High Incidence of the Cardiac Variant of Fabry Disease Revealed by Newborn Screening in the Taiwan Chinese Population

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Background—Fabry disease is a treatable lysosomal storage disorder, which is often misdiagnosed or belatedly diagnosed.

Methods and Results—To determine the disease incidence in the Taiwan Chinese population, a Fabry disease newborn screening study was initiated. A total of 110,027 newborns were screened by assaying the α-galactosidase A (α-Gal A) activity using dry blood spots. Low plasma α-Gal A activity and presence of a Fabry mutation was demonstrated in 45 neonates (3 females). Eight different mutations were identified, including 3 known missense mutations (R112H, A143T, and R356W), 4 novel missense mutations (G104V, M296L, G360C, and K391T), and one known intronic mutation (IVS4+919G→A). The IVS4+919G→A mutation was most common (82% of patients). A total of 20 maternal grandparents of infants harboring this intronic mutation were evaluated by echocardiography, mutation analysis and α-Gal A activity assay. The intronic mutation was found in 9 grandfathers and 11 grandmothers. Of these grandparents, 3 grandfathers (33%) but none of the grandmothers had hypertrophic cardiomyopathy. Additionally, 16 males who had been diagnosed with idiopathic hypertrophic cardiomyopathy were screened by mutation analysis and α-Gal A activity; 4 (25%) showed deficient plasma α-Gal A activity in combination with the intronic mutation.

Conclusion—We found an unexpected high prevalence of the cardiac variant Fabry mutation IVS4+919G→A among both newborns (1 in 1600 males) and patients with idiopathic hypertrophic cardiomyopathy in the Taiwan Chinese population. The early identification of undiagnosed patients allows timely therapeutic intervention providing a better clinical outcome.

Key Words: hypertrophy • Fabry disease • hypertrophic cardiomyopathy • newborn screening • Taiwan Chinese population

Fabry disease (MIM 301500) is an X-linked recessive lysosomal storage disorder resulting from deficient α-galactosidase A (α-Gal A) activity. It has been estimated that this disease affects 1 in ≈50,000 males in the general population.α–γ α-Gal A is an enzyme involved in the metabolic breakdown of globotriaosylceramide (GL-3) and deficient activity of this enzyme results in GL-3 accumulation in the walls of small blood vessels, nerves, dorsal root ganglia, renal glomerular and tubular epithelial cells, and cardiomyocytes. It is a complex multisystemic disorder characterized clinically by peripheral neuropathic pains (chronic burning and acute episodes of severe pain), gastrointestinal disturbances, characteristic skin lesions (angiokeratomata), progressive renal impairment, cardiomyopathy, and early stroke.1

Clinical Perspective on p 456

In the past decades, 2 variant types of Fabry disease with manifestations primarily involving the heart4–8 or kidneys9,10 have been reported, and several studies found that the Fabry cardiac variants usually mimic idiopathic hypertrophic cardiomyopathy.
diomyopathy (HCM). Patients with the cardiac variant lack the classical symptoms of Fabry disease and present in the 5th to 8th decades of life with left ventricular hypertrophy, arrhythmias, and/or cardiomyopathy. Previous studies have shown that 1% to 4% of male patients with left ventricular hypertrophy or HCM had undiagnosed Fabry disease.

Enzyme replacement therapies (ERT) are available, and experiences to date indicate that early therapeutic intervention results in a better outcome. Therefore, early detection of Fabry disease, especially of the variant types, is important. In the past decade, a new fluorimetric α-Gal A activity assay using dried blood spots (DBS) has been successfully developed and is a useful tool for Fabry disease screening initiatives. Spada et al were the first to report the use of this assay in their Italian newborn screening program. This group found a higher than expected incidence of α-Gal A deficiency (1 in ≈3100 newborns) with a late-onset to classic type ratio of 11:1.

Our newborn screening study aimed at assessing the incidence of Fabry disease in the Taiwan Chinese population and is the largest Fabry screening study performed to date. In addition, our study aimed at identifying unrecognized Fabry patients among family members of diagnosed newborns and among individuals with idiopathic HCM.

Patients and Methods

Participants

The large-scale newborn screening program for Fabry disease was based on assessment of the α-Gal A enzyme activity using DBS on filter paper and was conducted at 2 newborn screening centers, the Chinese Foundation of Health and the Taipei Institute of Pathology, Taipei, Taiwan. The centers screen ≈55% of all newborns in Taiwan. Routine newborn screening DBS samples collected by the age of 3 days in 110,027 newborns between January 2008 and January 2009 were analyzed. Parental informed written consent was obtained for each sample collected. The study was approved by the ethics committee of the Taipei Veterans General Hospital, Taipei, Taiwan.

DBS Test

Alpha-Gal A activity in DBS on filter paper was determined using a fluorescence-based high-throughput method with modifications of a reported procedure. To establish a normal population mean, α-Gal A activity was measured in 10,000 anonymous newborn samples. The normal mean of α-Gal A activity was 7.54 ± 3.69 mmol/h/mL plasma. The activity of α-Gal A was rechecked if the newborns’ α-Gal A activity was <3 μmol/h/L (i.e. <40% of the normal mean). If the re-tested activity of α-Gal A was still <40%, “screen positive” was considered. For these individuals a second blood spot was requested and assayed. In the second blood spot, newborns with blood spot α-Gal A activities <2 μmol/h/L (i.e. <25% of the normal mean) were considered “double DBS screen positive”, and were recalled to Taipei Veterans General Hospital for confirmatory testing, including genetic analysis of the α-Gal A gene (Figure 1).

Plasma α-Gal A Enzyme Activity Assay

α-Gal A enzyme activity was determined using the substrate 4-methylumbelliferyl α-D-galactopyranoside (5 mmol/L) freshly prepared in 117 mmol/L N-acetyl-l-t-glucosamine/50 mmol/L citric-phosphate buffer, pH 4.6, before every assay. In brief, 50 μL of plasma was mixed with 300 μL of the substrate solution, incubated at 37°C for 2 hours, and 0.2 N glycine-NaOH was added to stop the reaction. Fluorescence intensity was measured with the excitation and emission wavelengths of 365 and 450 μm, respectively.

α-Gal A Gene Mutation Analysis

Patients with low α-Gal A enzyme activities (normal range: 7.9 to 16.9 mmol/h/mL plasma) were subject to genetic analysis. Blood samples were obtained from these patients in blood collecting tubes containing ethylene diamine tetraacetic acid, and samples were stored at 4°C. DNA was isolated from whole blood using the GFX genomic Blood DNA Purification Kit (Amersham Biosciences, UK) following the manufacturer’s instructions. The human α-Gal A gene consists of 7 exons. Each exon of α-Gal A gene was amplified by polymerase chain reaction using appropriate primers. The polymerase chain reaction products were analyzed by 1.5% agarose gel electrophoresis and then eluted in the polymerase chain reaction Advanced PCR Clean Up System (Viogene, USA). Direct sequencing of the α-Gal A gene was processed using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) and ABI Prism 3730 Sequencer.

Pedigree Studies

For each patient, a complete pedigree was drawn and genetic counseling and pedigree analysis were provided to family members. Parents and grandparents of these patients were offered the combination of α-Gal A activity assay, mutation analysis, and related medical evaluations.

Screening of Patients With Idiopathic HCM in Cardiac Clinics

Twenty-three patients (16 men, 7 women; mean age 50.6 ± 14.3 years; age range 18 to 67 years), who had been diagnosed with idiopathic HCM, were subject to analyses of plasma α-Gal A activity and the IVS4+919G→A mutation.

Results

Fabry Screening in Newborns

Of the 110,027 newborns screened, 57,451 (52.2%) were males and 52,576 (47.8%) females. There were 67 “double DBS screen positive” newborns (9 females) recalled to our hospital for confirmatory testing, of whom 45 newborns (3 females) were identified to have low plasma α-Gal A activity and a α-Gal A mutation (Table 1). Eight mutations were detected, including 3 known missense mutations (R112H, A143T, and R356W) and 4 novel missense mutations (G104V, M296L, G360C, and K391T), and one known intronic splicing mutation (IVS4+919G→A). None of these mutations were found in 50 unrelated healthy females. The IVS4+919G→A mutation was noted to be the most common mutation among these newborns (82% of patients). Although this splicing mutation has been found in
Table 1. Results of the Newborn Screening Program for Fabry Disease in Taiwan (January 2008–January 2009)

<table>
<thead>
<tr>
<th>Newborns ⩾ 3 d of Age Tested With DBS, n</th>
<th>Incidence (%)</th>
<th>Incidence (%)</th>
<th>Total, 110 027</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, 57 451</td>
<td>1 943</td>
<td>1.90 ± 0.11</td>
<td>1 609</td>
<td>1.46 ± 0.07</td>
</tr>
<tr>
<td>Females, 52 576</td>
<td>58</td>
<td>0.10 ± 0.03</td>
<td>9</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>Newborns with Fabry mutations,‡ n</td>
<td>42</td>
<td>0.07 ± 0.02</td>
<td>3</td>
<td>0.006 ± 0.007</td>
</tr>
</tbody>
</table>

Intronic splicing mutation:
- IVS4+919G (male) or IVS4+919GA (female), n 35 0.06 ± 0.02 2 0.004 ± 0.005 45 0.04 ± 0.01

*Normal reference range, 7.9 to 16.9 nmol/hr/mL.

First DBS test positive,† n 1 943 1.90 ± 0.11 515 0.98 ± 0.08 1 609 1.46 ± 0.07
Second DBS test positive,‡ n 58 0.10 ± 0.03 9 0.02 ± 0.01 67 0.06 ± 0.01
Newborns with Fabry mutations,§ n 42 0.07 ± 0.02 3 0.006 ± 0.007 45 0.04 ± 0.01

Japanese Fabry patients with a cardiac variant, its incidence in Japan is still unknown. In our study, the incidence of Fabry mutations was 1 in 1368 for males. If the 4 novel missense mutations were excluded, the incidence of the known disease-causing mutations would be 1 in 1512 males.

Pedigree Studies

Data on enzyme activity levels and genetic analyses from the newborn screening program in Taiwan Chinese showed the high prevalence of the Fabry cardiac variant mutation IVS4+919G–A among the Taiwan Chinese population, we paid attention to the cardiac conditions of family members with the IVS4+919G–A mutation. Among 9 maternal grandfathers with the IVS4+919G–A mutation, 3 (33%) had HCM, compared with none of the 11 grandmothers with this disease (Table 3). The plasma α-Gal A activities of the 9 grandfathers ranged from 0.56 to 2.40 nmol/h/mL, whereas those of the 11 grandmothers ranged from 3.87 to 10.72 nmol/h/mL (Table 3).

Screening of Patients With Idiopathic HCM in Cardiac Clinics

To explore the occurrence of the cardiac variant mutation IVS4+919G–A in Taiwan Chinese idiopathic HCM patients, we analyzed the plasma α-Gal A activities and presence of this mutation in 23 patients diagnosed with HCM in the outpatient clinics. Four of 16 male patients (25%) had both deficient plasma α-Gal A activities (ranging from 0.65 to 0.98 nmol/h/mL) and the IVS4+919G–A mutation (Table 4). In contrast, the plasma α-Gal A activities in male patients without the IVS4+919G–A mutation ranged from 9.39 to 14.53 nmol/h/mL. It is noteworthy that none of the female patients was detected to have the IVS4+919G/A mutation and that their plasma α-Gal A activities ranged from 6.59 to 16.12 nmol/h/mL.

Histologic examination of endomyocardial tissue of Patient 4 in Table 4, a 67-year-old male patient with HCM, showed disorderly arranged myocytes with marked hypertrophy and

Table 2. Results of α-Gal A Gene Mutation Analysis and α-Gal A Enzyme Activity Screening in 110 027 Newborns

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Gender</th>
<th>Location</th>
<th>α-Gal A Mutation</th>
<th>DBS α-Gal A Activity, nmol/hr/mL</th>
<th>Plasma α-Gal A Activity, nmol/hr/mL</th>
<th>Potential Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misssense mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>Exon 2</td>
<td>c.311 G→T, p.G104V</td>
<td>0.50</td>
<td>0.60</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Exon 2</td>
<td>c.334 G→A, p.R112H</td>
<td>0.35</td>
<td>1.70</td>
<td>Renal/cardiac variant24,25</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Exon 3</td>
<td>c.427 G→A, p.A143T</td>
<td>0.94</td>
<td>3.42</td>
<td>Renal/cardiac variant26,27</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Exon 6</td>
<td>c.886 A→T, p.M296L</td>
<td>0.01</td>
<td>1.04</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Exon 7</td>
<td>c.1066 C→T, p.R356W</td>
<td>0.01</td>
<td>3.13</td>
<td>Mild Classic24,28</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Exon 7</td>
<td>c.1078 G→T, p.G360C</td>
<td>0.97</td>
<td>7.40</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Exon 7</td>
<td>c.1078 G→T, p.G360C</td>
<td>0.37</td>
<td>3.60</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Exon 7</td>
<td>c.1172 A→C, p.K391T</td>
<td>1.37</td>
<td>1.70</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total No. of Patients</th>
<th>Gender</th>
<th>Location</th>
<th>α-Gal A Mutation</th>
<th>DBS α-Gal A Activity, nmol/hr/mL</th>
<th>Plasma α-Gal A Activity, nmol/hr/mL</th>
<th>Potential Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intronic splicing mutation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>M</td>
<td>Intron 4</td>
<td>IVS4+919G–A</td>
<td>1.00 ± 0.42</td>
<td>2.80 ± 0.71</td>
<td>Cardiac variant29</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Intron 4</td>
<td>IVS4+919G/A</td>
<td>1.08 ± 0.21</td>
<td>4.61 ± 2.27</td>
<td>Cardiac variant29</td>
</tr>
</tbody>
</table>

*Normal reference range, 7.9 to 16.9 nmol/hr/mL.
large perinuclear and sarcoplasmic vacuoles, accompanied by focal interstitial fibrosis, which is consistent with the diagnosis of Fabry disease (Figure 2).

**Discussion**

One of the important findings of our large-scale newborn screening study in the Taiwan Chinese population is the high incidence of Fabry mutations. The incidence of Fabry mutations was 1 in 1368 for males. This incidence is 30 times higher than previous estimates and 2 times higher compared with the incidence found in an Italian newborn screening study. Eight different mutations were identified, including 3 known missense mutations (R112H, A143T, and R356W), 4 novel missense mutations (G104V, M296L, G360C, and K391T), and one known intronic mutation (IVS4/919G3A). The IVS4/919G3A mutation was most common (82% of patients). The 3 known mutations

### Table 3. Plasma α-Gal A Activity and Echocardiographic Features in Maternal Grandparents With α-Gal A Mutations IVS4+919G→A (Grandfather) or IVS4+919G/A (Grandmother)

<table>
<thead>
<tr>
<th>Family</th>
<th>Maternal Grandparents</th>
<th>Age, y</th>
<th>Plasma α-Gal A Activity,* nmol/hr/mL</th>
<th>α-Gal A Mutation</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Grandfather</td>
<td>67</td>
<td>0.72</td>
<td>IVS4+919G→A</td>
<td>HCM, mild MR, TR</td>
</tr>
<tr>
<td>17</td>
<td>Grandfather</td>
<td>57</td>
<td>1.12</td>
<td>IVS4+919G→A</td>
<td>Minimal PR, MR</td>
</tr>
<tr>
<td>18</td>
<td>Grandfather</td>
<td>53</td>
<td>1.26</td>
<td>IVS4+919G→A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>22</td>
<td>Grandfather</td>
<td>52</td>
<td>1.16</td>
<td>IVS4+919G→A</td>
<td>Minimal PR, mild TR</td>
</tr>
<tr>
<td>23</td>
<td>Grandfather</td>
<td>54</td>
<td>0.84</td>
<td>IVS4+919G→A</td>
<td>Minimal MR, mild TR</td>
</tr>
<tr>
<td>26</td>
<td>Grandfather</td>
<td>62</td>
<td>2.40</td>
<td>IVS4+919G→A</td>
<td>HCM, mild AR, MR, TR</td>
</tr>
<tr>
<td>33</td>
<td>Grandfather</td>
<td>57</td>
<td>0.64</td>
<td>IVS4+919G→A</td>
<td>HCM, mild TR</td>
</tr>
<tr>
<td>34</td>
<td>Grandfather</td>
<td>56</td>
<td>0.56</td>
<td>IVS4+919G→A</td>
<td>Minimal PR, mild TR</td>
</tr>
<tr>
<td>35</td>
<td>Grandfather</td>
<td>54</td>
<td>0.63</td>
<td>IVS4+919G→A</td>
<td>Minimal TR</td>
</tr>
<tr>
<td>10</td>
<td>Grandmother</td>
<td>56</td>
<td>6.51</td>
<td>IVS4+919G/A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>12</td>
<td>Grandmother</td>
<td>45</td>
<td>5.53</td>
<td>IVS4+919G/A</td>
<td>Minimal TR</td>
</tr>
<tr>
<td>19</td>
<td>Grandmother</td>
<td>51</td>
<td>5.81</td>
<td>IVS4+919G/A</td>
<td>Moderate MR, mild to moderate TR, mild AR</td>
</tr>
<tr>
<td>30</td>
<td>Grandmother</td>
<td>49</td>
<td>3.87</td>
<td>IVS4+919G/A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>32</td>
<td>Grandmother</td>
<td>62</td>
<td>5.96</td>
<td>IVS4+919G/A</td>
<td>Moderate TR, mild MR, MVP</td>
</tr>
<tr>
<td>36</td>
<td>Grandmother</td>
<td>56</td>
<td>10.72</td>
<td>IVS4+919G/A</td>
<td>Minimal TR</td>
</tr>
<tr>
<td>37</td>
<td>Grandmother</td>
<td>57</td>
<td>8.13</td>
<td>IVS4+919G/A</td>
<td>Minimal MR, TR</td>
</tr>
<tr>
<td>40</td>
<td>Grandmother</td>
<td>51</td>
<td>5.97</td>
<td>IVS4+919G/A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>41</td>
<td>Grandmother</td>
<td>54</td>
<td>9.33</td>
<td>IVS4+919G/A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>43</td>
<td>Grandmother</td>
<td>55</td>
<td>5.98</td>
<td>IVS4+919G/A</td>
<td>Mild TR</td>
</tr>
<tr>
<td>45</td>
<td>Grandmother</td>
<td>54</td>
<td>5.36</td>
<td>IVS4+919G/A</td>
<td>Minimal TR</td>
</tr>
</tbody>
</table>

*Normal reference range, 7.9 to 16.9 nmol/hr/mL.

### Table 4. Clinical Profiles, Plasma α-Gal A Activity, and Echocardiographic Features in 4 Patients With Both the Intronic Splicing Mutation (IVS4+919G→A) and HCM From the Outpatient Clinics

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Gender</th>
<th>Plasma α-Gal A Activity,* nmol/hr/mL</th>
<th>α-Gal A Mutation</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>0.65</td>
<td>IVS4+919G→A</td>
<td>HCM, mild TR</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>M</td>
<td>0.69</td>
<td>IVS4+919G→A</td>
<td>HCM, minimal AR, mild PR, MR</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>M</td>
<td>0.88</td>
<td>IVS4+919G→A</td>
<td>HCM</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>M</td>
<td>0.98</td>
<td>IVS4+919G→A</td>
<td>HCM, mild AS, MR, TR</td>
</tr>
</tbody>
</table>

*Normal reference range, 7.9 to 16.9 nmol/hr/mL.

MR indicates mitral regurgitation; TR, tricuspid regurgitation; PR, pulmonary regurgitation; AR, aortic regurgitation; MVP, mitral valve prolapse.
have been reported to be associated with mild classic (R356W) or late-onset renal or cardiac (R112H, A143T) forms. The intronic mutation (IVS4+919G→A) was reported to be a cardiac variant Fabry mutation.29

None of the 4 novel mutations were found in 50 unrelated healthy females, which makes the possibility of polymorphisms unlikely. However, whether these mutations will eventually cause Fabry disease remains unknown. Further comprehensive family studies and long-term follow-up for identified individuals with these mutations are warranted. If the 4 novel missense mutations are excluded, the incidence of the known disease-causing mutations would be 1 in 1512 males.

In our study, only 1 newborn was noted to have a previously reported mutation (R356W) causing a classic phenotype. Therefore, the calculated incidence of classic Fabry disease in the Taiwan Chinese population is ≈1 in 57,000 males, which is equivalent to previous estimates.1,2

There was a surprisingly high incidence of the IVS4+919G→A mutation among newborns with α-Gal A deficiency. This intronic mutation was detected in 83.3% of the 42 male newborns found with Fabry mutations, which translates in an incidence of ≈1 in 1600 male newborns. This IVS4+919G→A mutation has been reported to be associated with cardiac variant Fabry disease by Ishii et al29 It can activate an alternative splicing in intron 4 causing insertion of a 57-nucleotide sequence between exons 4 and 5 of the α-Gal A cDNA and subsequent premature termination after 7 altered amino acid residues downstream from exon 4. In general, the alternatively spliced transcript was present in a small amount (<5% of normal transcript) in most normal human tissues. However, in Fabry patients with the IVS4+919G→A mutation, the alternatively spliced transcript will be largely increased (>70% in lymphoblasts) and the enzyme activity will be decreased to <10% of normal activity (lymphoblast).

Another interesting finding of our study is that the mild-form pathogenic mutation IVS4+919G→A apparently does not consistently cause Fabry-related HCM in all affected individuals. Of the 9 maternal grandfathers with the IVS4+919G→A mutation, only 3 had HCM. It remains to be elucidated why some patients with this mutation suffer from cardiomyopathy as early as in their 40s, whereas others with this same mutation do not have any symptoms or signs of cardiomyopathy even in their 70s. In this study, no correlation between the plasma α-Gal A activity and the existence of HCM was found. However, the sample size is too small to make definite conclusions regarding the likelihood of the IVS4+919G→A mutation leading to the cardiac variant of Fabry disease. Because the newborn screening is still ongoing, we hope that we will be able to eventually expand the database and get a clearer picture of this. Further investigations are required to identify genes or other factors involved in the modification of clinical expression of Fabry disease and to elucidate if there are other pathogenic mutations related to mild phenotypes.

Fabry disease has historically been described as an X-linked recessive disease, however, a substantial proportion of heterozygous females will develop disease manifestations. In some, the disease presentation may be as severe as seen in young males and others may remain relatively asymptomatic until late adulthood.30,31 This phenomenon is, in part, caused by skewed X chromosome inactivation. If most of the mutation-harboring X chromosomes are inactive in females, then the clinical presentation will be rather mild. On the other hand, the clinical presentation can be severe when most of the normal X chromosomes are inactive. With regard to cardiac involvement in female Fabry patients, Fabry disease may account for up to 12% of females with late-onset HCM.32 Kampmann et al33 evaluated 55 affected females and reported echocardiographic evidence of cardiac involvement in 56% of women younger than 38 years, in 86% of women older than 38 years, and in all female patients older than 45 years of age. Schiffmann et al34 reported natural history data on 168 ERT-naive female Fabry patients of whom 35% had developed a cardiac event (eg, arrhythmia, angina, myocardial infarction, and cardiac surgery) by a mean age of ≈44 years.

X-inactivation patterns vary widely between female Fabry patients and different tissues, and the enzyme activity measured in lymphocytes can be very different from other tissues, such as heart or kidney. Therefore, in females, the result of the lymphocyte enzyme activity assay is not predictive of disease severity in a particular organ, and the result may fall within the normal range although the female can be clinically affected.35 Thus, the lymphocyte enzyme activity assay is not suitable as a screening tool in female populations, and it is not surprising that only a very few females were detected via the enzyme activity screening in this study. Screening for hot spot mutations may be an alternative method to detect unidentified female Fabry patients in high-risk populations.

Although only ½ of the grandfathers with the IVS4+919G→A mutation had significant HCM, the high prevalence of this mutation in the Taiwan Chinese population points at an important presence of the cardiac variant of Fabry disease among patients with HCM in this particular population. Although the studied sample size of HCM is small and the Fabry screening in patients with HCM is still ongoing, we strongly recommend...
that Fabry disease must be ruled out before the diagnosis of idiopathic HCM is made in the Taiwan Chinese population, both in males and females.

There are few debates that early detection, genetic counseling, regular follow-up, and timely early therapeutic intervention for the classic Fabry disease is beneficial. However, for the individuals who have atypical Fabry mutations, particularly, for those whose residual enzyme activities are >10% to 20% of normal, the strategy for regular follow-up and therapeutic intervention should be different from those with the classic type, because our study showed that a significant proportion of the individuals older than 50 years of age with IVS4+919G→A mutation still have not developed any symptoms or signs of this disease. Therefore, the early detection of babies with atypical Fabry mutations results in several clinical impacts: When is the best time to start evaluating the cardiac conditions of these individuals with IVS4+919G→A mutation? When is the best time to start ERT? Do we need to start ERT early, when there are only controversial or minimal manifestations of heart problems? Or do we need to wait until the cardiac manifestations become marked? Several reports indicate that ERT for the advanced form of Fabry cardiomyopathy is not very effective.3 Therefore, further investigations are needed to find out the best way for early detection of meaningful cardiac manifestations in patients with atypical Fabry mutations, and to identify the most appropriate time for them to start ERT.

In summary, this study in the Taiwan Chinese population demonstrates the feasibility of a large-scale neonatal screening program for Fabry disease. The incidence of Fabry mutations among newborns was unexpectedly high (≈1 in 1400 male newborns), as was the prevalence of the cardiac variant mutation IVS4+919G→A. The diagnosis of Fabry disease should be considered in all patients with idiopathic HCM. The early identification of undiagnosed patients allows timely medical intervention providing a better clinical outcome.

Disclosures

None.

References

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**CLINICAL PERSPECTIVE**

This study in the Taiwan Chinese population demonstrates the feasibility of a large-scale neonatal screening program for Fabry disease. The incidence of Fabry mutations among newborns was unexpectedly high (≈1 in 1400 male newborns), as was the prevalence of the cardiac variant mutation IVS4+919G→A. Awareness of this information may be important for physicians evaluating Chinese patients with hypertrophic cardiomyopathy because some patients could represent cardiac Fabry disease. The early identification of Fabry disease may allow timely therapeutic intervention with enzyme replacement therapy, possibly resulting in better clinical outcome.
High Incidence of the Cardiac Variant of Fabry Disease Revealed by Newborn Screening in the Taiwan Chinese Population
Hsiang-Yu Lin, Kah-Wai Chong, Ju-Hui Hsu, Hsiao-Chi Yu, Chun-Che Shih, Cheng-Hung Huang, Shing-Jong Lin, Chen-Huan Chen, Chuan-Chi Chiang, Huey-Jane Ho, Pi-Chang Lee, Chuan-Hong Kao, Kang-Hsiang Cheng, Chuen Hsueh and Dau-Ming Niu

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