Rare Variant Mutations in Pregnancy-Associated or Peripartum Cardiomyopathy

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Background—The term peripartum cardiomyopathy (PPCM) describes dilated cardiomyopathy (DCM) without known cause that occurs during the last month of pregnancy to 5 months postpartum. A related term, pregnancy-associated cardiomyopathy (PACM), refers to DCM onset earlier in pregnancy. Multiple studies have focused on inflammatory, immunologic, and environmental causes. An alternative hypothesis is that PPCM and PACM result, in part, from a genetic cause. In this study, we sought to test the hypothesis that rare DCM-associated mutations underlie a proportion of PACM or PPCM cases.

Methods and Results—A systematic search of our DCM database designed for family-based genetic studies was undertaken for cases associated with pregnancy and the postpartum period; in the identified cases, clinical and molecular genetic data, including exonic and near intron/exon boundaries of DCM genes, were analyzed. Of 4110 women from 520 pedigrees in the Familial Dilated Cardiomyopathy Research Project database, we identified 45 cases of PPCM/PACM. Evidence of familial clustering with DCM was present in 23 unrelated cases. Of the 45 cases, 19 had been resequenced for known DCM genes, and 6 carried mutations. Five had PPCM, of which 3 were familial with mutations found in MYH7, SCN5A, and PSEN2, and 2 were sporadic with mutations in MYH6 and TNNT2. One case had PACM and carried a mutation in MYBPC3.

Conclusions—These findings suggest that a proportion of PPCM/PACM cases results from a genetic cause. (Circulation. 2010;121:2176-2182.)

Key Words: cardiomyopathy ■ genetics ■ pregnancy complications

In 1971, Demakis et al introduced the term peripartum cardiomyopathy (PPCM) and proposed diagnostic criteria, as follows: heart failure onset in the last month of pregnancy or within 5 months postpartum; no determinable cause for the cardiac failure; and no heart disease before the last month of pregnancy.1,2 Since then, additional diagnostic criteria have been added, including reduced left ventricular ejection fraction and left ventricular enlargement.3 A related term, early pregnancy-associated cardiomyopathy (PACM), was used in a study to refer to onset occurring before the last month of pregnancy.4 In that study, the clinical characteristics of 23 women identified as having PACM (earliest diagnosis reported at week 17 gestational age) were compared with those of 100 women with PPCM; no clinical differences were observed between groups.4 Phenotypically, PPCM and PACM are indistinguishable from dilated cardiomyopathy (DCM), which is characterized by systolic failure and left ventricular enlargement. Thus, PPCM and PACM can be conceived as phenotypic descriptors for DCM occurring during or after pregnancy.

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Therefore, to test the hypothesis that rare variant DCM mutations underlie a proportion of PPCM/PACM cases, a systematic search of our DCM database designed for family-based genetic studies was undertaken for cases associated with pregnancy and the postpartum period. In the identified cases, available clinical and molecular genetic data were analyzed.

**Methods**

**Patient Population**

Subjects with IDC (with or without FDC) were enrolled, as described previously. Written informed consent was obtained. A blood sample was obtained for genetic research. Medical family history was obtained, and a pedigree was constructed. Medical records were obtained to confirm IDC and assign familial or sporadic status. IDC was defined as left ventricular enlargement with systolic dysfunction, with coronary artery disease, cardiotoxic exposures, and other known causes ruled out. FDC cases were defined as those in which the patient and at least 1 relative had IDC. Kindreds with confirmed and probable familial disease were classified as having FDC. Individuals with a negative family history or possible FDC were classified as sporadic. Patient information was stored in Progeny, a relational database (Progeny Software, South Bend, Ind).

**Database Query and Medical Records Review**

A database query among 4110 women whose data were part of the FDC study cohort, from either enrollment or reported family history, was conducted for DCM cases associated with pregnancy and the postpartum period. Medical records and family history were reviewed for each of the identified cases.

**Selection Criteria**

Cases were selected if medical records or family history intake indicated a diagnosis or history of PPCM or PACM. All available medical records were reviewed for onset during pregnancy or 5 months after pregnancy and for cardiovascular data indicating an ejection fraction <50% and/or M-mode fraction <30% and left ventricular end-diastolic dimension >97.5th percentile based on a gender- and height-based method, as reported previously.

**Genetic Data**

Genetic data from comprehensive resequencing studies were available from 19 unrelated subjects; all coding exons and near intron/exon boundaries underwent bidirectional capillary-based Sanger sequencing, as described previously. Fourteen cases were resequenced for 14 genes, including CSRP3, LDB3, MYH7, SCN5A, TCAP, TNN2, LMNA, PSEN1, and PSEN2, as reported, as well as MYBPC3, MYH6, TNNC1, TNNI3, and TPM. An additional case was resequenced for the aforementioned genes except for LMNA, PSEN1, and PSEN2. One case was resequenced for all genes except for PSEN1 and PSEN2. One case was only sequenced for the LMNA gene. Another case was resequenced for LMNA, PSEN1, PSEN2, MYBPC3, MYH6, TNNC1, TNNI3, and TPM. Her father, who had IDC, was resequenced for the remaining 6 of 14 genes (CSRP3, LDB3, MYH7, SCN5A, TCAP, and TNN2). One case was only sequenced for the SCN5A mutation identified in a relative with DCM.

**Results**

**Clinical Data**

A search of 4110 women from 520 families enrolled in the Familial Dilated Cardiomyopathy Research Project cohort identified 45 cases with PPCM/PACM (Table 1). This group includes 2 first cousins, 2 sisters, and a half-aunt/half-niece pair for a total of 42 unrelated cases. Of the 42 unrelated cases, 23 had familial disease, and 12 were apparently sporadic. The remaining 7 unrelated cases had insufficient family data to be categorized. Nineteen women met PPCM criteria. Two of these 19 PPCM cases were sisters; their mother had DCM (diagnosed at age 60 years). Eight other cases met criteria for PACM. For the remaining 18 cases, insufficient clinical data were available for cases to be categorized (Table 1).

Medical records were available for 32 cases, and cardiovascular characteristics of these cases are provided (Table 2).

**Pedigree and Genetic Data**

Genetic data were available for 19 (13 familial, 6 sporadic) of the 42 unrelated cases. The remaining cases were not sequenced because either the family’s proband was sequenced and a mutation was not found or the subject was not enrolled in the FDC study so that the subject’s DNA was not available when the sequencing occurred. Nonsynonymous mutations were identified in 6 cases, each from different genes.

**Table 1. Subject Demographics**

<table>
<thead>
<tr>
<th>Race, ethnicity, age, and parity</th>
<th>All Cases</th>
<th>PPCM</th>
<th>PACM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>45</td>
<td>19</td>
<td>8</td>
</tr>
<tr>
<td>Race and ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>24</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Hispanic white</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Non-Hispanic American</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Indian/Alaska Native</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age at diagnosis, median (y)</td>
<td>27 (33)</td>
<td>28 (19)</td>
<td>25 (8)</td>
</tr>
<tr>
<td>Parity, mean (y)</td>
<td>1.58 (33)</td>
<td>2 (19)</td>
<td>0.625 (8)</td>
</tr>
<tr>
<td>Parity, range</td>
<td>0–7</td>
<td>0–7</td>
<td>0–3</td>
</tr>
<tr>
<td>Familial or sporadic disease in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unrelated cases who had family</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>data available for analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>35</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>FDC</td>
<td>23</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>IDC</td>
<td>12</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 2. Clinical Characteristics of Cases With Cardiovascular Functional Data**

| Clinical presentation, n        | 32       |
| Heart failure                  | 26       |
| Arrhythmia                     | 11       |
| Other (fever, infection, nausea)| 3        |
| Echocardiographic findings, n  | 26       |
| Left ventricular end-diastolic dimension, mm, mean±SD | 24, 62.6±7.3 |
| Left ventricular end-diastolic dimension Z score, n, mean±SD | 21, 4.8±1.7 |
| Ejection fraction, n, mean±SD  | 24, 23.9±11.1 |
myosin binding protein C (MYBPC3),20 myosin heavy chain 7 (MYH7),15 cardiac troponin T2 (TNNT2),15,21 myosin heavy chain 6 (MYH6),20 sodium channel, voltage-gated, type V, α-subunit (SCN5A),15 and presenilin 2 (PSEN2).19 Medical records confirmed a PPCM diagnosis in 5 of the 6 cases with mutations. These 5 cases included 3 with familial disease (pedigree B, MYH7; pedigree C, SCN5A; and pedigree D, PSEN2) and 2 with sporadic disease (pedigree E, MYH6, and pedigree F, TNNT2). One, who carried a MYBPC3 mutation,20 met PACM criteria (pedigree A) and had familial disease.

**Pedigrees With Familial Disease**

**Pedigree A**

The proband, of non-Hispanic white ethnicity, presented with shortness of breath and pedal edema. She had advanced heart failure and required urgent cardiac transplant within 1 month postpartum. A diagnosis of PACM was made (Table 3). She
carried a MYBPC3 Arg272Cys variant (absent in 246 controls) that was not detected in her unaffected mother or brother. This variant has been reported previously in 1 subject with DCM.

Pedigree B
The proband, of non-Hispanic black ethnicity, presented with progressive dyspnea that began in the last trimester of pregnancy. PPCM was diagnosed (Table 3). She was homozygous or hemizygous for a nonsynonymous MYH7 Gly1808Ala variant not seen in 253 controls. According to pedigree intake, she had a family history consistent with FDC; however, DNA from her reportedly affected relatives was not available, and therefore segregation could not be assessed.

Pedigree C
The proband, of non-Hispanic white ethnicity, presented with palpitations, dyspnea on exertion, and dizzy spells after the birth of her second child. PPCM was diagnosed (Table 3). She carried a SCN5A (Arg222Gln) variant absent in 253 controls. The variant segregated in family members with DCM.

Pedigree D
The proband, of non-Hispanic white ethnicity, presented with severe shortness of breath and orthopnea 2 weeks postpartum. PPCM was diagnosed. Complaints of leg edema and intermittent chest pain noticed during the eighth month of pregnancy were attributed to normal pregnancy stress. A PSEN2 Ser130Leu variant that was absent in 413 controls was identified; it segregated with DCM in the family. The pedigree and molecular and functional data have been published previously.

Pedigrees With Sporadic Disease
Pedigree E
The proband, a Hispanic white woman, developed shortness of breath and edema a few days after delivery of her first child. Chest x-ray showed cardiomegaly. She was diagnosed with PPCM (Table 3). A biventricular assist device was implanted, and she eventually required heart transplantation.

Table 3. Clinical Characteristics of PPCM/PACM Cases and Family Members With DCM Mutations

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Age at Diagnosis, y</th>
<th>Gestational Age at Diagnosis (PPCM or PACM Cases)</th>
<th>Parity</th>
<th>ECG/Arrhythmia</th>
<th>LVEDD, mm (Z Score)</th>
<th>Ejection Fraction, %</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.6</td>
<td>F</td>
<td>PACM</td>
<td>21</td>
<td>34 wk</td>
<td>0</td>
<td>Sinus tachycardia, poor R-wave progression</td>
<td>66 (5.6)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>B.7</td>
<td>F</td>
<td>PPCM</td>
<td>40</td>
<td>1 wk postpartum</td>
<td>1</td>
<td>Tachycardia, IVCD, poor R-wave progression, LAE, NSSTT</td>
<td>64 (4.5)</td>
<td>15</td>
<td>Homozygous or hemizygous mutation</td>
</tr>
<tr>
<td>C.8</td>
<td>F</td>
<td>PPCM</td>
<td>22</td>
<td>Post delivery</td>
<td>2</td>
<td>Atrial ectopic rhythm</td>
<td>NA</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>C.9</td>
<td>M</td>
<td>IDC</td>
<td>30</td>
<td>NA</td>
<td>3</td>
<td>LAE, PACs, PVCs</td>
<td>57 (3.7)</td>
<td>30</td>
<td>HF</td>
</tr>
<tr>
<td>C.10</td>
<td>M</td>
<td>IDC</td>
<td>32</td>
<td>NA</td>
<td>NA</td>
<td>Bigeminy</td>
<td>74 (5.6)</td>
<td>18</td>
<td>HF, ICD</td>
</tr>
<tr>
<td>C.12</td>
<td>F</td>
<td>IDC</td>
<td>20</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>70 (6.6)</td>
<td>15</td>
<td>HF, ICD</td>
</tr>
<tr>
<td>C.15</td>
<td>M</td>
<td>IDC</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>Multifocal PVCs, bigeminy</td>
<td>78 (6.3)</td>
<td>13</td>
<td>Presented with arrhythmia</td>
</tr>
<tr>
<td>E.7</td>
<td>F</td>
<td>PPCM</td>
<td>37</td>
<td>2 wk postpartum</td>
<td>7</td>
<td>Sinus tachycardia, NSSTT</td>
<td>69 (5.8)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>F.3</td>
<td>F</td>
<td>PPCM</td>
<td>20</td>
<td>1 wk postpartum</td>
<td>1</td>
<td>NA</td>
<td>62.5 (4.9)</td>
<td>Reduced</td>
<td></td>
</tr>
</tbody>
</table>

LVEDD indicates left ventricular end-diastolic dimension; IVCD, intraventricular conduction delay; LAE, left atrial enlargement; NSSTT, nonspecific ST-T wave changes; NA, not applicable; PAC, premature atrial complex; PVC, premature ventricular complex; HF, heart failure; LBBB, left bundle-branch block; and ICD, implantable cardioverter-defibrillator.

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A novel MYH6 Arg568Cys variant not seen in 246 controls was detected.\textsuperscript{20} DNA from additional relatives was not available.

**Pedigree F**

The proband, a non-Hispanic white woman, presented with paroxysmal nocturnal dyspnea, cardiomegaly on chest x-ray, and heart failure. PPCM was diagnosed 1 week postpartum (Table 3). A nonsynonymous \textit{TNNT2} Arg159Gln variant was identified that occurred at a conserved site and was absent in 253 controls.\textsuperscript{15} Functional studies demonstrated decreased calcium sensitivity, which indicated that this mutation was likely to be disease causing.\textsuperscript{21}

**Discussion**

From our database designed for DCM genetic studies, we present cases of DCM onset occurring in pregnancy or the immediate postpartum period and their molecular genetic rare variant data, suggesting genetic causation. Among the 4110 women in the 520 pedigrees analyzed in our FDC cohort, we identified 45 PPCM or PACM cases. In 6 of the 19 cases for which resequencing data were available, mutations were identified in genes that have been shown previously to be associated with DCM. PPCM was diagnosed in 5 (pedigrees B, C, D, E, F) and PACM in 1 (pedigree A). To our knowledge, this is the first cohort of PPCM/PACM cases with sequencing data from genes that are relevant for genetic DCM.

Identifying the cause or causes of PPCM/PACM has been elusive, and no compelling data have previously supported any 1 central hypothesis.\textsuperscript{23} Numerous causes have been proposed, including autoimmune processes, myocarditis, abnormal hemodynamic responses to pregnancy, and selenium deficiency.\textsuperscript{23–26} Other proposed risk factors include maternal age >30 years old, twinning, hypertension, preeclampsia, and tocolytic therapy.\textsuperscript{1,4,23,24,27} Although African descent has also been proposed as a risk factor, this association may be confounded by socioeconomic status in some populations.\textsuperscript{27} Genetic cause has also been suggested in some studies, as noted above.

Because our \textit{≥}15-year study has been devoted primarily to identifying patients with DCM who may have familial disease, it is not surprising that some of the participants whom we identified, otherwise meeting criteria established for the diagnosis of PPCM or PACM, had familial disease. Previous reports\textsuperscript{6–11} of individual familial cases are at variance, as is this report, with several series of PPCM cases that have reported sporadic disease. For example, none of the PPCM subjects reported in 2 key studies\textsuperscript{2,4} had positive family histories. One possible explanation for this difference is that the pathogenic basis of the PPCM in those reports\textsuperscript{2–4} may have been different (and nonhereditary) from that seen in our series of patients. Another possibility is that evidence of familial disease was not detected because neither of the prior studies\textsuperscript{2,4} specified that a family history had been obtained. The fact that a careful, prospective 3- to 4-generation family history is essential to detect familial disease has been well established for DCM.\textsuperscript{5,28,29} It has also been well established that the family history is insensitive to detect familial DCM compared with clinical screening (history, examination, ECG, and echocardiography) of closely related family members. This latter fact has led to the recent guideline recommending clinical screening for first-degree relatives of all patients newly diagnosed with DCM.\textsuperscript{30} We suggest that this clinical guideline recommendation also be considered for cases of suspected PPCM/PACM and that a 3- to 4-generation family history (and consideration of clinical screening of first-degree family members) be integrated into all ongoing PPCM/PACM research study designs.

Some have suggested that the PPCM diagnosis should be distinguished from FDC.\textsuperscript{30} However, we suggest the alternative possibility, that genetic DCM may underlie a significant proportion of PPCM cases, regardless of a positive family history. This point is illustrated by pedigrees E and F, in which both probands met PPCM criteria and were the only known affected individuals in their family yet carried possibly or likely disease-causing DCM mutations, respectively. Prospective registries assessing the presence of DCM clinical findings and mutations in first-degree relatives of PPCM/PACM probands will be necessary to further evaluate this possibility.

**Limitations**

Because of the nature of our study design, we were unable to obtain all cardiovascular data from all subjects with a history of PPCM/PACM. However, we restricted our cardiovascular and clinical genetics assignments to those for whom requisite clinical data were available. The previously published data or the data presented herein to prove causation varied for each mutation. For mutations in 2 genes, \textit{TNNT2} and \textit{PSEN2}, the previously published functional data\textsuperscript{19,21} in concert with the segregation of the variant with DCM in multiple family members supported their role as highly likely disease-causing variants. For other mutations, segregation of DCM with the variant in \textit{SCN5A} in multiple other family members (pedigree C; Figure) or the prior report of the \textit{MYBPC3} variant in association with DCM\textsuperscript{22} supports their likely disease-causing roles. Mutations in 2 genes (\textit{MYH6, MYH7}) had no functional or segregation data available. However, the \textit{MYH7} gene encodes the key sarcomeric protein \(\beta\)-myosin heavy chain, which has had multiple previous mutations reported in association with DCM,\textsuperscript{12,13,31–33} and the \textit{MYH7} mutation identified as pedigree B met usual criteria (a rare, nonsynonymous variant) to be considered as possibly causing disease. The \textit{MYH6} gene encodes \(\alpha\)-myosin heavy chain, another sarcomeric gene with variants that have been reported previously in association with DCM.\textsuperscript{20,34} Although the \textit{MYH6} variant we identified in pedigree E was also nonsynonymous and rare, because the role of \textit{MYH6} variants in DCM is overall less well established, the evidence that this variant is possibly disease causing is not as strong as that of the \textit{MYH7} variant. We also note that our resequencing data were limited to those genes known to cause DCM in male and female subjects of all ages without regard to the PPCM/PACM diagnosis, and therefore it is possible that genes more relevant to cardiac function during pregnancy or the immediate postpartum period were missed; resequencing studies of additional genes will be required to assess this possibility. We
are unable to specify the degree to which our cases are representative for PPCM/PACM because our study was not designed specifically to identify PPCM/PACM cases per se, and the PPCM/PACM case series have not presented systematically obtained family history and pedigree data. However, our cases met usual criteria for PPCM or PACM and are relevant to establish that a genetic cause may underlie some proportion of PPCM/PACM.

Implications for Clinicians

This report has implications for clinicians caring for PPCM and PACM patients, as well as their families. For PPCM/PACM patients, the approach taken should be the same as that recommended for a new IDC diagnosis,29 which includes consideration of the possibility of FDC and of genetic cause. A genetic evaluation including family history, clinical screening, and genetic counseling and testing should be conducted for the proband and for first-degree relatives.29 Although PPCM and PACM are rare, these conditions may occur more frequently among relatives of patients with IDC, and therefore reproductive risk counseling about PPCM/PACM is appropriate for female first-degree relatives of probands with IDC in the context of a genetic cardiomyopathy evaluation.29

Conclusion

Mutations associated with DCM were present in some subjects meeting formal criteria for PPCM/PACM, suggesting that a proportion of PPCM/PACM may result from a genetic cause and even in the absence of a disease-positive family history. These findings have implications for further research and may be of critical importance in the management of women with PPCM and their families.

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Disclosures

None.

References

The term *peripartum cardiomyopathy* (PPCM) describes dilated cardiomyopathy (DCM) without known cause that occurs during the last month of pregnancy to 5 months postpartum. A related term, *pregnancy-associated cardiomyopathy* (PACM), refers to DCM onset earlier in pregnancy. Despite multiple studies focused on inflammatory, immunologic, and environmental causes, no unifying hypothesis has been proven. An alternative hypothesis is that PPCM and PACM result from a genetic cause. In an effort to identify preliminary support for this hypothesis, a systematic search of a large database, collected for family-based genetic DCM studies over the past 15 years, was undertaken for cases associated with pregnancy and the postpartum period. When cases were identified, available clinical and molecular genetic data were analyzed. Of the 4110 women from 520 pedigrees in the Familial Dilated Cardiomyopathy Research Project database, 45 cases of PPCM/PACM were identified, 23 with familial clustering, of which 19 had been resequenced for known DCM genes. Six of these 19 carried mutations in genes shown previously to be associated with DCM. These data indicate that PPCM/PACM may have a genetic basis in some cases. Thus, we recommend that clinicians caring for PPCM/PACM patients be aware that PPCM/PACM may have a genetic basis and that guidelines for evaluation of genetic cardiomyopathy be followed. Specifically, this includes clinical screening (family history, medical history, examination, ECG, echocardiography) of the patient and her first-degree relatives. Genetic counseling, including reproductive risk counseling about PPCM/PACM, is recommended, in addition to consideration of genetic testing.
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