Truncation and microdeletion of \textit{EVC} accompanied by novel \textit{EFCAB7} missense mutation in Ellis-van Creveld syndrome with atypical congenital heart defect

\textit{NGUYEN Tran Quynh Nhu, MD.}

\textit{Department of Developmental Medical Sciences}
\textit{School of International Health, Graduate School of Medicine}
\textit{The University of Tokyo}

\textbf{PEDIATRIC 2016}
Atlanta, Georgia, U.S
Mar 30 2016
BACKGROUND

• Academic education:
  2015-2018: Ph.D
    School of Medicine, The University of Tokyo, JAPAN
  2013-2015: M.Sc
    School of Medicine, The University of Tokyo, JAPAN
  2009-2011: DIU (pediatric emergency and neonatology)
    Universities of France + Pham Ngoc Thach Medical University, VIETNAM
  2001-2007: Medical doctor
    Ho Chi Minh City University of Medicine & Pharmacy, VIETNAM

• Licenses & certificates:
  2011: DIU (Diplôme inter-universitaire d’urgence pédiatrique)
  2010: Medical license
  2010: PALS (Certificate of Pediatric Advanced Life Supports)
  2009: Certificate of echocardiography and cardiac pathology

• Work:
  2008-2013: Cardiologist
    Children’s Hospital 2, VIETNAM
Congenital defects 2013-2015 in Children’s Hospital 2, Vietnam

The number of congenital defects per year

Details of Congenital Heart defects

- VSD
- ASD
- PDA
- AVSD
- TOF
- Others

Children’s Hospital 2, Ministry of Health, Vietnam 2013-2015
Ellis-van Creveld syndrome

- Rare autosomal recessive ciliopathy
- Abnormalities: ectodermal, skeleton, heart (60%)
- 30% consanguineous couples
- Prevalence:
  - 1/60000, 300 cases (worldwide)
  - 5/1000 (Old Order Amish)
- Causative genes: EVC & EVC2
  - 60-70% Mutation-positive cases
Mutations in *EVC/EVC2* disrupt cilia-mediated Hedgehog signaling

- **EVC/EVC2 protein:** located at basal bodies (EvC zone) of primary cilia
- **Function:** regulate Hedgehog signaling in skeletal, cardiac development

EFCAB7&IQCE regulate Hh signaling by tethering the EVC-EVC2 complex

EVC
- SP
- TM

EVC2
- SP
- βsan
- TM

EFCAB7
- EF
- EF
- EF
- EF
- EF
- ECH1
- EF
- EF
- EF
- EF

IQCE
- HP
- Coiled coil conserved
- Coiled coil divergent
- IQ
- IQ
- IQ
- AcidE
OBJECTIVES

• To identify genetic background for Vietnamese EvC patients

• To identify molecules associated with pathogenesis of EvC syndrome
**MATERIALS**

- **Place**: Dept. Cardiology, Children’s Hospital 2 Ho Chi Minh City, Vietnam
- **Duration**: 09/2013 up to present
- **Materials**: whole blood, buccal mucosa & medical data

**DIAGNOSIS** at 16th ~20th weeks of gestation by fetal echography: morphology, echocardiology

After birth: collect medical data, samples

**FOLLOW-UP**

- **Congenital heart defects**
  - Every month
  - AVSD-CA: operation at 6~12 months
  - After operation: every 3~6 months

- **Oral and skeletal defects**
  - Every 3~6 months
  - Intervention: ~3 year-old
  - After intervention: every year
<table>
<thead>
<tr>
<th>Features</th>
<th>E1</th>
<th>E2</th>
<th>E3</th>
<th>E4</th>
<th>E5</th>
<th>E6</th>
<th>E7</th>
<th>E8</th>
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</thead>
<tbody>
<tr>
<td>Polydactyly</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+(R)</td>
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<tr>
<td>Syndactyly</td>
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<td>++</td>
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<tr>
<td>Congenital heart defects</td>
<td>cAVSD</td>
<td>pAVSD, PS</td>
<td>cAVSD, PS</td>
<td>CA</td>
<td>cAVSD</td>
<td>CA</td>
<td>ASD</td>
<td>pAVSD</td>
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<tr>
<td>Narrow chest</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
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<tr>
<td>Short stature</td>
<td>25th</td>
<td>&lt;2nd</td>
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<td>&lt;2nd</td>
<td>&lt;2nd</td>
<td>+</td>
<td>25th</td>
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<tr>
<td>Distal limb shortening</td>
<td>+</td>
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<tr>
<td>Dysplastic nails</td>
<td>+++</td>
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<tr>
<td>Tooth shape abnormalities</td>
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<tr>
<td>Excess frenule</td>
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<td>Hypodontia</td>
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<td>Neonatal teeth</td>
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<tr>
<td>Others</td>
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cAVSD complete atrio-ventricular septal defect  
pAVSD partial atrio-ventricular septal defect  
CA common atrium  
ASD atrial septal defect  
PS pulmonary stenosis
Case E2: two novel compound heterozygous EVC2 mutations

- Short stature
- Weyer acrofacial dysostosis

<table>
<thead>
<tr>
<th>Father</th>
<th>E2</th>
<th>Mother</th>
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</thead>
<tbody>
<tr>
<td>6</td>
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<tr>
<td>14</td>
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- c.2476C>T
- c.769G>T
Case E3: novel mutations in *EVC* and mRNA expression

- c.1717C>G/EVC
- 16.4 kb microdeletion/EVC
- CGH array result
16.4 kb microdeletion of EVC

Control

E3/Mother

~ 4:5752479, intron8
4:5755743 - 4:575841; 4:5755639 - 4:575840, intron 10
4:5768927 - 4:5769006; 4:5669007~, intron11

Inserte fragment, unknown origin
**EFCAB7** point mutation

Pusapati et al., *Developmental cell* (2014)28:483-496
**Case E3: SHORT CHORDAE**

**Hypothesis:** EFCAB$^{1171C}$ may cause short chordae in EvC by tethering with EVC, EVC2, IQCE at the base body of cilium.
**DISCUSSION**

- Different heterozygous mutations resulted in various severity of phenotype
  → Phenotype-genotype relationship remains elucidated.

- Novel *EFCAB7* variant was found in patients with atypical cardiac defect; short chordae.
  - Short chordae has never been reported in EvC
  - *EFCAB7* knockout mice showed AVSD
  → *EFCAB7* might have roles in heart development and formation.
• The novel compound heterozygous mutations in \textit{EVC2} (c.769G>T, c.2476C>T) were disease-causative.

• A novel point mutation (c.1717C>G) and 16.4 kb heterozygous deletion of \textit{EVC} caused EvC phenotype.

• \textit{EFCAB7} variant (c.1171T>C) was detected for the first time in EvC.
ACKNOWLEDGEMENTS

Children’s Hospital 2, Ho Chi Minh city, Vietnam
Patients and Colleagues
Dr. Trinh Huu Tung

Dept. Pediatrics, University of Tokyo

Dept. Developmental Medical Sciences, University of Tokyo
Prof. Masashi Mizuguchi
Asso. Prof. Makiko Saitoh

Asian Development Bank

Tokyo Marine Kagami Memorial Foundation
THANK YOU VERY MUCH