Letter to the Editor

The search of ‘novel’ mtDNA mutations in hypertrophic cardiomyopathy: MITOMAPping as a risk factor

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Received 13 February 2007; accepted 16 February 2007
Available online 7 May 2007

Abstract

MITOMAP is by far the most frequently cited Web resource that is referred to in substantiating novelty of an mtDNA mutation. This database, as is now known, has quite an incomplete coverage of the mtDNA mutations from the literature. This circumstance has seduced many scholars of medical genetics in the past to claim novelty of rather ‘worn-out’ mtDNA mutations. What is, however, really novel in the field is that researchers take advantage of this situation and deliberately suppress information from other sources, as it appears to have occurred in two recently published cases of hypertrophic cardiomyopathy.

Keywords: Hypertrophic cardiomyopathy; Noonan syndrome; Mitochondrial DNA mutation; Haplogroup; MITOMAP

1. Introduction

How could one know whether an array of non-silent mtDNA mutations is implicated in a certain syndrome? Quite often, some anecdotal finding in a single case is regarded as the first evidence for pathogenicity of mtDNA mutations — turned into a publication, even without having carried out any functional analysis. Instead, the ‘novelty’ of a number of mtDNA mutations observed in the patient would be emphasized. Such a kind of approach, however, which is being exercised on an ever growing number of diseases, is beset with a conceptual shortcoming: there is no compelling evidence to date that, say, half a dozen of non-silent mtDNA mutations could realistically arise in the germline just within a few generations [1]. Rather, it would typically take several thousand years before such an array of mutations is attained in the matriline. Thus, there is a good chance that related mtDNA lineages bearing only a subset of those targeted mutations thrive in the patient’s ethnic group or regional population. Then a focussed large-scale study could attempt to determine whether some particular mutation of that array is mildly deleterious or whether there is some synergistic effect of several mutations, possibly enhanced by interaction with nuclear DNA.

‘Novelty’ of mutations found in patients with certain diseases is often tagged to titles and abstracts of articles, which has probably enhanced their publication. Traditionally, MITOMAP (http://www.mitomap.org/) appears as the sole witness for the novelty of an mtDNA mutation. But straightforward Internet searches in the ‘warehouse’ of mitochondrial variation may quickly reveal that just the usual suspects of pathogenic mutations or the known polymorphisms have actually been revisited [2].

2. Hypertrophic cardiomyopathy (HCM)

In a recent study, entitled “Novel mitochondrial DNA mutations in a rare variety of hypertrophic cardiomyopathy”, Prasad et al. [3] have claimed novelty of six mutations observed in an Indian HCM patient. A quick screening of the
mtDNA literature allows us to re-evaluate their claim of novelty. Entering queries for these mutations in mtDB (http://www.genpat.uu.se/mtDB/) reveals that four of those mutations were published in population studies before the submission (July 2005) of the paper. A fifth mutation (C1556T) was not novel either, as one learns after entering the query ‘1556 mtDNA patient’ into Google (Table 1).

Therefore only the mutation G3407A seemed to have been unknown at the stage of submission. But, the subsequent paper [4] exhibited a new mtDNA lineage (sample #OR89) of haplogroup M5a (with T12477C being diagnostic together with G709A, C3921T, and G14323A) possessing G3407A and T11365C as well. Therefore, it is very likely that the mtDNA of the patient analysed in [3] belongs to a branch of haplogroup M5a (with T12477C being diagnostic together with G709A, C3921T, and G14323A). This means that the necessary publication order had been reversed, by first describing a single case and then systematically investigating mtDNA mutations in the general population.

3. Noonan syndrome

Dhandapany et al. [5] have studied the case of a Noonan patient with hypertrophic obstructive cardiomyopathy and sequenced the entire mtDNA, but did not disclose the corresponding complete mtDNA sequence which they claimed to have obtained. Instead, as many as eight ‘novel’ mutations were listed along with one mutation deemed to be associated with prostate cancer (according to MITOMAP, but see [2] for a critical assessment of some mutations claimed to be implicated in prostate cancer). In fact, all except two mutations (A10316G and C14436T) were known before 2005 and can conveniently be retrieved from the mtDB database (Table 1). The existence of the mtDB Web site could not really have escaped the attention of the corresponding author because his research group actually used this resource in another paper [6] that was submitted in December 2005 (accepted February 2006), well before the submission date (July 2006) of the subsequent paper [5].

Entering ‘A10316G mtDNA’ into Google yields the reference to [7], where this mutation was recorded in the sample #B177 belonging to haplogroup M4’30. The latter paper was cited in the paper by Thangaraj et al. [4], which was submitted in December 2005 and published in June 2006, thus prior to the submission of the paper [5]. Putting the meagre information offered in [5] into phylogenetic perspective, it is obvious that A2755G signifies the entire Indian mtDNA haplogroup R8, whereas three further mutations discussed there (A5510G, C5911T, and C13782T) define a branch of R8 in India [8]. Thus, there remains very little substance for constructing a disease association story.

4. Discussion

What was then novel in the studies [3] and [5]? Certainly not the polymorphisms of two particular branches of the familiar

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Position</th>
<th>Change</th>
<th>Gene</th>
<th>Occurrences in the literature</th>
<th>MITOMAP tree</th>
<th>Haplogroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>1391</td>
<td>T→C</td>
<td>12S rRNA</td>
<td>[13] (2); [14] (3); [15]; [8]; [16]; [17]</td>
<td>Yes (R1)</td>
<td>B4b1b (3); Q1 (4); R1 (2)</td>
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<tr>
<td>[3]</td>
<td>11365</td>
<td>T→C</td>
<td>ND4</td>
<td>[20]; [21]; [4]; [22]</td>
<td>Yes (D5;N)</td>
<td>A2b; D5a2; M5a; N22</td>
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<tr>
<td>[3]</td>
<td>12477</td>
<td>T→C</td>
<td>ND5</td>
<td>[23]; [24]; [9]; [20]; [14] (3); [25]; [26]; [7] (6); [4]; [27]; [28]; [29]; [30]</td>
<td>Yes (L1; M5; M*; M11)</td>
<td>J*; J2a1; K1a2; L1c1a (2); L1c2a (2); M5a (9); M11a; M33; Q1; X2</td>
</tr>
<tr>
<td>[3]</td>
<td>2755</td>
<td>A→G</td>
<td>16S rRNA</td>
<td>[9]; [20] (2); [14] (4); [8]</td>
<td>Yes (L1; M; R8)</td>
<td>L0a; L1c1a (7); M*; R8 (3); ?</td>
</tr>
<tr>
<td>[3]</td>
<td>5911</td>
<td>C→T</td>
<td>COI</td>
<td>[31]; [9]; [14]; [32]; [8] (2); [10] (4); [39]</td>
<td>Yes (L0; R8)</td>
<td>L3b; L0a (5); L0a1; L0a1a; R8 (2); U</td>
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<td>10283</td>
<td>A→G</td>
<td>ND3</td>
<td>[9]; [14]; [33] (3); [34]</td>
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<td>H*; Q2 (3); U5b (2)</td>
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<td>K2c; L0a2 (18)</td>
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<tr>
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<td>12127</td>
<td>G→A</td>
<td>ND4</td>
<td>[9] (2); [37] (3); [10]</td>
<td>Yes (L0)</td>
<td>J1c (2); L0a; M29 (3)</td>
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<td>[5]</td>
<td>13782</td>
<td>C→T</td>
<td>ND5</td>
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<td>Yes (R8)</td>
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<td>[5]</td>
<td>14436</td>
<td>C→T</td>
<td>ND6</td>
<td>–</td>
<td>No</td>
<td>–</td>
</tr>
</tbody>
</table>

* References to the articles where the referred mutations were also reported. Most of these instances were thus published before [3, 5] and can be retrieved from the mtDB database. Multiple occurrences of a particular mutation in one publication are indicated by the italicized number in round brackets.

b MITOMAP tree column refers to the presence or absence of the corresponding variants in the worldwide phylogeny displayed at http://www.mitomap.org/mitomap-phylogeny.pdf; in round brackets we indicate the haplogroup status as it is designated in that tree.

c Haplogroups in which the corresponding mutation thrives; the italicized number in round brackets counts the sequences with that mutation in the corresponding haplogroup (when >1). A question mark indicates that haplogroup status could not be determined.
Indian haplogroups, M5a and R8, respectively. It is also unlikely that the remaining mutations are inflicted in HCM. One cannot firmly exclude the possibility, of course, that some mutation only sporadically observed otherwise might be involved in the disease. But in any case such an implication would need more evidence from solid and systematic analyses. Only one single mutation, C14436T, might really be considered to be novel, but this would not automatically entail its pathogenicity since many coding region sequences from population studies carry their own private mutations not seen anywhere else so far. Since mtDNA variability is high in populations, the discovery of new polymorphisms is to be expected when sequencing any mtDNA whatever, especially in populations characterized by high mtDNA diversity, which is not yet fully documented, as is the case for India.

It is quite a common malpractice in the field to analyse the entire mitochondrial genome without documenting the full variation (or storing it e.g. in GenBank) but instead reporting only a handful of mutations [1]. Worse, false claims of novelty of mutations, as blessed by MITOMAP, may misguide future research by setting the agenda for rather futile projects, such as the search for specific mtDNA mutations involved in the Noonan syndrome. In this way, unguided MITOMAPping can be a risk factor in exploring the genetic causes of HCM.

References


