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<td>Author(s)</td>
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<tr>
<td>Issued Date</td>
<td>2015</td>
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<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/10722/235186">http://hdl.handle.net/10722/235186</a></td>
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Congenital myopathies: characteristics and subtypes in Hong Kong

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Background: Congenital myopathies (CMs) are a genetically and clinically heterogeneous group of neuromuscular disorders. Historically, the congenital myopathies are classified according to muscle biopsy findings - Rods (Nemaline myopathy) (NM), central (core) disease and multiminicore disease) (CNDM), Centronuclear/ myotubular myopathy (CNM), myopathy; and selective hydropathy of type I fibres (congenital fibre type disproportion (CFD)). Over twenty genes have been implicated in CMs. The overlapping clinical presentations among different histopathological findings and different mutations poses major diagnostic challenge.

Objective: We investigated the characteristics of children with congenital myopathies in Hong Kong.

Patients and methods: We identified all patients with a confirmed diagnosis of CM between 2012-March 2015. Their clinical presentation, muscle biopsy, muscle MRI and genetic analysis results were evaluated.

Results: Patients: Total 15 patients have been diagnosed to have CM. Nine were males (60%), 6 were females (40%).

Genetic findings: (1) A genetic diagnosis could be established in 11 (73%) out of 15 patients. Among those 11 patients, 4 (36%) were mutated in RYR1, 3 (27%) in ACTA1, 2 (18%) in KLHL40, 1 (9%) in MTM1 and 1 (9%) in DNM2. A total of 15 mutations were identified. (2) The missense RYR1 mutation (c.3523G>A) was found in 2 patients, and the missense KLHL40 mutation (c.3526A>C) was found in another 2 patients, suggesting that these variants could probably be the hot spots mutation among Chinese patients. (3) Pathological heterogeneity caused by RYR1 mutation is shown in our 4 patients showing different findings including nemaline rods, central cores, multiminicores, or type I fibre predominance.

Histopathological features: (1) Muscle biopsy evaluation were available in all 15 patients. Nemaline myopathy were the most frequent histopathological diagnosis, in 5 patients (33%), followed by core myopathy, in 4 patients (26%), centronuclear myopathy in 2 patients (13%), congenital fibre type disproportion in 2 patients (13%), zebra bodies in 1 (6.7%) patient and type I predominance in 1 (6.7%) patient. (2) Genetic heterogeneity is illustrated in our patients with nemaline myopathy: Amongst the 5 patients, 1 had RYR1, 2 had ACTA1 and 2 had KLHL40 mutation.

Clinical features: (1) Of the 15 patients, 9 (60%) had age of onset at birth or before one month, 3 (20%) between 1 and 12 months, and 3 (20%) between 1 and 5 years. Out of the 9 patients with early neonatal presentation, 3/9 (33%) patients died before 15 months. (2) The functional abilities varied from very severe weakness required tube feeding and ventilation support , to intermediate functional abilities with possible independent sitting , to mild limb girdle weakness only. (3) RYR1, ACTA1, KLHL40, DNM2 and MTM1 mutations are associated with severe presentation with early neonatal onset. (4) RYR1 mutations are associated with a milder phenotype with all the affected patients maintain independent walking

Muscle imaging: Selective muscle involvement with Rectus Femoris sparing provides helpful clues to a possible underlying RYR1 mutation.


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**Gene** | **Muscle Biopsy** | **Mutation** | **Inheritance Pattern** | **Parents’ carrier status**
---|---|---|---|---
1 Ac 14q | MT | c.8987G>T (p.Glu2999Lys) | AD | No
2 ACRD | NT | c.8218C>A(p.Ala2739Thr) | AD | No
3 ACTA1 | NT | c.3523G>A | AD | No
4 KLHL40 | NT | c.3526A>C (p.Asp1176Asn) | AR | No
5 RYR1 | NM | c.1270G>A(p.Gly423Arg) | AR | Yes
6 RYR1 | NT | c.1586A>G(p.Glu529Arg) | AR | Yes
7 RYR1 | CM | c.1516A>C (p.Thr506Pro) | AR | Yes
8 RYR1 | CM | c.7523G>A (p.Arg2508His) | AR | Yes
9 RYR1 | CM | c.802T>C (p.Phe268Leu) | AR | Yes
10 RYR1 | CM | c.7523G>A (p.Arg2508His) | AR | Yes
11 RYR1 | CM | c.3523G>A (p.Glu1175Lys) | AR | Yes
12 RYR1 | CM | c.1516A>C (p.Thr506Pro) | AR | Yes
13 RYR1 | CM | c.802T>C (p.Phe268Leu) | AR | Yes
14 RYR1 | CM | c.7523G>A (p.Arg2508His) | AR | Yes
15 RYR1 | CM | c.3523G>A (p.Glu1175Lys) | AR | Yes

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**Gene** | **Muscle Biopsy** | **Mutation** | **Initial signs or symptoms** | **Fibres** | **Edema** | **Involution** | **PEG feeding**
---|---|---|---|---|---|---|---
1 Ac 14q | MT | c.8987G>T (p.Glu2999Lys) | Large | + | + | + | +
2 ACRD | NT | c.8218C>A(p.Ala2739Thr) | Large | + | + | + | +
3 ACTA1 | NT | c.3523G>A | Large | + | + | + | +
4 KLHL40 | NT | c.3526A>C (p.Asp1176Asn) | Large | + | + | + | +
5 RYR1 | NM | c.1270G>A(p.Gly423Arg) | Large | + | + | + | +
6 RYR1 | NT | c.1586A>G(p.Glu529Arg) | Large | + | + | + | +
7 RYR1 | CM | c.1516A>C (p.Thr506Pro) | Large | + | + | + | +
8 RYR1 | CM | c.7523G>A (p.Arg2508His) | Large | + | + | + | +
9 RYR1 | CM | c.802T>C (p.Phe268Leu) | Large | + | + | + | +
10 RYR1 | CM | c.7523G>A (p.Arg2508His) | Large | + | + | + | +
11 RYR1 | CM | c.3523G>A (p.Glu1175Lys) | Large | + | + | + | +