarification of risks to future offspring being one of the main motivations for PST (Paneque et al., 2019). This paper aims to contribute to the filling of that gap by examining retrospective accounts of reproductive decisions in people affected by or at risk for TTR-FAP or MJD, and their family members.

2. METHODS

2.1. Design

This exploratory, qualitative study was drawn from a larger study examining processes of communication about genetic risks in families affected by LONDS (Mendes, Sousa, Sequeiros, & Clarke, 2017; Mendes, Paneque, Clarke, & Sequeiros, 2019). We present here the sub-corpus of data relating to participants' accounts about reproduction, a relevant theme that emerged during that analysis. The research perspective draws on work on the context-specific distribution of knowledge and awareness for the formation of familial and personal beliefs about genetic risks (Arribas-Ayllon, Sarangi, & Clarke, 2011; Atkinson, Featherstone, Gregory, 2013; Featherstone et al., 2006). The study was approved by the IBMC Human Ethics Committee.

2.2. Recruitment and sampling

By using the convenience and snowball sampling methods (Silverman, 2005), we recruited participants through the Portuguese patients' associations (PAs) for TTR-FAP and hereditary ataxias (in the case of MJD). Inclusion criteria involved persons of three categories – either those affected, those at-risk or other family members –, who had to be competent to give consent. An invitation letter and a leaflet with information about the study was circulated and published in newsletters and websites of the PAs and broader social media, calling potentially interested participants to contact the researcher. The information leaflet stated that the study aimed to explore the participants' experiences of communication about the condition within their families. We also stated that any reports quoting their response in academic publications and presentations would be anonymized. PAs also made the study known directly at members' meetings; those agreeing to participate authorized their contact information to be sent to the researcher, who then called them..

2.3. Participants

Data pertaining to reproductive decisions involved a sub-corpus of 18 of the 32 interviews. Seven were group interviews, involving multiple family members (cf. Table 1). Overall, this study comprised 35 participants out of 68 in all. Subsequent contact with two potential participants failed and one family interview with five participants was excluded because no confirmed familial diagnosis had been obtained at the time of the interview. All participants were of white European ethnic background; further social and demographic details are provided in Table 2.

INSERT TABLE 1 HERE

INSERT TABLE 2 HERE

2.4. Data collection

Semi-structured interviews were conducted face-to-face by ÁM between April 2014 and June 2017, at a location chosen by participants (cf. Table 1). The interviewer had no previous relationship with the participants. All participants had the opportunity to ask questions about the study and their informed consent was documented before they participated. Interviews were audiotaped, transcribed and translated into English. Each lasted approximately one hour. Social, demographic and disease-related data were collected first, followed by an open question about experiences of living with the disease or the risk for it. Interviews covered themes such as the value of genetic information, motivation and engagement with genetic testing, and experiences of talking to relatives about test results or genetic risks more broadly. The interviewer probed participants about issues they found important and prompted them to clarify and elaborate their arguments. He elicited thoughts and feelings about being a mutation carrier or being affected by a LOND, inheriting the disease and possibly having passed it to future generations. Participants provided accounts of their decisions around testing, reproduction, coping with the effects of the condition, medical treatments, and associated emotional consequences. Case summaries were created after each interview, highlighting the most relevant aspects, contextual observations and emerging ideas about topics to discuss in future interviews (Strauss & Corbin, 1998).

2.5. Data analysis

The transcribed interviews were analyzed thematically, using coding and constant comparison methods (Strauss & Corbin, 1998). Each transcript and the corresponding interview notes were read repeatedly by ÁM, and key topics mapped; any differences or similarities between participant accounts were noted. These were then manually coded by ÁM, using a system of open and axial coding (Strauss & Corbin, 1998). Open coding is the initial stage of analysis where each segment of the data is labelled and interpreted; axial coding is a process of inductively relating codes to each other within and among transcripts, to identify likely connections. Codes relating to reproduction were grouped together to develop categories in a process of ongoing reflection about the themes within the data, according to their main features and meaning. Findings were then interpreted with reference to a broad psychosocial framework, aimed at understanding the interpersonal context that surrounds individuals and families, as they communicate and live with risks for an inherited disease (Arribas-Ayllon, Sarangi, & Clarke, 2011; Atkinson, Featherstone, & Gregory, 2013; Featherstone, Atkinson, Bharadwaj, & Clarke, 2006). The analysis also drew on ideas about the social accountability of accounts (Buttny, 1993).

3. RESULTS

We have identified three main themes from the analysis: 1) containing risks: responsibility to prevent transmission of the family's disease; 2) ambivalence, blame and repentance; and 3) accepting risks: prioritizing parenthood, family life and hope in science.

Each theme is presented, along with data extracts to illustrate key points. Content in square brackets is used to add intelligibility to the participant's quote or suppress details that might compromise confidentiality (some minor details were also altered for that purpose); ellipsis with a single/double dot means a brief/extended pause; underscored text indicates louder, more emphatic speech; “. . .” indicates some words or sentences were omitted; and “~” indicates overlapping speech.

3.1. Containing risks: responsibility to prevent transmission of the family's disease

In this theme, participants clearly prioritized genetic risks in their decisions. Their accounts affirm a moral expectation to prevent transmission of the disease, either by not having children at all, or by using reproductive testing technologies, including PGD and embryo selection or PND and the selective termination of pregnancies (ToP) carrying an affected fetus. Decisions not to have children were commonly articulated as the enactment of a perceived moral responsibility for future generations:

L2: “I think it's very unfair to put children ‘out there in the world’ with such a huge burden (.) knowing there's no hope for them . . . We've learned that PGD [process] is too uncertain and very tough for her [L1's] body (.) it would be better not to take risks and to protect ourselves.”

In this passage, the couple also justified their decision by portraying the perceived limitations of PGD. This is also described among the reasons underlying decisions by TTR-FAP mutation carriers not to use PGD (Valdrez, Silva, Coelho, & Alves, 2014). Other participants engaged

successfully with PGD, which allowed them to have biological children not carrying the disease mutation:

D1: "I was very lucky because I managed to get pregnant at my very first [PGD] cycle . . . For my cousin it didn't work out for three times. They couldn't afford more [cycles; NHS in Portugal covers up to three cycles of PGD], so they took their chances (.) I respect that, but if you can stop the disease why take the risk?"

As D1 states, when risks are known, a 'responsible' decision regarding reproduction would, from that perspective, entail having children *as long as* they are risk-free. Those unwilling to accept genetic risks might consider PGD, PND (with ToP of carrier fetuses), sperm or egg donation, adoption, or remaining childless. Two of our participants were attempting to adopt (both still in the waiting process). Two participants mentioned they engaged with PND until a non-carrier fetus was identified, while three participants engaged immediately with PGD; gamete donation was never mentioned. Five participants chose to remain childless.

Next, E1 describes her decision not to have children, after several unsuccessful cycles of PGD. For her, ToP (after PND) was morally problematic, but not PGD:

E1: "I couldn't do a [prenatal] test to see if the baby would have it [the disease mutation] and then end it [pregnancy] (.) If it was something visible for the baby, then (.) but no, it's just (.) a protein in the liver of a baby that could be perfect, no!"

In her account, E1 clearly focused on prevention of the disease, while expressing discomfort with terminating a fetus with a TTR-FAP mutation. She further enacted responsibility by articulating the potential blameworthiness of those who choose to have children regardless of their genetic risks:

E1: "I didn't want to risk the 50:50 . . . When starting a family, one should think twice and have the test beforehand to avoid [imposing] a sentence upon the children (.). People have the right to decide, but bringing someone into the world who could spread the disease is selfish (.). it's just to fulfil a person's dream without thinking much about the consequences."

E1's formulation resembles the criticism noticed in some MJD families towards at-risk relatives who had opted to have children irrespective of having remained uninformed about their own risks (Mendes, Paneque, Clarke, & Sequeiros, 2019). This situates genetic risks within a "public health" framework that foregrounds the interest of the community and deflects attention from the individuals and their preferences.

It is interesting and important that E1's doubts about the acceptability of pregnancy termination would not arise if the condition led to a *visible* blemish on the child. She employs the rhetorical device of contrast (Sarangi & Clarke, 2002) to demonstrate that she would make the "responsible" decision – to test for and potentially terminate a pregnancy when the child might be affected by another, disfiguring condition – but is formulated here as a justification for not doing so in relation to *this* disease. This argumentation has profound implications for questions of stigma and identity outside this context (Mendes, Sousa, Sequeiros, & Clarke, 2017), including in relation to other genetic conditions (Clarke, 2016).

3.2. Ambivalence, blame and repentance

While the data extracts above indicated the determination to avoid genetic risks, this theme reflects the participants' ambivalence, their conflicted decision-making, and how this some-

times involved regret or even repentance. We highlight the participants' weighing of competing desires and concerns, and how they negotiate their presentation of self as demonstrating responsibility. Decisions about reproduction often involved ambivalence and, for some participants, (internally) conflicted decision-making. This emerged in accounts of couples who ended up having children at risk, even if their initial wish was to avoid it.

B1 learned she carried the TTR-FAP mutation in her early twenties; she described a family narrative marked by a strong sense of responsibility for "stopping" the disease. The passage below reports how she weighed competing desires and concerns over reproduction and how her positioning changed over time:

B1: "After I tested positive, I thought I shouldn't have children (.) I had seen all the suffering in my mother, my uncle (.), but we decided to have children anyway, we took our chances because my husband was very keen [to have a baby] (.) I wasn't so much, I was telling him we should adopt (.) In my head, all the suffering my mother went through was there. I guess my husband was not that aware of what the disease is (.) I didn't think about it so much, I guess I wanted to please him. A friend encouraged me to have a go (.) I could be lucky after all! (.) I just decided without too much thinking."

B1's account conveys the difficulty of abandoning the view of herself as the bearer of responsibility for either containing or transmitting her family's disease. This is heightened by having witnessed her close relatives' decline with the disease, and because, unlike her sisters, she was a mutation carrier. She could counter that stance as her husband's wish for a child allowed her account of how she came to have children to become less blameworthy. B1's assertions of a seemingly *thoughtless* deliberation, and the alignment of her decision with chance, further helped to remove a sense of blame.

Participants who had their children before knowing their own risks shared a different type of ambivalence. Most of these voiced repentance and feelings of guilt. In the excerpt below, R2 talks about her husband's disease, the risk to their daughter and of the value of life with genetic risks:

R2: "He [R1] only started to get sick around 40, so (.) it's a life. That makes me think of my daughter (.) it worries me she may have it, but she can still live a life, isn't it? (.) Even if she has it [MJD], it doesn't mean she cannot have a family . . . We were clueless about this (.) if it was today, we wouldn't have her."

In this account, ambivalence emerges as R2 voiced her worry about her daughter's 50% risk, particularly as she is reaching the age when she might want to have the test to know her genetic status. She then shares her repentance, although clearly a "blameless guilt". R2 projects the worth of her daughter's life despite the genetic risks by reasoning that the typically late onset may potentially allow her daughter to live a fulfilling life, including having children before the potential onset of illness. This is comparable to Aureliano's (2017) study in Brazilian families affected by MJD, in which age-of-onset was an important factor shaping reproductive choices.

The next excerpt illustrates the further use of mitigating factors to help navigate ambivalent feelings in relation to past reproductive decisions, while also minimizing blame:

A1: "I lost a pregnancy after PGD (.) After that I'd put that [to have children] aside really (.) But then I got pregnant without expecting it, it happened (.) and I did the [prenatal] test, and (.) I know this isn't right because I know my son is "positive" (.) The doctor insisted I should terminate but I didn't want it, I could never do an abor-

tion (..) [in Portugal, PND should not be performed at all, by law, if the couple states beforehand they would not select ToP] I think about it many times (..) I don't blame myself nor anyone, not even my mother, no (.) but I worry that he may know there were options I could have chosen but I didn't . . . But my son has a good life”.

By presenting her pregnancy as unplanned, *AI* seems to have made a “non-decision” (Kelly, 2009), thus removing personal accountability and responsibility. This is similar to the “reproduction roulette” described when couples leave conception to fate (Lippman-Hand & Fraser, 1979; Pond & Dimond, 2018). Moreover, *AI* acknowledges her refusal to terminate after a “mutation positive” PND as potentially blameworthy. She displays her ambivalence also by voicing her concern that her son may later blame her, thereby recognizing that her decisions about ToP may lead to harmful consequences for other family members.

3.3. Accepting risks: prioritizing parenthood, family life and hope in science

This theme presents the views of those most committed to having children naturally, regardless of genetic risks, and for whom injunctions against being parents would be unacceptable. Reproductive planning based on genetic risk was not a concern to a number of participants. They prioritized lifeworld considerations over concerns about transmitting their family's disease, while claiming these decisions should not be judged as unethical. The reasons for these attitudes were complex and nuanced, referring to the needs of their family, the value of parenthood and family continuity, as well as the value of life despite genetic risks. Indeed, these participants articulated their responsibility not through attempts to avoid genetic risks but rather by their responses to their personal, as well as social and relational concerns and needs:

HI: "I've always said I'd not quit from having children because of the disease. (.) We don't know what's going to happen tomorrow, right? . . . Look at my mother: alone, sick, no husband, nothing! What would there be for her now without us? We're lifesaving!"

HI suggests that children are instrumental for the provision of care to affected family members. Other participants described difficulties in affording a day-care facility for affected relatives; the solution often involves family members (most often women) quitting their jobs so they can look after their affected relatives. This highlights the burden of the caring obligations within these families for those in a disadvantaged socioeconomic position.

HI started to experience symptoms of TTR-FAP at 26; she got pregnant knowing her three children had a 50% chance of inheriting the disease gene. She then describes rejecting PND as acting responsibly:

HI: "In my last [pregnancy] I didn't want to do the [prenatal] test, because if it was positive I wouldn't do an abortion and (.) I couldn't imagine myself facing my other children . . . We deserve to be happy, we're already different because of this [TTR-FAP] (.) you should not give up [on being a mother]! . . . I already talked to my oldest [12y daughter] about whether she'd prefer not to have been born and she said no, she rather wants to live as it is (.) maybe something can come up in the future, like a vaccine or something (.) we live with this faith".

Accepting risks does not mean these participants were indifferent to the risk and seriousness of the disease. *HI* states her unwillingness to do PND/ToP and justifies this by recognizing that disclosing this to her other (at risk) children would have the potential to hurt them. She

decided not to treat her children differently in how she brought them up and, in doing so, she sought a positive endorsement of her three at-risk pregnancies and the value of her children's lives. This enabled her to present herself as a responsible parent in ways other than by minimizing the genetic risks. This is nevertheless experienced as a potential source of disapproval, and *HI* goes on to assert that her eldest daughter had "exonerated" her from blame by asserting her life to be worthwhile despite the risk. She also expressed her belief in the power of science to impact positively upon her children's future outcome. As in other participants' accounts, hope in the progress of science may also serve to preserve self-identity as a responsible parent.

In the family interview K, these factors are further taken into account:

K3: *"There's one [baby] coming; it happened (.) it wasn't planned". ~*

~ K2: *"It doesn't matter, I'd always be happy! Cancer is hereditary too and people still have kids, don't they?"*

K3: *"I don't think much about the disease, that's (.) I just want to be a good father, it's my first [baby]"*.

K2: *"I'd do the same (.) The doctor said this disease only stops if we stop having children, but that's (.) let me tell you, if I was their age I'd want to have children too, to have a life! If not, the family just ends! What happens then? . . . I always wanted to be a grandmother; I know it can be bad, but we have plenty of time, [the baby will have] time to live."*

K3: *"Yeah, and it might be that they discover something in the meantime."*

In this passage, *K3* affirms he chose “not to know” his genetic status, therefore avoiding the kind of imperatives set by genetic knowledge (Mendes, Paneque, Clarke, & Sequeiros, 2019; Taylor, 2004). This also highlights a sense of settled fatalism. Fatalistic statements may be employed to avoid self-blame, as well as when people need to manage uncertainty as the result of lack of control over health (Keeley, Wright, & Condit, 2009). He emphasizes he is focused on *his role* towards the upcoming child, while avoiding consideration of his own risk. He also explains the accidental nature of the pregnancy; this removal of personal accountability is a relevant rhetorical issue, as choosing to have children without first establishing one’s own genetic status when familial risks are known may be considered to be irresponsible, or at least controversial. His mother (*K2*) swiftly exonerates him from blame, expressing solidarity with him, thus mirroring her own situation as the mother of two at-risk sons (both present in the interview). This is somewhat surprising, as indifference to genetic risks in younger generations is commonly less prone to exoneration from blame than in older ones, because those in the younger generation are still active in their reproductive responsibilities (Arribas-Ayllon, Sarangi, & Clarke, 2008). In doing so, *K2* normalizes life irrespective of genetic risks, and highlights the importance of family life in its own right. As in the previous excerpt, hope that science will discover a cure for their family’s disease is put forward, which may function as a moral asset for the construction of a meaningful everyday life.

4. DISCUSSION

This is the first study to report on reproductive decision-making of persons at-risk or already affected by TTR-FAP and MJD. It adds to a body of literature exploring these decisions in the context of other LONDS, especially HD (Decruyenaere et al. 2007; Downing, 2005; Klitzman,

Thorne, Williamson, Chung, & Marder, 2007; Quaid et al., 2010). The data presented concern the participants' reconstruction of their own or their family members' past decisions in relation to reproduction, and how they account for them. In particular, our analysis provides insight into participants' negotiation between genetic risks and their sense of responsibility to self and others (including potential future offspring and the society at large). Participants drew on various – sometimes ambivalent or even competing – relations with genetic risk and their desire for children. Our findings resonate with other research on different conditions, showing that participants balanced their wish for children with broader moral concerns and factors, such as the nature and the (current and future) treatability of the disease, their accumulated experience with it and its perceived impact on affected family members, and attitudes towards PGD and PND (and selective ToP) (Kelly, 2009; Raspberry & Skinner, 2011a; b). Furthermore, participants' accounts also show how they attended to relational responsibilities and to emotional risks and potential harms to relationships in their decisions. Interpretation of their moral accountability was manifest in how participants made continued efforts to display their responsibility to others, as they portrayed moral issues and factors and attempted to mitigate responsibility and deflect blame (Arribas-Ayllon, Sarangi, & Clarke, 2011), especially those who already had children.

Reasoning in relation to reproductive genetic risks is not necessarily static but can shift and evolve over time. Situational and contextual factors shape people's understanding of risks and their choices about managing them. First, engagement with genetic healthcare has consequences for how people make their decisions and negotiate their personal responsibility for genetic risk. The majority of participants had undergone PST or diagnostic testing and some, particularly participants from TTR-FAP families, had contemplated PND or PGD. In some

accounts, avoiding risks was framed as *the* morally sound behavior, while accepting them was thought of as blameworthy. This makes clear the implicit normative expectation of the dominant genetic risk discourse, that renders those who are aware of their own genetic risks as having the responsibility to be (more) restrained about reproduction (Novas & Rose, 2000; Petersen, 2006). Other participants, however, seem to contest this discourse on prevention by enacting responsibility through a process of reconfiguring known genetic risks into knowledge that resonated with their and their family's lived experiences. In this process, they seemed to prioritize a set of social and relational values that go beyond physical health and control of disease, while attending to other dimensions of risk, such as the typical late onset and gradual course of the disease and (mainly) the possibility of future treatments. This adds to previous research highlighting modes of reasoning and of action for understanding and operating upon genetic risks, at odds with biomedical orientations (Aureliano, 2017; Carrieri, Farrimond, Kelly, & Turnpenny, 2017; Huniche, 2011; Mendes, Paneque, Clarke, & Sequeiros, 2019).

Second, life with the disease is still an ongoing experience for some of these families and, thus, reproduction is often experienced with acute sensibility. Exposure to such a destabilizing disease and caregiving for affected relatives may have prompted participants to project future lives with intolerable levels of suffering, and thus suppress the wish for (potentially at-risk) children. In choosing that path, these participants may have developed a sense of "not allowing history to repeat itself" (Decruyenaere et al., 2007; Hallowell, 1999). Conversely, multi-generational experience with the disease was framed differently by those who accepted or tolerated risks for offspring; indeed, they justified their actions either by the wish to assure continuity of the family, respond to family demands and respect the lives of at-risk or affected

relatives. For these participants, the accumulated experiential knowledge of the disease allowed them to accept risks, in spite of the difficulties associated with life with the disease (Boardman, 2014b). Furthermore, some accounts suggested that a heightened sense of responsibility framed ‘expressivist objections’ towards PND and ToP (Boardman, 2014a), as they explicitly considered the potentially devaluing meanings and messages it may hold in relation to the value of the lives of other at-risk and affected family members. Indeed, some participants shared personal and relational values that rejected decisions that might lead them to consider PND and ToP. Interestingly, such reluctance was described in markedly varied circumstances, namely by a woman who refused the expected termination of a proven carrier fetus after PND, by those with children conceived “naturally”, and by participants who chose not to have children at all. This has been studied within families affected by spinal muscular atrophy (Boardman, 2014 a; b) and X-linked hypohidrotic ectodermal dysplasia (Clarke, 2016), respectively autosomal recessive and sex-linked diseases. Although the mode of inheritance differs between these conditions, and the likely age at onset or diagnosis and the expected severity and burden differ too, people make their judgements about the value of their lives on the basis of what they have experienced and witnessed. The different contexts of each family highlight the importance of the emotional charge of the relationships among family members for decision-making about reproduction; these are not determined in any simple way by the biological and medical ‘matters of fact’ or even by the potential risks and burdens.

One further strategy employed by some family members was hope in future advances of science, which was particularly emphasized by participants already with children at-risk. While this may serve to pre-empt the emotional tension and cognitive dissonance that could arise from the risk that their family’s disease continues, it may also express the need to keep seeing

the future as being open and worthwhile, so that life becomes more “manageable” in the present. Particularly in rare diseases for which no effective treatment is yet available, hope in scientific progress is indeed a valuable resource to foster resilience, through preserving self-identity and the goal of becoming a parent.

4.1. Future research perspectives and implications for practice

As genetic technologies advance, the introduction of new therapeutical options is expected to expand clinical management. Further research could therefore explore whether perceptions on the improving “manageability” of these conditions make it more likely that some families will risk passing on the gene to their offspring. Discussion of these issues among health professionals, patients and families also needs to be considered. Further research may consider building on our results to see if genetic status and the age of onset in the family influence people’s perceptions of their responsibility towards reproduction. This study emphasizes the need for genetic counselors to be sensitive to the lived and experiential dimensions of genetic disease in counseling contexts. They may consider exploring how expectations at the social, familial and personal level influences patients’ decisions about reproduction. Taking stock of people’s experiences and the framing of their decisions will be of value for professional training and patient- and family-centred practice. Moreover, it is important that genetic counseling research addresses how best to access and document the experience of those involved in the making of these difficult and often stressful decisions.

4.2. Study limitations

Some limitations in this study need to be acknowledged. As the study was exploratory, interpretations and attempts to generalize the findings and apply them to reproductive decisions in other inherited diseases should be restricted and may not apply to other populations. Our participants were self-selected, which may have biased the data. They belong to families affected either by MJD, currently an incurable disease with no treatment, or by TTR-FAP, which already has some options for clinical management; this may have influenced how reproductive risks were perceived within these families.

Our analysis did not examine the themes by age of onset in the family, nor the potential distinctions that participants with different genetic status (affected, pre-symptomatic carriers, family members at 50% risk, other family members such as the unaffected grandparent, and non-biological relatives) may hold in relation to their or their family members' reproductive decisions. Indeed, given the modest number of participants and the three ways of categorizing them by (i) the two diseases, (ii) the five categories of 'relative' and (iii) the three orientations towards the risk of disease transmission, we could not make plausible claims of any generality. While acknowledging that, however, we observed different attitudes and behaviors reported by individuals in very similar family circumstances. Moreover, we also included participants from different geographic locations; the bulk of our participants live in specific regions where MJD and TTR-FAP are highly prevalent, respectively the Tagus valley and the Northwestern coastal area. This may have increased the cultural and social and demographic diversity and, thus, the range of reported experiences, which may in turn have been influenced by the disease prevalence (and awareness) in each region. The ways in which genetic risks are understood and dealt with, and the approaches to morality that underpin decisions in relation to reproduction, certainly differ among countries, regions and populations, and specific dis-

eases. Additionally, as some participants were involved in snowball recruiting to the research, they may have invited to participate with them in an interview those family members with whom they had a good relationship, and anticipated lesser dissent in discussing the themes of the interview. Finally, interviews that were conducted with multiple family members may have led participants to feel somewhat inhibited in sharing their views due to the presence of other family members, which marks a difference from the single interviews.

5. CONCLUSION

This study presents some the perspectives of people at-risk for or affected by MJD and TTR-FAP concerning their reproductive decisions. These are not determined by basic biology but emerge from each individual's personal and family circumstances. By highlighting the lived realities of family life, and the relational context that surrounds reproductive decision-making, this study shows how genetic responsibility is not only present in the accounts of those who chose not to have children, but also for participants who knowingly decided to have children at-risk.

Our findings show that “acting responsibly” when facing reproductive risks is a process that carries inherent ambivalences. Such “responsible decisions” are not made simply on the basis of rational consideration of risk and of disease burden and management or prevention, but also take into account the subjective lived experiences of individuals, couples and families. These insights should be of great value in genetic counselling, as well as for the provision of follow-up support to affected individuals and families.

AUTHOR CONTRIBUTIONS

ÁM and JS designed the study. ÁM was responsible for the data collection; and ÁM and AC contributed to the analysis and interpretation of data. ÁM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ÁM drafted the manuscript and JS and AC revised it critically, gave final approval of the submitted manuscript, and agreed to be accountable for all aspects of the work.

ACKNOWLEDGEMENTS

We are grateful to all participants, and to Associação Portuguesa de Ataxias Hereditárias and to Associação Portuguesa de Paramiloidose, for help with recruitment. We also thank Dr. Glória Matias for access to the facilities of the Chamusca's primary health centre for some of the interviews. ÁM acknowledges the funding from FCT - Fundação para a Ciência e Tecnologia (CEECIND/02615/2017). Part of this work has been also financed by FEDER (COMPETE 2020 - POCI, Portugal 2020), and by FCT, in the framework of the project "Instituto de Investigação e Inovação em Saúde" (POCI-01-0145-FEDER-007274).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest

Álvaro Mendes, Jorge Sequeiros, and Angus Clarke declare that they have no conflict of interest.

Human studies and informed consent

All procedures followed were in accordance with Portuguese legislation and the Helsinki Declaration of 2000. Informed consent was obtained from all participants included in the study.

Animal studies

No non-human animal studies were carried out by the authors for this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

Arribas-Ayllon, M., Sarangi, S., Clarke, A. (2011). *Genetic testing: Accounts of autonomy, responsibility and blame*. London: Routledge.

Arribas-Ayllon, M., Sarangi, S., Clarke, A. (2008). Managing self- responsibility through other-oriented blame: Family accounts of genetic testing. *Social Science & Medicine*, 6, 1521–32.

- Atkinson, P., Featherstone, K., Gregory, M. (2013). Kinscapes, genescapes & timescapes: Families living with genetic risk. *Sociology of Health & Illness*, 35, 1227-1241.
- Aureliano, W. (2015). Health and the value of inheritance: The meanings surrounding a rare genetic disease. *Vibrant*, 12, 109–40.
- Boardman, F. (2014a). The expressivist objection to prenatal testing: The experiences of families living with genetic disease. *Social Science & Medicine*, 107, 18-25.
- Boardman, F. (2014b). Knowledge is power? The role of experiential knowledge in genetically 'risky' reproductive decisions. *Sociology of Health & Illness*, 36, 137-150.
- Buttny, R. (1993). *Social accountability in communication*. London: Sage.
- Carrieri, D., Farrimond, H., Kelly, S., Turnpenny, P. (2016). Families dealing with the uncertainty of genetic disorders: The case of Neurofibromatosis Type 1. *Sociology of Health & Illness*, 38, 753–767.
- Carvalho, F. (2015). Preimplantation genetic diagnosis for TTR-FAP in Portugal. *Orphanet Journal of Rare Diseases*, 10, 15.
- Clarke, A. (2016). Anticipated stigma and blameless guilt: Mothers' evaluation of life with the sex-linked disorder, Hypohidrotic Ectodermal Dysplasia (HED). *Social Science & Medicine*, 158, 141-148.
- Coelho, T., Maia, L., Martins da Silva, A., Waddington-Cruz, M., Planté-Bordeneuve, V., Lozeron, P., Suhr, O., et al. (2012). Tafamidis for transthyretin familial amyloid polyneuropathy: A randomized, controlled trial. *Neurology*, 79, 785-792.

Coutinho, P., Ruano, L., Loureiro, J., Cruz, V., Barros, J., Tuna, A., Barbot, C., et al. (2013). Hereditary ataxia and spastic paraplegia in Portugal: A population based prevalence study. *JAMA Neurology*, *70*, 746–755.

Decruyenaere, M., Evers-Kiebooms, G., Boogaerts, A., Philippe, K., Demyttenaere, K., Dom, R., & Vandenberghe, W. (2007). The complexity of reproductive decision-making in asymptomatic carriers of the Huntington mutation. *European Journal of Human Genetics*, *15*, 453–462.

Donis, K., Saute, J., Krum-Santos, A., Furtado, G., Mattos, E., Torman, V. & Jardim, L. (2016). Spinocerebellar ataxia type 3/Machado-Joseph disease starting before adolescence. *Neurogenetics*, *17*, 107-113.

Downing, C. (2005). Negotiating responsibility: Case studies of reproductive decision-making and prenatal genetic testing in families facing hunting disease. *Journal of Genetic Counseling*, *14*, 219-234.

Duster, T. (1990). *Backdoor to Eugenics*. London: Routledge.

Featherstone, K., Atkinson, P., Bharadwaj, A., & Clarke, A. (2006). *Risky relations: Family, kinship and the new genetics*. New York: Berg.

Hallowell, N. (1999). Doing the right thing: Genetic risk and responsibility. *Sociology of Health & Illness*, *21*, 597–621.

Huniche, L. (2011). Moral landscapes and everyday life in families with Huntington's disease: Aligning ethnographic description and bioethics. *Social Science & Medicine*, *72*, 1810–1816.

- Inês, M., Coelho, T., Conceição, I., Duarte-Ramos, F., de Carvalho, M., & Costa, J. (2018). Epidemiology of transthyretin familial amyloid polyneuropathy in Portugal: A nationwide study. *Neuroepidemiology*, *51*, 177-182.
- Keeley, B., Wright, L., & Condit, C. (2009). Functions of health fatalism: Fatalistic talk as face saving, uncertainty management, stress relief and sense making. *Sociology of Health & Illness*, *31*, 734–747.
- Kelly, S. (2009). Choosing not to choose: Reproductive responses of parents of children with genetic conditions or impairments. *Sociology of Health & Illness*, *31*, 81-97.
- Klitzman, R., Thorne, D., Williamson, J., Chung, W., & Marder, K. (2007). Decision-making about reproductive choices among individuals at-risk for Huntington’s disease. *Journal of Genetic Counseling*, *16*, 347–362.
- Leefmann, J., Schaper, M., & Schicktanz, S. (2017) The concept of “genetic responsibility” and its meanings: A systematic review of qualitative medical sociology literature. *Frontiers in Sociology*, *1*, 18.
- Lipkin, M., & Rowley, P. (eds) (1974). *Genetic responsibility: On choosing our children’s genes*. New York: Plenum.
- Lippman-Hand, A. & Fraser, F. (1979). Genetic counseling—the post-counseling period: II. Making reproductive choices. *American Journal of Medical Genetics*, *4*, 73–87.

- Martins, S., Calafell, F., Gaspar, C., Wong, V., Silveira, I., Nicholson, G., ... Sequeiros, J. (2007). Asian origin for the worldwide-spread mutational event in Machado-Joseph disease. *Archives of Neurology*, *64*, 1502–1508.
- Mendes, Á., Sousa, L., Sequeiros, J., & Clarke, A. (2017). Discreditable legacy: Stigma and familial amyloid polyneuropathy in north-western Portugal. *Social Science & Medicine*, *182*, 73–80.
- Mendes, Á., Paneque, M., Clarke, A., & Sequeiros, J. (2019). Choosing not to know: Accounts of non-engagement with presymptomatic testing for Machado-Joseph disease. *European Journal of Human Genetics*, *27*, 353-359.
- Novas, C., & Rose, N. (2000). Genetic risk and the birth of the somatic individual. *Economy & Society*, *29*, 485-513.
- Paneque, M., Félix, J., Mendes, Á., Lemos, C., Lêdo, S., Silva, J., & Sequeiros, J. (2019). 20 anos de um protocolo de teste pré-sintomático para doenças neurológicas de início tardio em Portugal. *Acta Medica Portuguesa*, *32*, 295-304 .
- Parman, Y., Adams, D., Obici, L., Galán, L., Guergueltcheva, V., Suhr, O., & Coelho, T. (2016). Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Current Opinion in Neurology*, *29*, S3–S13.
- Petersen, A. (2006). The best experts: The narratives of those who have a genetic condition. *Social Science & Medicine*, *63*, 32-42.

Petersen, A., & Bunton, R. (2002). *The new genetics and the public health*. London: Routledge.

Pond, E., & Dimond, R. (2018). Reproductive decision making: Interviews with mothers of children with undiagnosed developmental delay. *Journal of Community Genetics, 9*, 315-325.

Quaid, K., Swenson, M., Sims, S., Harrison, J., Moskowitz, C., Stepanov, N., ... Westphal, J. (2010). What were you thinking? Individuals at risk for Huntington disease talk about having children. *Journal of Genetic Counseling, 19*, 606-617.

Raspberry, K., & Skinner, D. (2011a). Enacting genetic responsibility: Experiences of mothers who carry the fragile X gene. *Sociology of Health & Illness, 33*, 1-14.

Raspberry K., & Skinner, D. (2011b). Negotiating desires and options: How mothers who carry the fragile X gene experience reproductive decisions. *Social Science & Medicine, 72*, 992-998.

Richards, F., & Rea, G. (2005). Reproductive decision making before and after predictive testing for Huntington's disease: An Australian perspective. *Clinical Genetics, 67*, 404-411.

Sarangi, S. & Clarke, A. (2002). Constructing an account by contrast in counselling for childhood genetic testing. *Social Science & Medicine, 54*, 295-308.

Sequeiros, J., Maciel, P., Taborda, F., Lêdo, S., Rocha, J., Lopes, A., ... Jorge, C. (1998). Prenatal diagnosis of Machado-Joseph disease by direct mutation analysis. *Prenatal Diagnosis, 18*, 611-617.

Sequeiros, J., & Coutinho, P. (1993). Epidemiology and clinical aspects of Machado-Joseph disease. *Advances in Neurology, 61*, 139-153.

Sequeiros, J., Martins, S., & Silveira, I. (2012). Epidemiology and population genetics of degenerative ataxias. In Subramony, S., & Dürr, A. (Eds.). *Ataxic disorders: Handbook of clinical neurology*. Amsterdam: Elsevier, 227–251.

Sequeiros, J. (1996). Aconselhamento genético e teste preditivo na doença de Machado-Joseph. In Sequeiros, J. (Ed.). *O teste preditivo da doença de Machado-Joseph*. Porto: UNIGENE - IBMC, 97-112.

Silverman, D. (2005). *Doing qualitative research: A practical handbook*. London: Sage.

Sousa, A., Coelho, T., Barros, J., & Sequeiros, J. (1995). Genetic epidemiology of familial amyloidotic polyneuropathy (FAP) type I in Póvoa do Varzim and Vila do Conde (north of Portugal). *American Journal of Medical Genetics*, 60, 512-521.

Strauss, A., & Corbin, J. (1998). *Basic of qualitative research: Techniques and procedures for developing grounded theory*. London: Sage.

Taylor, S. (2004). Predictive genetic test decisions for Huntington's disease: Context, appraisal and new moral imperatives. *Social Science & Medicine*, 58, 137–149.

Valdrez, K., Silva, S., Coelho, T., & Alves, E. (2014). Awareness and motives for use and non-use of preimplantation genetic diagnosis in familial amyloid polyneuropathy mutation carriers. *Prenatal Diagnosis*, 34, 886-892.