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ARTICLE

Gene selection for the Australian Reproductive Genetic Carrier Screening Project ("Mackenzie's Mission")

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Abstract

Reproductive genetic carrier screening aims to offer couples information about their chance of having children with certain autosomal recessive and X-linked genetic conditions. We developed a gene list for use in "Mackenzie's Mission", a research project in which 10,000 couples will undergo screening. Criteria for selecting genes were: the condition should be life-limiting or disabling, with childhood onset, such that couples would be likely to take steps to avoid having an affected child; and/or be one for which early diagnosis and intervention would substantially change outcome. Strong evidence for gene-phenotype relationship was required. Candidate genes were identified from OMIM and via review of 23 commercial and published gene lists. Genes were reviewed by 16 clinical geneticists using a standard operating procedure, in a process overseen by a multidisciplinary committee which included clinical geneticists, genetic counselors, an ethicist, a parent of a child with a genetic condition and scientists from diagnostic and research backgrounds. 1300 genes met criteria. Genes associated with non-syndromic deafness and non-syndromic differences of sex development were not included. Our experience has highlighted that gene selection for a carrier screening panel needs to be a dynamic process with ongoing review and refinement.

Introduction

In reproductive genetic carrier screening, referred to hereafter as carrier screening, individuals are screened for variants in panels of genes to inform reproductive decision making. Most currently available panels are offered to individuals by commercial entities, typically on a user-pays basis [1]. Exceptions include targeted, population-specific screening for conditions such as hemoglobinopathies and a national screening program in Israel, which is tailored to conditions that are common in specific populations within the country [2]. Recent guidelines in several countries recommend that women who are planning a pregnancy or are early in a pregnancy should be provided with information about carrier screening [1, 3–5]. Many countries are investigating or developing carrier screening programs [6].

The Australian Reproductive Genetic Carrier Screening Project (ARGCSP; or "Mackenzie's Mission") is funded by the Australian Federal Government Medical Research Future Fund. Its goal is to develop a carrier screening model and evaluate uptake, reproductive decisions made by screened couples, psychosocial aspects, ethical considerations, and health economics. The long-term aim of the project is to prepare for national implementation of carrier screening, available free of charge to Australians who are planning a pregnancy or in the early stages of pregnancy. During the project, 10,000 couples will be screened, with analysis and reporting on a couples basis without provision of individual carrier results, other than for X-linked

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conditions. The project is known as "Mackenzie's Mission" in memory of Mackenzie Casella, who died aged 7 months of spinal muscular atrophy. Her parents (including a co-author on this paper, RC) advocated with the government for population-wide access to carrier screening. Here, we report the process used to generate the gene list for use in the project, and the list itself.

Although it is now technically feasible to offer exome or genome sequencing for carrier screening, there are potential disadvantages to analyzing the whole exome. There are many known autosomal recessive (AR) and X-linked (XL) conditions with mild or late-onset phenotypes. Examples include uncombable hair (MIM:191480) and hemochromatosis (MIM:235200). Knowledge of carrier state for such conditions is unlikely to change reproductive decision making, but the information has potential to cause anxiety and uncertainty for couples both identified as carriers, with the need for additional counseling resources. Given these considerations, careful selection of a panel of genes for use in carrier screening, especially when supported by public funding, is vital [1, 7].

Process

Constitution of gene review committee

A gene selection committee was established in June 2018. Its roles included: finalizing criteria for inclusion of genes, developing a standard operating procedure for evaluating genes (Supplementary Materials and Methods), and making final decisions on inclusion of genes identified by initial review as requiring further discussion. Committee membership included clinical geneticists with expertise in a range of sub-disciplines within the field (MDe, JM, EK), an ethicist (AN), genetic counselors (AA, KB, SE), a genetic pathologist (EK), a specialist obstetrician and gynecologist (TH), scientists from research and diagnostic backgrounds (NL, MDa, RO) and a parent (RC).

Assessing considerations for gene selection

Through extensive discussion and review of the literature, the committee identified seven key general considerations to take into account in gene selection, and reached consensus with respect to applying them. These were:

1. The severity of the associated phenotype, acknowledging the difficulty in defining "severity" and the inevitable requirement for subjective judgment

Many conditions have very variable phenotypes and there are some, such as Gaucher disease [8], in which the phenotype ranges from lethality in the perinatal period (MIM:608013) to onset of mild disease late in life and non-penetrance, as in some with type I Gaucher disease (MIM:230800).

2. The strength of evidence for a relationship between gene and phenotype

There is no value, and indeed there is the potential to cause harm, in including a gene if it will not be possible to confidently issue a report stating that variants affecting gene function are associated with the relevant phenotype [9].

3. Technical considerations

For some genes, the major mutational mechanism presents technical challenges for massively parallel sequencing (MPS). Examples include *SMN1*, associated with spinal muscular atrophy (small deletions in a highly repetitive region) [10] and *FMR1* associated with fragile X syndrome (triplet repeat expansion). For others, such as *CYP21A2*, associated with congenital adrenal hyperplasia (MIM:201910), the existence of a highly homologous pseudogene [11] presents technical challenges. If a gene is considered too important to exclude on technical grounds, an alternate methodology may be required [12]. Methodological advances, such as analysis for repeat expansions in short-read MPS data, [13] may overcome these limitations for some types of variant. The size of the gene panel also imposes potential technical constraints, in terms of the requirement to analyze and report large numbers of variants. For this study, the use of a couples-based approach to analysis, with autosomal variants reported only if both partners carry a variant that meets reporting criteria, means that the burden of analysis is markedly reduced compared with reporting individual variant information, removing this as a constraint on panel design [14, 15]. A couples-based approach also greatly reduces the genetic counseling requirements for the study [16].

4. The possibility of an important phenotype in heterozygotes

This is often an issue in XL conditions but can be relevant for AR conditions as well. An example is Fragile X-associated primary ovarian insufficiency (MIM: 311360) and Fragile X-associated tremor ataxia syndrome (MIM: 300623) in people with *FMR1* premutations [17, 18].

5. Ethical considerations

Implementation of screening using a large panel, particularly if government funded, may be seen as representing a

value judgment about the worth of the lives of people who live with the conditions for which screening is offered. The offer of free screening or the size of the panel may also be viewed as inducements to screening uptake.

6. Community expectations

Involvement of communities who live (or care for someone) with a genetic condition is important, to ensure that the program will be acceptable to those whom it is intended to serve. Where data are available, understanding current practice within such communities can inform program design. For example, information regarding whether people currently access preimplantation genetic testing for monogenic disorders (PGT-M) or prenatal diagnosis for a condition may help in understanding the perceived severity of a condition where this is not clear.

7. Local factors

There may be country or community-specific issues that impact the assessment of a gene or condition [2, 6, 19]. For example, the Dor Yeshorim screening program is structured using premarital, anonymous screening in which screened individuals do not receive individual results, to address religious and cultural issues specific to the Ultra-Orthodox Jewish communities for whom the program was designed [20].

Criteria for gene selection

The goal was to create a gene list best suited to the Australian healthcare system (which comprises both publicly funded and privately provided care), the population-based model of Mackenzie's Mission and Australian social values. The committee agreed on four overarching criteria for gene selection. These were used, together with the seven general considerations above, to assess whether a gene should be included in the gene list for this project. The criteria were:

1. The condition is one for which an "average" couple would take steps to avoid the birth of a child with that condition

This includes conditions with lethality in childhood, which are significantly disabling (mindful that what constitutes a disability can be socially constructed or contested on other grounds), or otherwise have a severe impact on quality of life for an affected child and significant negative impact on the family. Conditions for which there was effective but very burdensome treatment were also included. This criterion was not intended to imply or assume that couples *should* take steps to prevent the birth of a child with the condition, but that they have the opportunity to discuss the options with an appropriately trained health professional [4]. We also recognize the ongoing debates surrounding aspects such as how conditions are described to couples, and the achievement of non-directive counseling in reproductive health care. We are actively considering these in Mackenzie's Mission.

2. There is potential benefit from knowing about the condition to inform management in the neonatal period

This criterion was particularly important if the condition was treatable but not included in existing newborn screening programs, or where intervention prior to results from newborn screening being available may be beneficial. This criterion also serves an important ethical purpose, by reinforcing that carrier screening is not predicated on detection and elimination, but on informing a range of decisions.

3. There is strong evidence that variants in the gene are associated with the condition in question, sufficient to allow confidence in informing couples of their chance of having a child with the condition in question

The ClinGen framework [9] was adapted to allow rapid assessment of large numbers of genes, with particular reliance on sufficient affected individuals being reported with variants causative of the condition in question. The ClinGen framework considers evidence in several categories, including case-level data (e.g., number of affected individuals with variants in the gene, segregation in families); case–control data (where available); evidence regarding protein function; evidence of alteration of function, and evidence from model systems. The first two categories, collectively "genetic evidence", are most strongly weighted. See SOP, Supplementary Materials and Methods.

4. There are no technical barriers to testing for variants in the gene

For a gene to be included, either of criterion 1 or 2 needed to be met, along with criterion 3. Criterion 4 was considered as a second phase of the process once a list of genes meeting 1 and/or 2, and 3 was complete.

Identification of genes for assessment

Genes to include in the assessment were identified through searching the OMIM database [21] (last accessed 30/07/2018) and reviewing genes currently screened by 23 existing commercial providers and/or listed in published carrier screening gene lists [22, 23] (Supplementary Online Materials, Table S1).

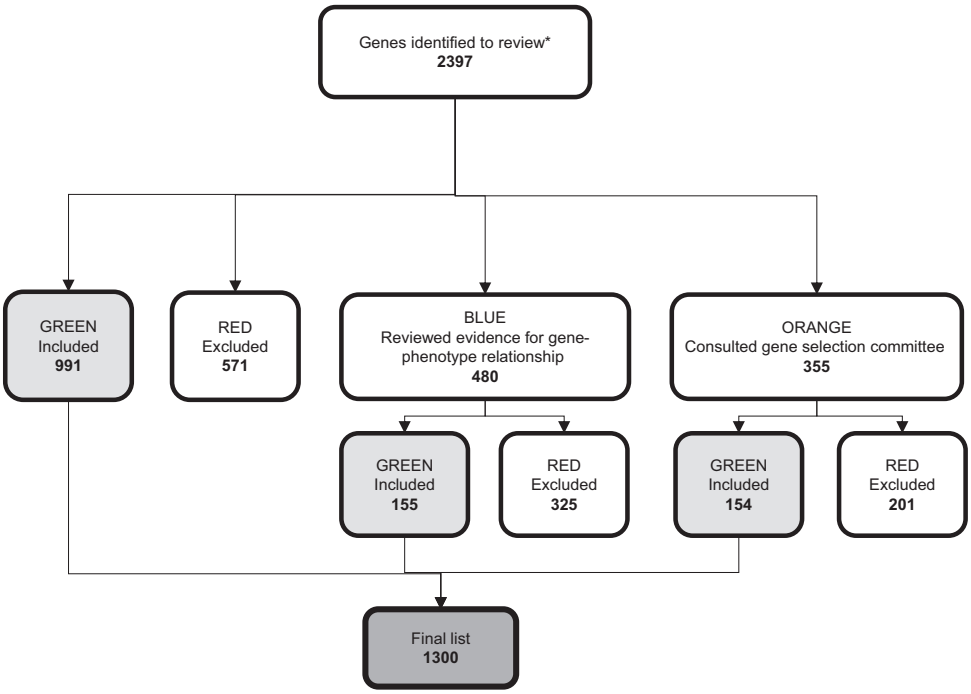

Fig. 1 The Mackenzie's Mission gene list selection process. 2397 genes were assessed in total, identified from two sources: the OMIM database and existing gene lists used for carrier screening. Review by clinical geneticists divided the genes into four categories: GREEN—Include; RED—Exclude; BLUE—Review evidence for gene-phenotype relationship; ORANGE—Consult gene selection committee. BLUE genes were reviewed for evidence of a gene-phenotype relationship. ORANGE genes were discussed by the gene selection committee. The result was a list of 1300 genes selected for use in Mackenzie's Mission.

Review by clinical geneticists

Every gene was reviewed by at least one clinical geneticist, according to the SOP developed by the gene review committee. Sixteen clinical geneticists (DA, MB, CC, AC, MDe, RJ, BK, EK, JL, AM, JM, NP, SR, AR, TR, MW) participated in this process. A subset of 195 randomly selected genes were assessed by two or more clinical geneticists (distributed across all 16) to assess for consistency in the classification process. The clinical geneticists classified genes as follows:

Green - include:

Those assessed as meeting criteria for inclusion.

Red - exclude:

Those assessed as not meeting criteria for inclusion.

Blue - review evidence for gene-phenotype relationship:

Those assessed as being associated with a phenotype that met criteria, but with uncertainty regarding whether there was sufficient evidence for a gene-phenotype relationship, with further review required.

Orange - consult gene selection committee:

Those for which the clinical geneticist felt further discussion/consideration by the gene selection committee was warranted. The most common reason for this was that there was a question regarding whether the phenotype was sufficiently severe to meet criteria. Genes were also referred for discussion of other issues, such as heterozygote phenotype or a wide spectrum of severity.

Review of blue genes for evidence of gene-phenotype relationship

Genes classified as blue were assessed by one of three reviewers (RO, TH, EK). The Human Gene Mutation Database (Professional) [24] was used to identify relevant literature.

Review of orange genes by the gene selection committee

Orange genes were discussed by the committee, with the goal of reaching a final classification for each gene as either Green (include) or Red (exclude). For some genes, it was considered necessary to seek input from a relevant subspecialist to aid decision making. Specialists who were consulted included a dermatologist, pediatric nephrologists, pediatric endocrinologists, pediatric neurologists, a pediatric immunologist, a pediatric respiratory physician, and metabolic disease specialists (see "Acknowledgements"). The committee also commissioned a written submission from an ethics researcher and advocate (see "Acknowledgements", MC) regarding inclusion of genes involved in differences (or "disorders") of sex development (DSD); also known as intersex traits.

The Mackenzie's Mission Laboratory Committee was consulted regarding their perspectives on whether there

were any perceived technical barriers to inclusion of genes on list (i.e., to ensure genes met criterion 4). A genetic counselor (KB) reviewed the entire list of Green genes, with two aims: developing a list of conditions grouped by phenotype, and performing a final check (in consultation with a clinical geneticist, EK) to ensure all classified as Green met our established criteria.

Results

Figure 1 provides a summary of the outcomes of the Mackenzie's Mission gene selection process. Overall, 2397 genes associated with an AR or XL condition were included in this assessment (Supplementary Online Materials, Table S2). Clinical geneticists classified 991 genes as Green, 564 as Red, 480 as Blue and 355 as Orange. For the 195 genes assigned to two or more clinical geneticists for classification there was 75% concordance between reviewers.

Of the 480 genes classified as Blue by the clinical geneticists, 155 were reclassified as Green and 325 as Red. The genes classified as Red included nine removed for technical reasons (Supplementary Online Materials, Table S3), two of these on recommendation of the study Laboratory Committee. Fragile X syndrome and spinal muscular atrophy were considered too common [25] to exclude FMR1 and SMN1 on technical grounds; these genes remained Green and targeted assays for the major variant type will be used instead. The 355 Orange genes were considered by the Gene Review Committee over a series of meetings. Of these, 154 were subsequently classified as Green (included) and 201 as Red (excluded). The 201 genes classified as Red included 36 genes associated with non-syndromic deafness (see "Discussion").

Of the Green genes, we identified 90 genes (the majority of which were for XL conditions) in which heterozygotes had been reported as having a significant phenotype. A single gene, *BRCA2*, was classified as Red by the committee on the basis of phenotype in heterozygotes (see Discussion). No other genes were identified as having comparable penetrance and severity of phenotype in the heterozygote.

The final list of 1300 genes is available as Supplementary Online Table S4. This list and any future updated versions will also be available at PanelApp Australia (https://panelapp.agha.umccr.org).

Discussion

In designing this gene selection process, severity was a key consideration. We recognized ongoing clinical and ethical debate over this concept and that views on severity will be influenced by individual experiences and values. This emphasis on phenotype required input from clinicians familiar with a range of different genetic conditions. Clinical geneticists, as a group, have experience in conditions that affect all body systems and are skilled at assessing literature about rare conditions, including conditions with which they may not have direct clinical experience.

It was important that any gene to be included should have strong evidence for gene–phenotype association, and a relatively conservative approach was taken to assessing this. Of 480 genes initially classified as Blue by a clinical geneticist—i.e., where the phenotype was sufficiently severe for inclusion but it was not clear whether the gene-phenotype evidence was strong enough—325 were excluded from the list on the grounds of insufficient evidence. The likely accumulation of evidence for many of these genes, combined with the rapid pace at which new gene-disease associations are being identified, emphasizes that the process of gene selection for such carrier screening panels needs to be dynamic and incorporate processes for reassessment and review of genes. This will likely lead to certain genes being added, while others may be removed. Annual review of the list is planned for this project.

There were 195 genes (8.7% of the initial list) that were reviewed by more than one geneticist, with 75% concordance in classification for inclusion. Gene classification was considered discordant in two situations. The first was if one reviewer classified a gene as Red and another reviewer independently classified the same gene as Green (11% of genes classified by multiple reviewers). The second situation was if one reviewer classified a gene as Red or Green and the other classified the gene as Blue or Orange with the resulting final classification resulting in a discordance as above (an additional 14% of genes). An overall 25% discordance suggests that, not surprisingly, there was some inconsistency between individual clinical geneticists in their application of the criteria. Two independent checks were instituted to address possible inconsistency; comparison with lists developed by others, and a final comprehensive review of all included genes by a genetic counselor.

A single autosomal gene, *BRCA2*, was excluded from the list because of the associated heterozygote phenotype. Biallelic variants in *BRCA2* are associated with Fanconi anemia, complementation group D1 (MIM:605724). Fanconi anemia meets our criteria for inclusion, and other genes associated with this condition are included in the list. However, heterozygous *BRCA2* variants are associated with a high risk of various cancers, particularly breast and ovarian cancer. Although the study consent process includes the possibility that there may be a finding of relevance to the participant's own health, it was considered that the implications of finding a pathogenic *BRCA2* variant in both members of the tested couple could not be adequately

addressed in the context of this research program, which focuses on informing reproductive decisions. Sub-studies within this program are examining participants' attitudes to obtaining information relevant to their own health.

Phenotypic heterogeneity is very common, with numerous genes associated with more than one phenotype or spectrum of severity that may include phenotypes that would not meet criteria for inclusion. We decided that if there was sufficient evidence for a gene-phenotype relationship in relation to a phenotype severe enough for inclusion, then the gene should be included regardless of the existence of less severe phenotypes. However, pairs of variants known to be associated only with mild disease, or with adult-onset disease only, will not be reported. Clearly, it will not always be possible to make distinctions of this nature, raising ethical considerations and increasing the complexity of variant calling [26].

Conditions already included in newborn screening (NBS) panels are a category needing careful consideration. Some conditions—such as methylmalonic acidemia (MIM:251000) have significant impacts even when diagnosed before the onset of symptoms. Others are effectively treatable but the treatment can be burdensome to the child and family—for example, phenylketonuria (MIM:261600). On the other hand, there are some conditions, such as various forms of congenital hypothyroidism (e.g., MIM: 275200) and medium chain acyl-CoA dehydrogenase deficiency (MIM:201450) for which treatment following diagnosis by NBS is very effective and is not considered overly burdensome. As a result, the latter were excluded.

Two groups of conditions were the subject of extensive discussion, debate and consultation: non-syndromic deafness and DSD. For both deafness and DSD, there are a number of syndromic conditions which were included because other serious or severe clinical features (alone or in combination with deafness or DSD) meant that the condition met criteria for inclusion. Examples include Usher syndrome (various genes, including *USH2A*, MIM:276901) and the autosomal recessive form of Antley-Bixler syndrome (MIM:201750). In relation to non-syndromic deafness without other clinical features, it is notable that most (18/23) of the published and commercial carrier screening panels that we identified included at least one relevant gene (*GJB2*). Some couples do use PGT-M or prenatal diagnosis to avoid having a child affected by non-syndromic deafness, although data are limited regarding the proportion of carrier couples who make this choice [27]. There are effective interventions available for most children living with non-syndromic deafness, as well as an established discourse on the question of whether deafness is indeed a disabling condition [28–30]. Our conclusion, following extended debate within the group and extensive discussion with stakeholders, was that in general, non-syndromic deafness is a condition which is not sufficiently disabling to meet our criteria. However, further ethical consideration, professional deliberation and public discussion regarding the acceptability of offering all couples information about their chance of having a child with non-syndromic deafness is needed. The pilot nature of this project, and the potential problems of de-listing genes in the future also informed the discussion. Over the course of the project, there are several studies planned to investigate community attitudes in Australia to this question, to inform the design of a future screening program. This may include offering testing for non-syndromic deafness genes to a sub-cohort of couples.

The discussion in relation to DSD focused on the impact of these conditions on the lives of individuals who live with them. Adverse impacts associated with DSD tend to draw on societal norms rather than intrinsic clinical features [31]. This includes the experience of stigma, discrimination and other harms arising from a person's body not conforming to norms of gender or biological sex. In particular, concerns were raised about the use of medical intervention to "fix" children born intersex without sound clinical rationale. There was also discussion of the message that inclusion of DSD in an carrier screening panel is premature, not least because of ongoing ethical debate regarding selecting against DSD [32]. Thus, DSD that occurs in the absence of other serious clinical features did not meet our criteria for inclusion.

The activities and deliberations of the Gene Selection Committee were underpinned by a broad recognition of the ethical significance of designing a panel for publicly funded carrier screening. The Committee sought to balance the range of issues raised throughout this paper, as seen from the perspective of multiple stakeholders. Of particular relevance was the concept of severity, and the "messages" signaled by certain genes being included [33]. We were mindful of the project's focus on reproductive decisions rather than individual diagnoses. The final gene list is one for which it is reasonable to offer couples the chance to deliberate and reflect on their values.

To our knowledge, this is the largest published carrier screening gene list to date. The large size of the list was made possible in part by the technical capacity to deliver screening at this scale. Two of the participating laboratories are using exome sequencing with bioinformatic extraction of data for the selected genes; the third is using a large panel. We will compare and contrast the two approaches. Initially there was consideration of restricting the list to ~500 genes, for example by excluding genes associated with syndromes that had only been reported in population isolates not represented in Australia. However, we considered that, beyond the most common conditions, it was difficult to develop a rational basis for ranking genes, and in the absence of a known technical barrier to

inclusion (see "Introduction"), the best approach was to include all genes that met our criteria. As mentioned, the provision of couples-based results was also relevant to the size of the panel being feasible for implementation at population scale.

Strengths of our approach include an initial inclusive approach to gene identification and the iterative process with checks for consistency, group deliberation, and debate, as well as comparison with other commercial and academic gene lists. Every gene was reviewed by at least one clinical geneticist using a standard operating procedure. A multidisciplinary team was involved in refining the criteria for gene selection and in the process of selecting the genes. Importantly, the team included an ethicist, whose role was to help frame and address the ethical challenges inherent in the decision making processes required to generate such a list. We also included a parent at every stage of the process. Limitations include the difficulty of ensuring that a large group of clinicians interpret and apply criteria consistently, a lack of ethical consensus regarding the criteria for including genes on a carrier screening panel, and the difficulty of capturing a complete initial list of genes for consideration. There may be technical limitations on our ability to comprehensively screen some genes that will only become apparent in the course of practical application of screening using the list.

A gene list of this type should be considered dynamic, informed by ongoing gene discovery and research and be responsive to community attitudes and expectations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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