Expanded carrier screening using next-generation sequencing of 123 Hong Kong Chinese families: a pilot study

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A B S T R A C T

Introduction: To determine the carrier frequency and common mutations of Mendelian variants in Chinese couples using next-generation sequencing (NGS).

Methods: Preconception expanded carrier testing using NGS was offered to women who attended the subfertility clinic. The test was then offered to the partners of women who had positive screening results. Carrier frequency was calculated, and the results of the NGS panel were compared with those of a target panel.

Results: In total, 123 women and 20 of their partners were screened. Overall, 84 (58.7%) individuals were identified to be carriers of at least one disease, and 68 (47.6%) were carriers after excluding thalassaemias. The most common diseases found were *GJB2*-related DFNB1 nonsyndromic hearing loss and deafness (1 in 4), alpha-thalassaemia (1 in 7), beta-thalassaemia (1 in 14), 21-hydroxylase deficient congenital adrenal hyperplasia (1 in 13), Pendred's syndrome (1 in 36), Krabbe's disease (1 in 48), and spinal muscular atrophy (1 in 48). Of the 43 identified variants, 29 (67.4%) were not included in the American College of Medical Genetics and Genomics or American College of Obstetrics and Gynecology guidelines. Excluding three couples with alpha-thalassaemia, six at-risk couples were identified.

Conclusion: The carrier frequency of the investigated members of the Chinese population was 58.7% overall and 47.6% after excluding thalassaemias. This frequency is higher than previously reported. Expanded carrier screening using NGS should be provided to Chinese people to improve the detection rate of carrier status and allow optimal pregnancy planning.

Hong Kong Med J 2021;27:177–83
https://doi.org/10.12809/hkmj208486

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This article was published on 19 Feb 2021 at www.hkmj.org.

New knowledge added by this study

- The carrier frequency of Mendelian variants in the Chinese population is higher than previously reported.
- Next-generation sequencing should be used in the Chinese population to increase the detection rate of carriers of Mendelian variants.

Implications for clinical practice or policy

- Expanded carrier screening with next-generation sequencing should be provided to Chinese people to identify carrier status of Mendelian variants for pregnancy planning.

Introduction

Carrier screening aims to identify couples at risk of conceiving children affected by recessive genetic diseases. Carrier couples of most recessive genetic conditions are typically asymptomatic, and the only way to identify them is by carrier screening. If a couple are both carriers of the same autosomal recessively inherited condition, their offspring have a 1 in 4 chance of being affected. The risk is as high as 1 in 2 in male offspring if the mother is an X-linked recessive carrier. Carrier screening facilitates informed prenatal testing options such as pre-implantation genetic diagnosis, prenatal invasive testing, and other reproductive options such as donor gametes and adoption for carrier couples. Prenatal genetic diagnosis could provide parents

透過次世代基因檢測123個家庭進行擴展帶因者測試：先導研究

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引言：使用次世代基因檢測確定華籍夫婦中孟德爾變體的帶因者頻率和常見突變。

方法：利用次世代基因檢測為生育指導診所就診的女性提供孕前擴展帶因者測試，然後為篩查結果呈陽性的女性伴侶提供相關測試。計算帶因者頻率並將次世代基因檢測結果與標靶基因組結果進行比較。

結果：共篩選123名婦女及其當中的20名伴侶。總體而言，84人（58.7%）為至少一種疾病的帶因者，排除地中海貧血後的帶因者有68人（47.6%）。最常見疾病是*GJB2*基因相關的DFNB1非綜合徵型聽力缺損及喪失（1/4）、甲型地中海貧血（1/7）、乙型地中海貧血（1/14）、缺乏21-羥化酶引致的先天性腎上腺增生症（1/13）、耳聾—甲狀腺腫綜合（1/36）、嬰兒家族性瀰漫性硬化（1/48）以及脊髓性肌肉萎縮症（1/48）。在43種已鑑定變異中，有29種（67.4%）未包含在美國醫學遺傳學與基因組學學院或美國婦產科學院指南中。除了三對患有地中海貧血的夫婦，還確定了六對高危夫婦。

結論：研究對象的總體帶因者比例為58.7%，剔除地中海貧血後的帶因者比例則為47.6%，較以往報告為高。應擴展華籍人口次世代基因檢測篩查，以提高帶因者檢出率並制定最理想的生育計劃。

with more information, appropriate counselling, and preparation to take care of the child.[1]

Various carrier screening programmes targeting specific populations have been developed for single gene diseases such as cystic fibrosis, thalassaemia, and Tay-Sachs disease.[2,3] The American College of Obstetrics and Gynecology (ACOG) published guidelines on ethnically based carrier screening programmes, eg, screening for haemoglobinopathies in individuals of Southeast Asian, African and Mediterranean descent and screening for cystic fibrosis, Tay-Sachs disease, familial dysautonomia, and Canavan disease for individuals of Ashkenazi Jewish descent.[2,4] However, race and ethnicity can only be determined by patient self-report, and measures to ascertain ethnicity are restrictive.[5] Ancestry-based screening could also lead to unequal distribution of genetic testing and may miss diagnosis of diseases in populations without screening.[3] Thus, both the American College of Medical Genetics and Genomics (ACMG) and ACOG recommended carrier screening for cystic fibrosis in all couples in 2001.[6,7] The ACMG and ACOG have also recommended carrier screening for spinal muscular atrophy (SMA) in all couples since 2008 and 2017, respectively.[8,9]

With advancements in genomic technology providing access to next-generation sequencing (NGS), expanded screening panels that cover a wide variety of disorders could be offered to individuals regardless of ethnic background.[9]

The common mutations in the screening panel are mainly chosen based on studies performed in the Caucasian and Ashkenazi Jewish populations. Those known common mutations may not be ethnicity-specific and may not cover all mutations present in the Chinese population. Thus, the approach of sequencing the entire disease-causing gene would be more useful than the targeted common mutations approach for the Chinese population.

Studies that evaluate carrier frequencies and common mutations in the Chinese population are lacking in our locality. Further study to review carrier frequency and the identified variants in the Chinese population is essential to guide the future design of carrier screening platforms specific to the Chinese population and improve the cost-effectiveness of carrier screening for genetic diseases.

Methods

Subjects

Expanded carrier screening testing was offered to women who attended the subfertility clinic and pre-pregnancy counselling clinic of the study unit between March 2016 and March 2017. They were counselled about the prevalence and inheritance of recessive conditions, and the chance of having affected offspring for a silent carrier couple, using examples and figures. The purpose, testing methods, interpretation of results, potential benefits, risks, and limitations of the expanded carrier screening were also explained.

A generic consent form for the expanded carrier screening testing prepared by the laboratory was used. Consent for the use of data obtained for research or audit purposes was also obtained. The test was then ordered by the clinician as self-financed testing. The expanded carrier screening test was offered to both members of the couple separately during pre-test counselling. During post-test counselling, if a woman was identified to be a carrier of an autosomal recessive disease, but her partner had not completed the test, her partner was also counselled for carrier testing using the same method as self-financed testing. If both the male and female members of the couple were carriers of a same autosomal recessive disorder or the female was the carrier of an X-linked recessive disorder, they were identified as at-risk couples having the possibility of an affected pregnancy. Genetic counselling was arranged for at-risk couples to discuss reproductive options such as preimplantation genetic testing and prenatal diagnostic testing. Finally, the carrier frequencies of individual diseases and the identified variants were reviewed. STROBE reporting guidelines were implemented in this manuscript.

Disease panels

The expanded carrier screening panel consisted of 104 conditions inherited in autosomal recessive or X-linked manner (online supplementary Appendix). The severity of these conditions ranged from debilitating diseases with neurological impairment (eg, SMA), reduced lifespan (eg, thalassaemia), or intellectual disability (eg, fragile X syndrome) to diseases requiring early intervention in the prenatal or early neonatal period (eg, 21-hydroxylase deficient congenital adrenal hyperplasia [CAH]).

Laboratory tests

The screening platform (Family Prep Screen 2.0; Counsyl, South San Francisco [CA], United States), which was reported by Lazarin et al,[10] uses NGS techniques to analyse the listed exons, as well as selected intergenic and intronic regions, of the genes responsible for the recessive conditions. The selected regions were sequenced to high coverage and compared with standards and references of normal variation. High-throughput sequencing detects approximately 94% of known clinically significant variants according to the test provider. Variants classified as 'predicted' or 'likely' pathogenic have been reported.[11] Fragile X specific polymerase chain reaction assay was used to determine the CGG repeat size in the 5′ untranslated region of the *FMR1* gene. Targeted copy number analysis was used to determine the copy number of exon 7 of the *SMN1* gene. g.27134T>G variant testing for identification of silent SMA carriers is not included in this platform.[12] The turnaround time of the test was approximately 3 weeks.

Results

A total of 123 Chinese women (age range, 20-45 years) opted for expanded carrier screening, and 69 (56.1%) of them were found to be carriers of at least one disease. Twenty of the women's partners (29.0%, 20/69) were willing to complete the screening test after genetic counselling. Screening for possible carrier status before contemplating pregnancy was the indication in all individuals. Excluding one woman who was positive for fragile X syndrome, 48 women who screened positive opted not to screen their partners. Seventeen of them were solely carriers of alpha- or beta-thalassaemia (10 and 7, respectively), which could be accurately screened by mean corpuscular volume. The results also included 20 *GJB2* carriers, especially the c.109G>A (p.Val37Ile) mutation, which has low penetrance and is prevalent in the Chinese population.[13,14] Carrier status for CAH, SMA, Pendred's syndrome, and other very rare diseases was found in three, one, one, and six individuals, respectively. After integrating partners' data, 84 subjects (58.7%) were found to be carriers for at least one recessive disease, including thalassaemias. Excluding thalassaemias, 68 subjects (47.6%) were found to be carriers of at least one disease (Tables 1 and 2).

TABLE 1. Carrier frequency of genetic diseases identified in a cohort of 143 adults, listed according to their frequency and alphabetic order

Disease	No. (%) of cases identified	Carrier frequency
GJB2-related nonsyndromic hearing loss	40 (28.0%)	1 in 4
Alpha-thalassaemia	22 (15.4%)	1 in 7
21-Hydroxylase deficient congenital adrenal hyperplasia	11 (7.7%)	1 in 13
Beta-thalassaemia	10 (7.0%)	1 in 14
Pendred's syndrome	4 (2.8%)	1 in 36
Krabbe's disease	3 (2.1%)	1 in 48
Spinal muscular atrophy	3 (2.1%)	1 in 48
CLN5-related neuronal ceroid lipofuscinosis	2 (1.4%)	1 in 72
Fanconi's anaemia type C	2 (1.4%)	1 in 72
Biotinidase deficiency	1 (0.7%)	1 in 143
Congenital Finnish nephrosis	1 (0.7%)	1 in 143
Familial Mediterranean fever	1 (0.7%)	1 in 143
Fragile X syndrome	1 (0.7%)	1 in 143
Galactosaemia	1 (0.7%)	1 in 143
Gaucher's disease	1 (0.7%)	1 in 143
Glutaric academia	1 (0.7%)	1 in 143
Glycogen storage disease type Ia	1 (0.7%)	1 in 143
GRACILE syndrome	1 (0.7%)	1 in 143
Metachromatic leukodystrophy	1 (0.7%)	1 in 143
Polyglandular autoimmune syndrome	1 (0.7%)	1 in 143
Glycogen storage disease type II (Pompe's disease)	1 (0.7%)	1 in 143
Primary carnitine deficiency	1 (0.7%)	1 in 143
Pseudocholinesterase deficiency	1 (0.7%)	1 in 143
Walker–Warburg syndrome	1 (0.7%)	1 in 143

TABLE 2. Frequency of multiple-disease carriers (n=143)*

	Carrier of at least 1 disease	Carrier of at least 2 diseases	Carrier of at least 3 diseases	Carrier of 4 diseases
Including thalassaemias	84 (58.7%)	24 (16.8%)	3 (2.1%)	1 (0.7%)
Excluding thalassaemias	68 (47.6%)	11 (7.7%)	1 (0.7%)	0

* Data are shown as No. (%)

Prevalence of carriers of various diseases

A total of 24 recessive diseases were identified in 84 (58.7%) of the 143 subjects. The data are summarised in Table 1. The most common condition identified was *GJB2*-related hearing loss (frequency: 1 in 4). One subject was also found to be a homozygote for the p.V37I mutation in the *GJB2* gene. The subject was aged 34 years and did not complain of hearing impairment at the time of recruitment. Both alpha- and beta-thalassaemia were prevalent in this cohort (1 in 7 and 1 in 14, respectively), as shown in Table 1. Eleven subjects (1 in 13) were identified as carriers of the 21-hydroxylase deficient type of CAH. Four subjects were heterozygous carriers of Pendred's syndrome (1 in 36), and three subjects were heterozygous carriers for each of SMA and Krabbe's disease (1 in 48). Two carriers were identified for both CLN5-related neuronal ceroid lipofuscinosis and Fanconi's anaemia type C, and one carrier was identified for each of 15 other recessive conditions (Table 1).

Multiple-disease carriers

The frequency of multiple-disease carriers is shown in Table 2. Carrier status of at least two recessive conditions was identified in 24 subjects (24/143, 16.8%) including thalassaemias and 11 subjects (7.7%) excluding thalassaemias.

At-risk couples

One woman was a fragile X syndrome premutation carrier, and 20 women had positive results for carrier status, and their male partners were sequentially tested. After integrating the sequential testing results, we identified nine at-risk couples, including three of alpha-thalassaemia, two of CAH, two of *GJB2*-related hearing loss, one of Pendred's syndrome, and one of fragile X syndrome (Table 3). The rate of at-risk couples was 12.0% (9/75) overall and 8.0% (6/75) excluding thalassaemias.

Comparison between traditional screening guidelines and next-generation sequencing

Forty three variants were identified by the NGS panel (Table 4). Of the 43 variants, 29 (67.4%) were not included in the ACMG or ACOG guidelines.[9,11]

Discussion

This study demonstrated the application of NGS to investigate carrier frequency status of members of the Chinese population in Hong Kong. The overall positive yield of this expanded carrier screening panel in our cohort was 58.7%. Not surprisingly, both alpha- and beta-thalassaemia account for a significant proportion of them. However, even after excluding thalassaemias that could be screened by mean corpuscular volume, the positive yield using NGS was still as high as 47.6%, with 6 out of 75 at-risk couples (8.0%) identified and potentially benefiting from further pre-conception genetic counselling.

Although NGS has been increasingly used for genetic carrier screening in Western countries in recent years, there is a scarcity of data about the carrier frequency of various recessive diseases in the Chinese population. In 2013, Lazarin et al[10] reported the carrier frequencies of a sample of approximately 20 000 people from different ethnic groups using a targeted mutation panel. East Asians had the lowest carrier frequency (8.5%) compared with Ashkenazi Jews (43.6%) or Caucasians (21%-32.6%). The most common genetic disease identified among East Asians was *GJB2*-related hearing loss (1 in 22), followed by beta-thalassaemia/sickle cell disease (1 in 78) and SMA (1 in 85). However, the assay used by Lazarin et al[10] was partially based on targeted genotyping, so carriers of variants other than the included common mutations were not detected. Thus, the reported carrier frequencies are likely underestimated, particularly among East Asians, as the common mutation panel was mainly based on the Caucasian and Ashkenazi Jewish populations.

TABLE 3. Diseases identified in nine at-risk couples

Couple	Disease	Variants	Family history
1	Alpha-thalassaemia	SEA, SEA	No
2	Alpha-thalassaemia	SEA, SEA	No
3	Alpha-thalassaemia	SEA, alpha 3.7	No
4	21-Hydroxylase deficient congenital adrenal hyperplasia	c.293-13C>G; *CYP21A2* deletion	Family history of neonatal death with uncertain cause
5	21-Hydroxylase deficient congenital adrenal hyperplasia	c.844G>T (non-classic); c.293-13C>G	No
6	*GJB2*-related nonsyndromic hearing loss	c.235delC; c.109G>A	No
7	*GJB2*-related nonsyndromic hearing loss	c.109G>A; c.109G>A	No
8	Pendred's syndrome	c.919-2A>G; c.1160C>T	No
9	Fragile X syndrome	29/58 CGG repeats	No

TABLE 4. Identified variants of recessive diseases

Disease	Gene	Variant identified	No. of cases
GJB2-related nonsyndromic hearing loss	*GJB2*	c.109G>A	35
		c.235delC	3
		c.176_191del	2
Alpha-thalassaemia	*HBA1/HBA2*	SEA deletion	11
		3.7 deletion	6
		HBA1+HBA2 deletion	1
		4.2 del	3
		Haemoglobin Constant Spring	1
21-Hydroxylase deficient congenital adrenal hyperplasia	*CYP21A2*	c.955C>T	4
		c.293-13C>G	3
		CYP21A2 deletion	2
		c.1069C>T	1
		c.844G>T	1
Beta-thalassaemia	*HBB*	c.126_129delCTTT	5
		c.316-197C>T	3
		-28A>G	1
		c.130G>T	1
Pendred's syndrome	*SLC26A4*	c.2168A>G	1
		c.919-2A>G	1
		c.754T>C	1
		c.1160C>T	1
Krabbe's disease	*GALC*	c.1901T>C	2
		c.946C>T	1
Spinal muscular atrophy	*SMN1*	Exon 7 deletion	3
CLN5-related neuronal ceroid lipofuscinosis	*CLN5*	c.595C>T	1
		c.51delG	1
Fanconi's anaemia type C	*FANCC*	c.520C>T	1
		c.1377_1378delCA	1
Biotinidase deficiency	*BTD*	c.637delC	1
Congenital Finnish nephrosis	*NPHS1*	c.3478C>T	1
Familial Mediterranean fever	*MEFV*	c.2282G>A	1
Fragile X syndrome	*FMR1*	29/58 CGG repeats	1
Galactosaemia	*GALT*	c.436G>T	1
Gaucher's disease	*GBA*	c.1448T>C	1
Glutaric acidaemia	*GCDH*	c.1240G>A	1
Glycogen storage disease type Ia	*G6PC*	c.648G>T	1
GRACILE syndrome	*BCS1L*	c.493A>T	1
Metachromatic leukodystrophy	*ARSA*	c.1344dupC	1
Polyglandular autoimmune syndrome	*AIRE*	c.652+1G>T	1
Glycogen storage disease type II (Pompe's disease)	*GAA*	c.1411_1414delGAGA	1
Primary carnitine deficiency	*SLC22A5*	c.1400C>G	1
Pseudocholinesterase deficiency	*BCHE*	c.401dup	1
Walker–Warburg syndrome	*FKTN*	c.919C>T	1

In particular, alpha-thalassaemia and CAH are not included in their panel.

Recently, Guo and Gregg[15] investigated the carrier prevalence of 415 recessive diseases using an exome sequencing database of approximately 120 000 samples. The consistent finding is that

Ashkenazi Jews had the highest carrier frequency (62.9%), followed by Caucasians, Africans, and Hispanics; South and East Asians had the lowest carrier frequency, but that frequency rose to 32.6% with a more comprehensive panel. However, because neither alpha-thalassaemia nor SMA was included in the panel, the most common diseases for which carrier status was found among East Asians were autoimmune polyendocrinopathy syndrome type 1, beta-thalassaemia, Usher's syndrome type IIa, and CAH. The carrier frequency of each of those diseases was 1% to 2%. In 2018, Zhao et al[16] reported >10 000 mainland Chinese couples in whom NGS was used to screen for 11 recessive diseases. That study showed a high carrier frequency of 27.49%, and 2.4% of couples were carriers of the same genetic disease. The authors found that the diseases with the highest carrier frequencies were alpha-thalassaemia (15.1%), beta-thalassaemia (4.8%), phenylketonuria (3.6%), Wilson's disease (2.0%), *GJB2*-related hearing loss (1.7%), and Pendred's syndrome (1.6%). However, that study excluded SMA, CAH, and fragile X syndrome.[16] Our study's findings are distinguished from those of Lazarin et al,[10] Guo and Gregg,[15] and Zhao et al[16] in that we observed a much higher carrier rate for *GJB2*-related hearing loss (28.0%), which is consistent with our previous report (15.9%) using target-enriched massively parallel sequencing.[14] In addition, we found higher carrier frequencies for CAH (7.7%) and Pendred's syndrome (2.8%). Our study's observed carrier frequency for SMA (2.1%) is similar to that found in Western populations,[17-21] indicating that SMA affects all ethnic groups.

One of the major limitations of our study was the small sample size. More data are required before we can draw precise conclusions regarding the carrier frequency of individual recessive conditions in the Chinese population. Second, patients in this cohort were referred for subfertility or pre-pregnancy counselling for genetic conditions, and give out of this 123-patient cohort had a positive family history, including thalassaemias, balanced translocation carriers, family history of autism, neonatal death, and previous pregnancy with structural abnormality. Thus, some of the results might have been over-represented. For example, one woman who presented with subfertility was discovered to be a fragile X permutation carrier, and this may have elevated the carrier frequency of fragile X in our cohort of 123 women. In our previous study, in which we used a robust polymerase chain reaction–based assay to quantify fragile X CGG repeats for screening of 3000 low-risk Chinese pregnant women, the permutation frequency was approximately 1 in 800.[22] Another couple in the present study had a previous baby with neonatal death of unknown cause in Mainland China and were found to be 21-hydroxylase deficient CAH carriers. Nonetheless, even after excluding these two CAH cases, the CAH carrier frequency in our study (1 in 16) remains high.

Currently, both the ACOG and ACMG recommend carrier screening for SMA and cystic fibrosis only in individuals of East Asian ethnicity.[7,9] If those ethnic-based carrier screening strategies advocated by the guidelines had been followed, many carriers and all five carrier couples identified in our cohort would have been missed. The results of our pilot study suggest that recessive genetic conditions may not be as uncommon as previously thought. Many of the diseases identified in our cohort are debilitating conditions that are associated with progressive neurological derangement and reduced life span, such as SMA, Krabbe's disease, and biotinidase deficiency. More importantly, some conditions such as CAH may require intervention during the early prenatal or early neonatal periods to avoid irreversible complications. Hence, public and professional awareness of expanded carrier screening should be improved, and genetic counselling and expanded carrier screening should be an option for the Chinese population, especially in the setting of subfertility clinics.

Yet, genetic carrier screening has not been popular among the Chinese population or in Hong Kong because of the high cost of the test and the perceived low carrier rate in Chinese people. As the cost for NGS has dropped recently, and our pilot study demonstrated an overall high yield of 8.0% of couples at risk of conceiving foetuses with genetic diseases (even after excluding thalassaemias), further studies of couples are warranted. Potential candidates for expanded carrier screening in Hong Kong also include couples in consanguineous marriages, which are common in minor ethnic groups such as Pakistani and Indian. A recent local study showed that they had a higher prevalence of congenital abnormality (10.5%), unexplained intrauterine fetal demise (4.2%), and unexplained neonatal death (4.6%).[23]

In our cohort, NGS was used to analyse the listed exons, as well as selected intergenic and intronic regions, of the genes responsible for certain recessive conditions. The high-throughput sequencing technique was able to detect approximately 94% of known clinically significant variants irrespective of ethnicity. Of 43 variants identified using NGS, 29 (67.4%) were not included in the ACMG or ACOG guidelines. Thus, our study demonstrated that the NGS technique increased the detection rate of carrier status for recessive conditions in the Chinese population. Yet, further study with a larger sample size should be conducted to study the prevalence of carrier status, which conditions should be included, and ethical issues related to carrier screening testing such as reproductive options.

Conclusion

The observed carrier frequency in the Chinese population was 58.7% overall (47.6% after excluding thalassaemias) and was higher than previously reported. Expanded carrier screening using NGS should be provided to Chinese people to improve the detection rate of carrier status and facilitate optimal pregnancy planning.

Author contributions

All authors contributed to the concept or design of the study, acquisition of data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, JPW Chung was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This research project was partially funded by the Liauw's Family Reproductive Genomics Programme.

Ethics approval

This study obtained ethical approval from The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref CREC2019.138). All participants gave informed consent before the study.

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