# Truncation and microdeletion of *EVC* accompanied by novel *EFCAB7* missense mutation in Ellis-van Creveld syndrome with atypical congenital heart defect

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**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

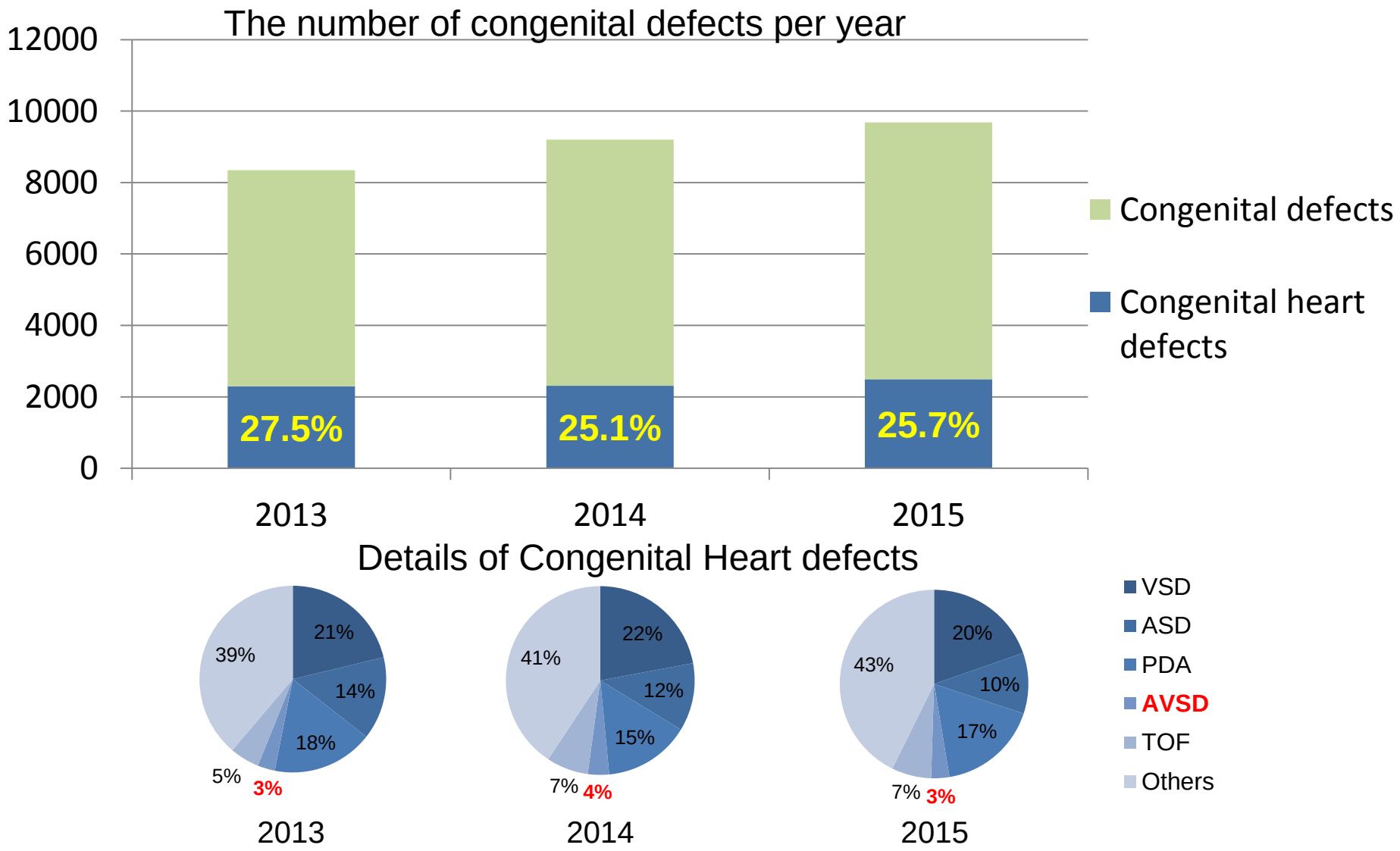
- **Licenses & certificates:**

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



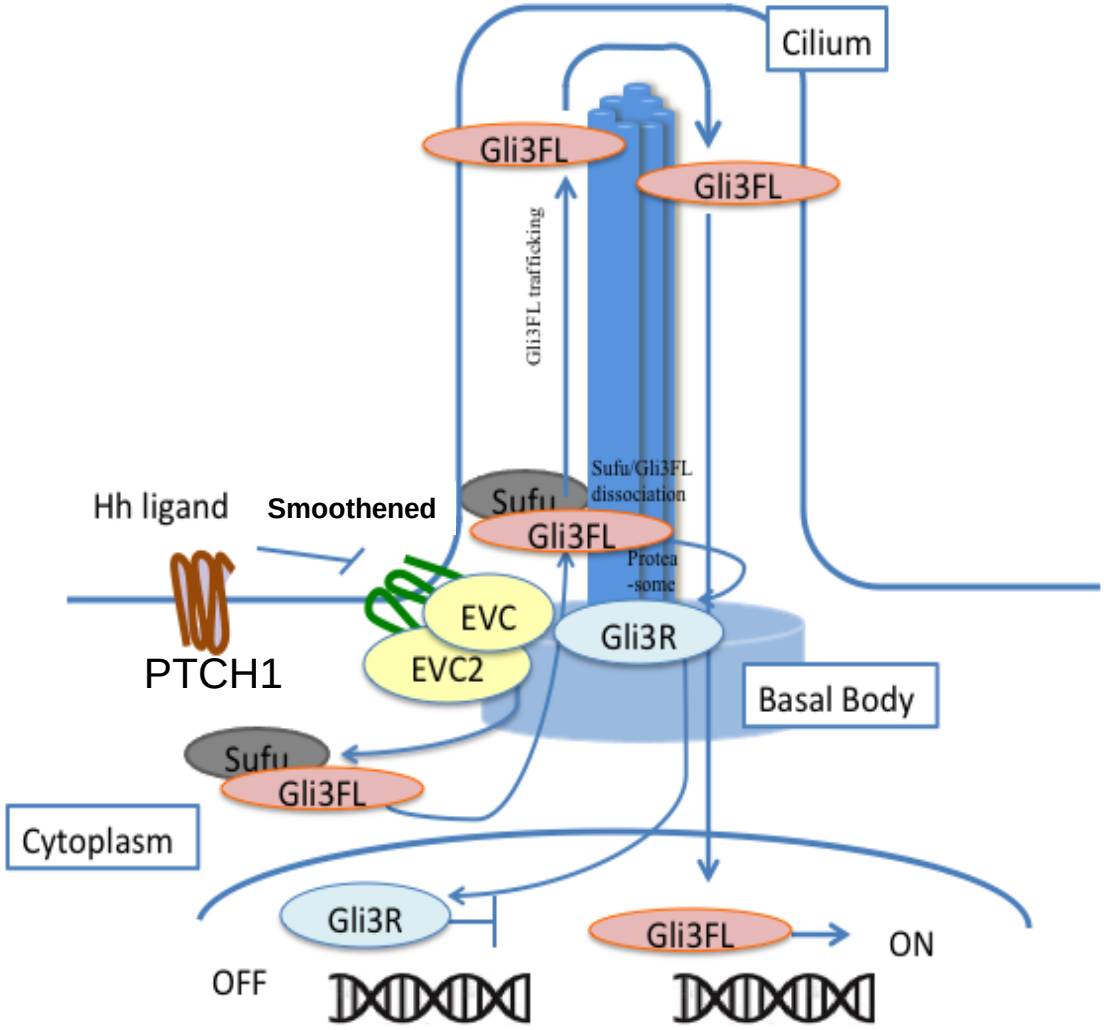

Children's Hospital 2, Ministry of Health, Vietnam
2013-2015

# 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

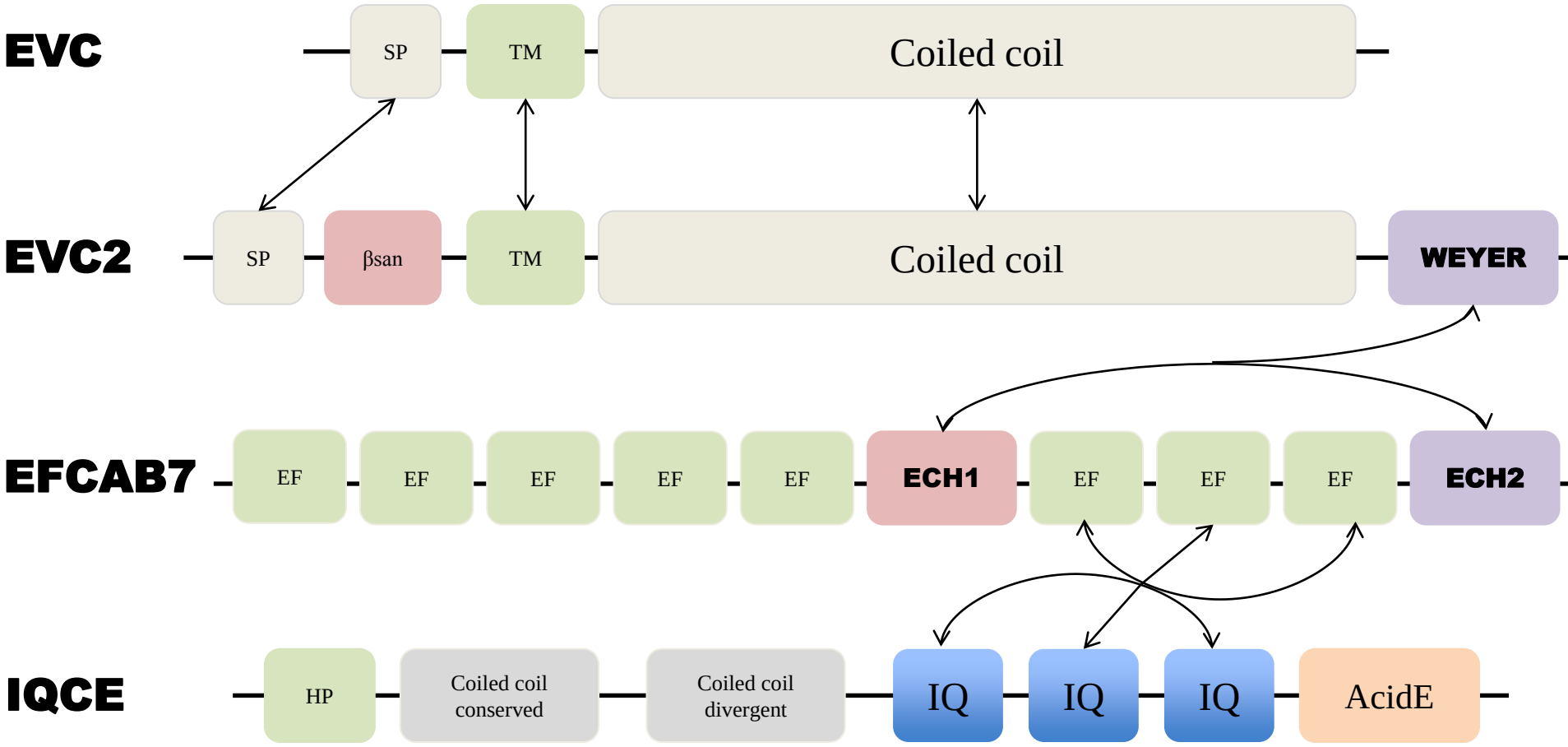
# Mutations in *EVC/EVC2* disrupt cilia-mediated Hedgehog signaling

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




Caparros-Martin et al.,*Human Molecular Genetics*(2013)22:124-139

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



# 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 16$^{th}$ ~20$^{th}$ 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

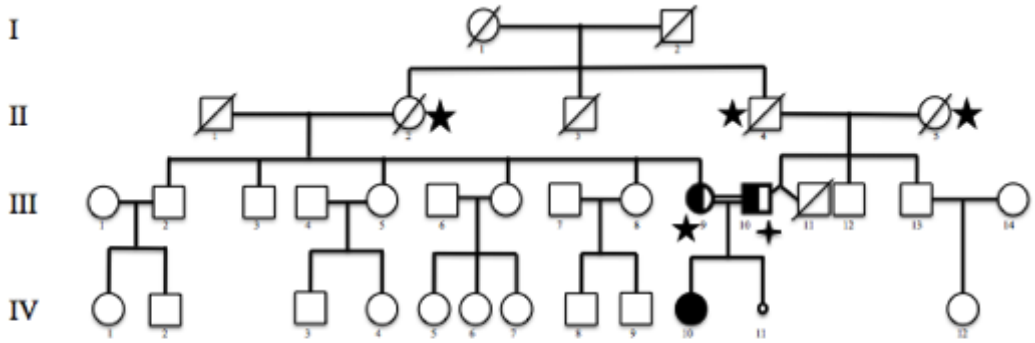
After intervention: every year

# Clinical features of patients

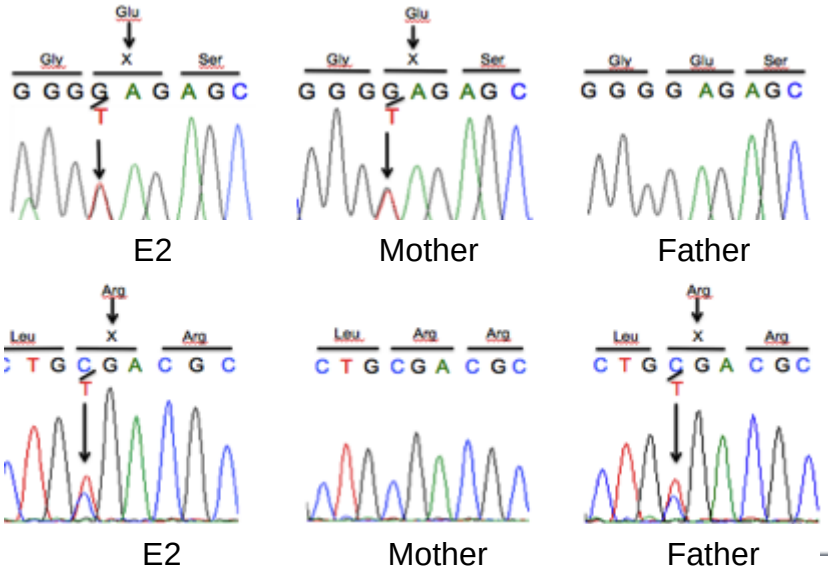
| Features | E1 | E2 | E3 | E4 | E5 | E6 | E7 | E8 |
|---|---|---|---|---|---|---|---|---|
| Polydactyly | +++ | ++ | ++ | +++ | ++ | +(R) | - | - |
| Syndactyly | - | - | - | - | + | - | + | ++ |
| Congenital heart defects | cAVSD | pAVSD, PS | cAVSD, PS | CA | cAVSD | CA | ASD | pAVSD |
| Narrow chest | + | + | + | ++ | + | - | + | - |
| Short stature | 25$^{th}$ | <2$^{nd}$ | <2$^{nd}$ | <2$^{nd}$ | <2$^{nd}$ | <2$^{nd}$ | + | 25$^{th}$ |
| Distal limb shortening | + | + | + | + | + | - | - | - |
| Dysplastic nails | +++ | +++ | +++ | +++ | +++ | - | + | - |
| Tooth shape abnormalities | - | - | - | - | - | + | + | - |
| Excess frenule | - | + | - | ++ | - | - | - | + |
| Hypodontia | - | - | +/- | - | - | - | - | - |
| Neonatal teeth | - | + | - | + | - | - | - | - |
| Others | - | - | - | - | + | + | - | - |

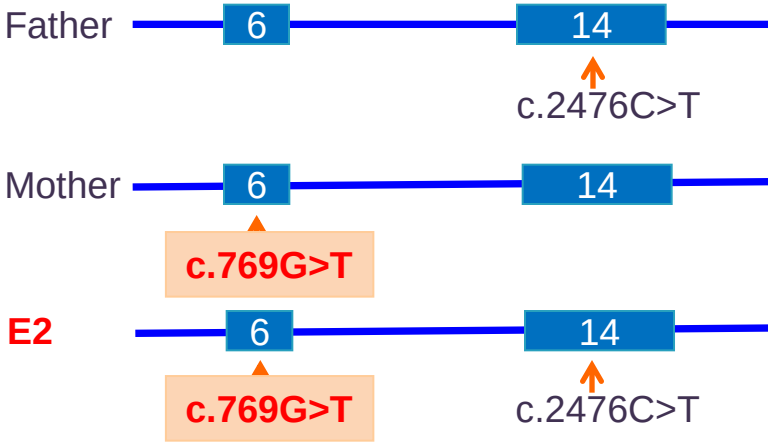
cAVSD complete artio-ventricular septal defect
pAVSD partial atrio-ventricular septal defect
CA common atrium
ASD atrial septal defect
PS pulmonary stenosis

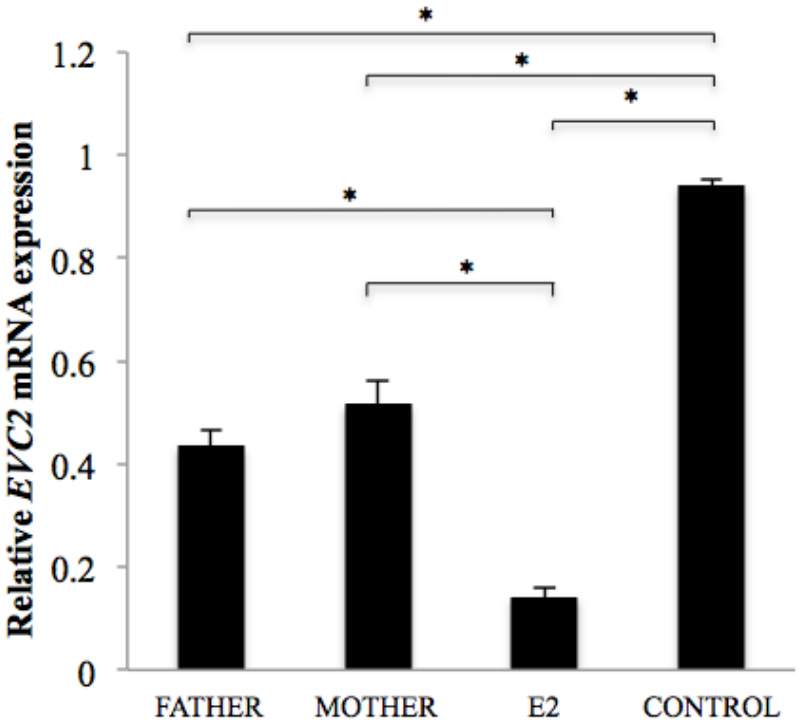
# Case E2: two novel compound heterozygous *EVC2* mutations




★ Short stature
✦ Weyer acrofacial dysostosis

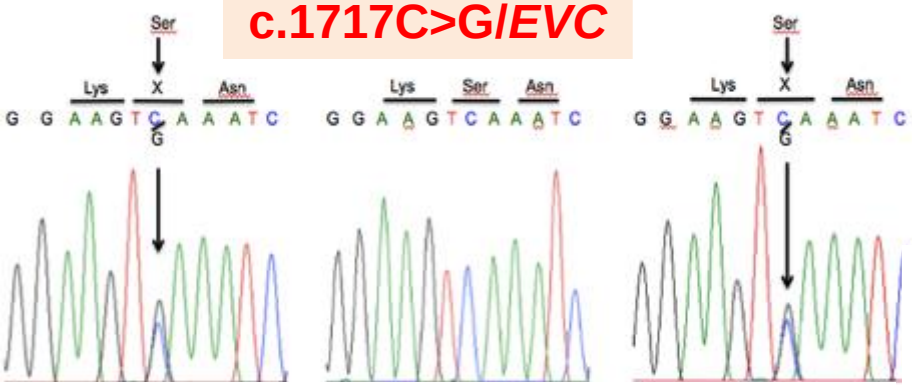


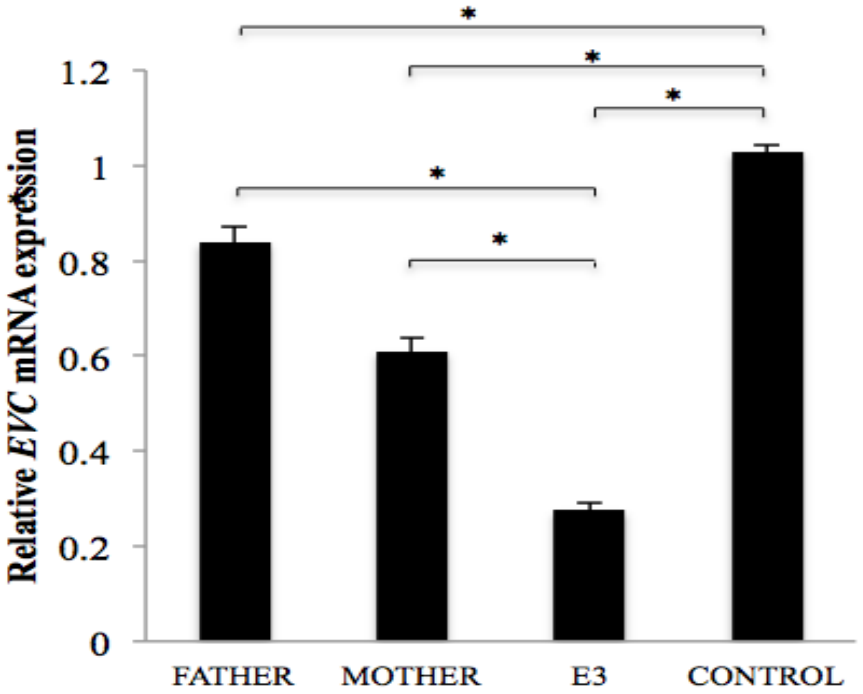
# Case E3: novel mutations in *EVC* and mRNA expression

**c.1717C>G/*EVC***

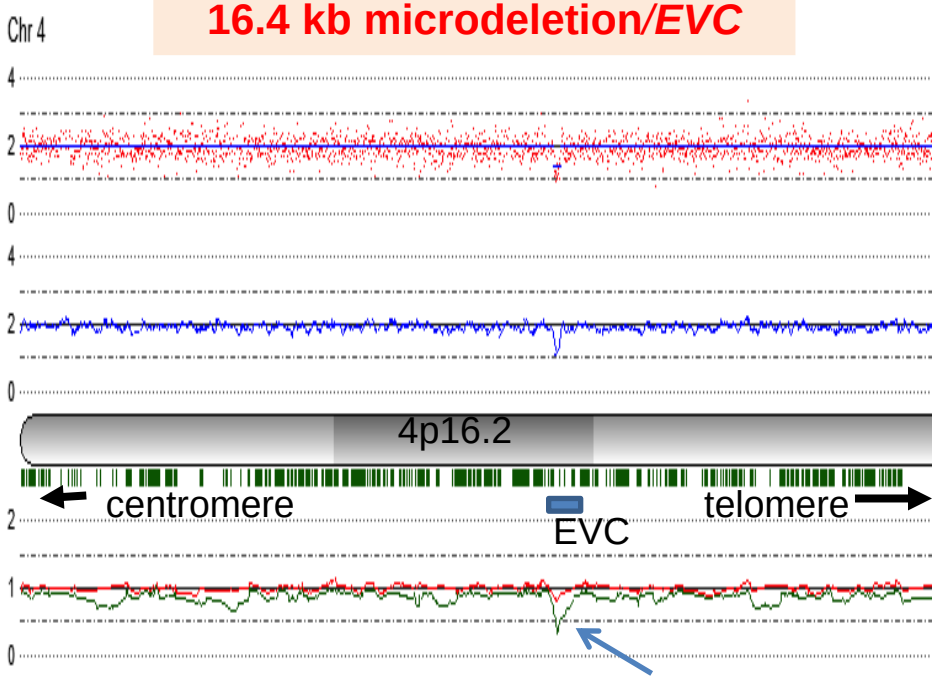



E3 Mother Father

**No mutation**

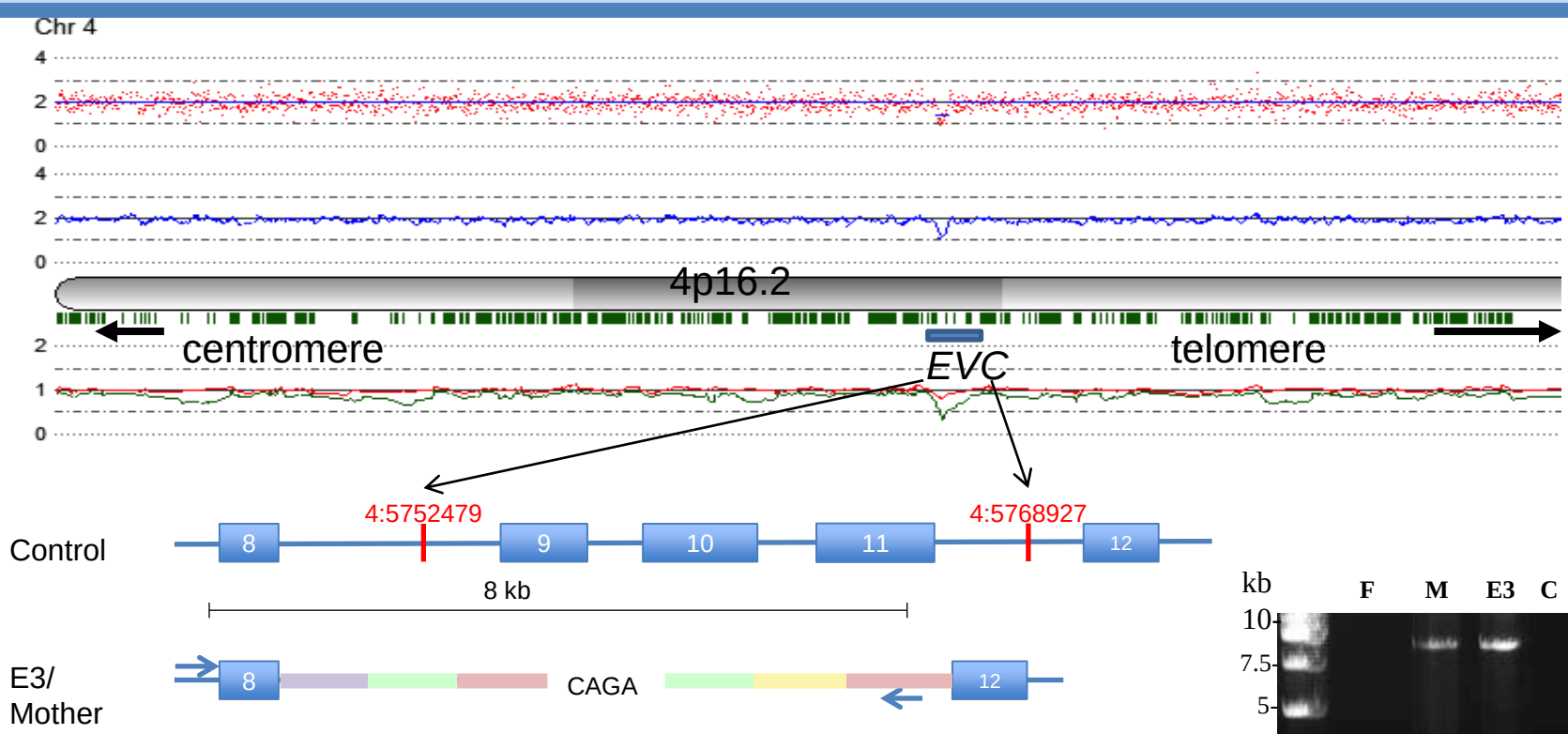



**16.4 kb microdeletion/*EVC***




**CGH array result**

# 16.4 kb microdeletion of *EVC*







~ 4:5752479, intron8

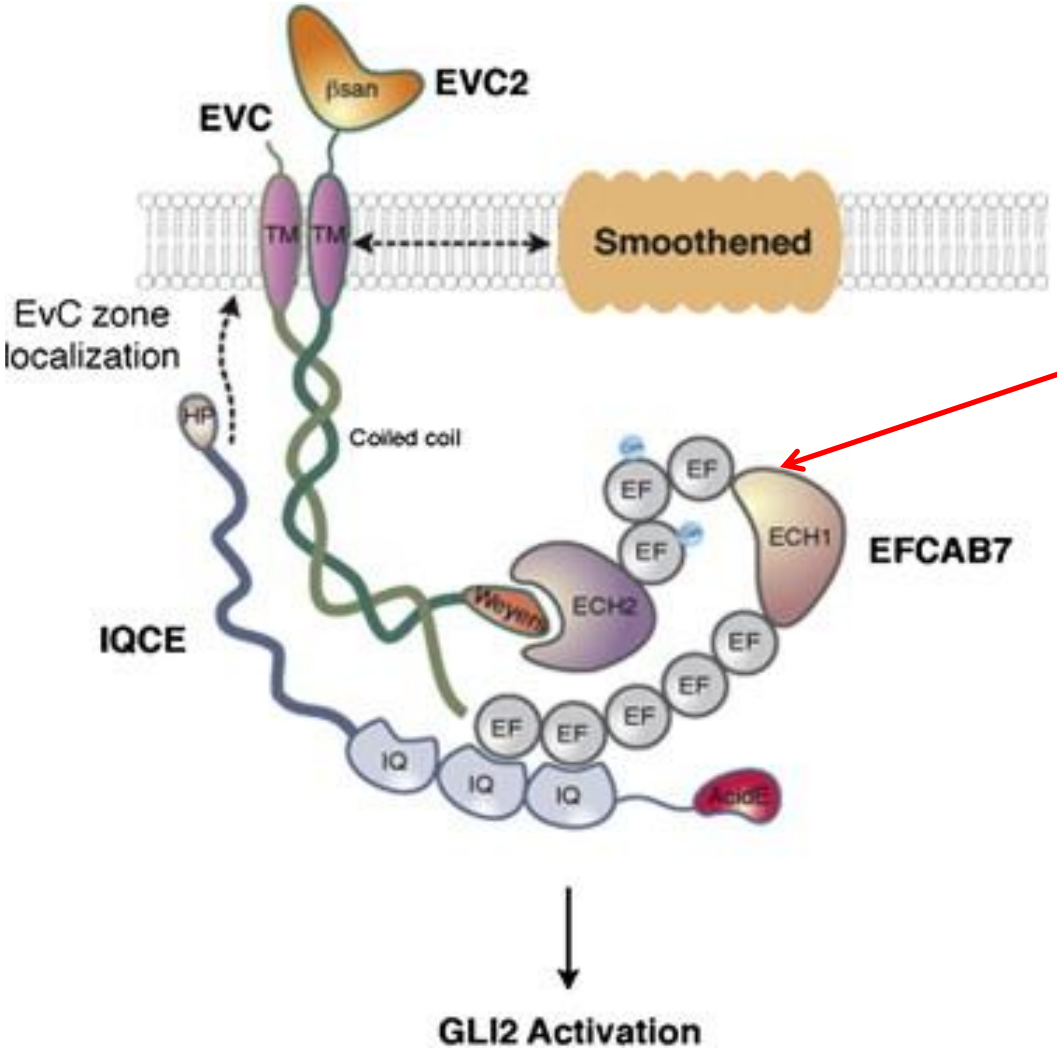
4:5755743 - 4:5755841; 4:5755639 - 4:5755840, intron 10

4:5768927- 4:5769006; 4:5669007~, intron11

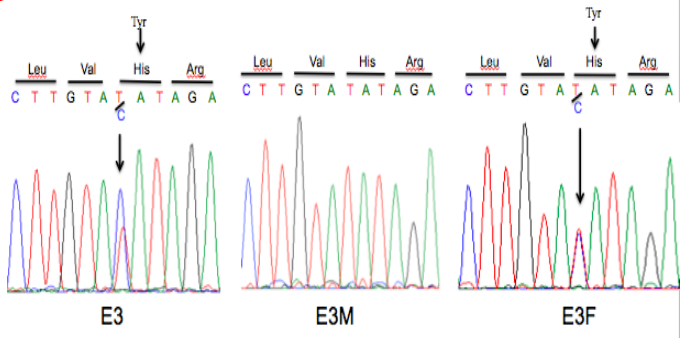
Inserted fragment, unknown origin

CTGACTGCCGGGGAGTCGTGTTGGAAGCCAATCATTCCCCCTGAAAATC
TCGGCCCGTCCTCAGCAGTCAGGCTCTCTGGGGGCTCTAACAAAAGCCCA
GGAACTGCCTGGCACTTTGCATTTCCTCCACAGCCCCTGTGGGGGGCCCAC
AGGGTGGAGGCCCCTTCCCTGAGGACCCCAGCAGAGGCAGCAGGAGAC
TGGGCTAACCCCGGGAATCAGCAGGGGGGAGACCCAGCCAGCCCCTAAAAC
AGAGCATCAGAGGTACCCTGCCTTGCTGGCTGGCTGGCTGTGCCCCAG
GCCCCAGGCACACAGAGGCATCATTTTACCCCTTCTTTGGGCATCAGA
GAGGGGCGAGGTGGGGCAGAAGGACAGAGGAACAGACCCTTCTCAG
GGAAGGGTTGCAGGAGAAAATTCCCTGTTGGGGAGATGTTTCAATGG
AGTCTCTAAGCATAAGTGTTATGTCCTTAGCATAACACTGATCATGAT
ATTGCAGGCACAGTGGCTGTGAGATACATTTGATGGTCACCTATATTA
ATTTGTTCTCACACTTGTAATAAAGATATACCCGAGACTGAGTAATTT
ATAAAGGAAACAGGTTTAACAGACTCACAGTTCCACGCCTCACAGTTA

# *EFCAB7* point mutation

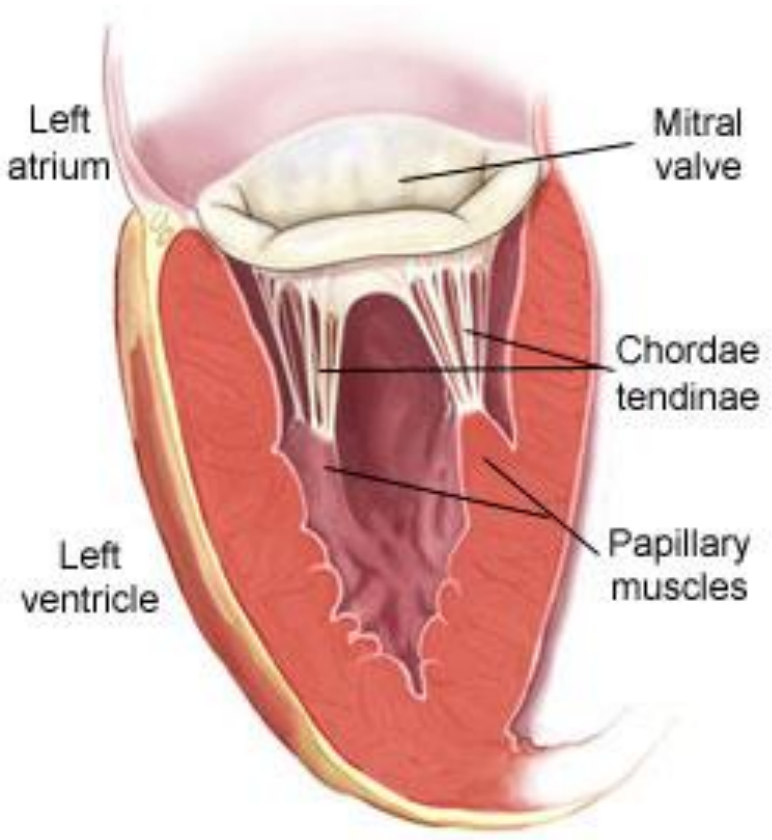



c.1171T>C/*EFCAB7*

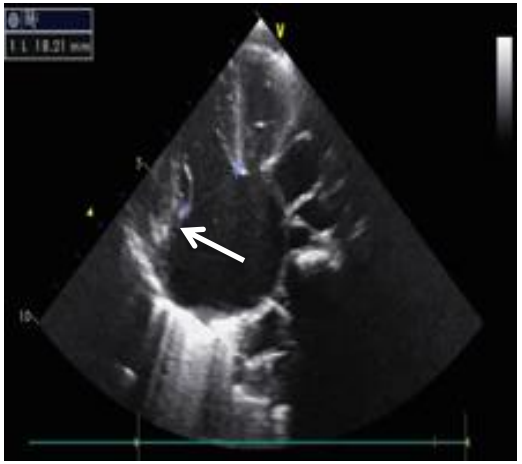



Pusapati et al., *Developmental cell* (2014)28:483-496

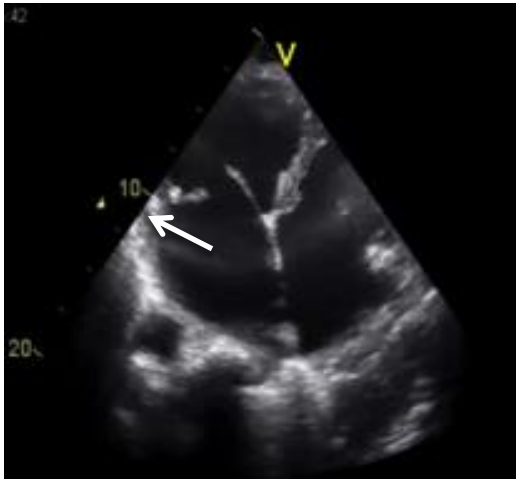
# Case E3: SHORT CHORDAE




**Patient E3**



**Father E3**




**Hypothesis:** EFCAB7$^{1171C}$ 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.

# CONCLUSION

- The novel compound heterozygous mutations in *EVC2* (c.769G>T, c.2476C>T) were disease-causative.
- A novel point mutation (c.1717C>G) and 16.4 kb heterozygous deletion of *EVC* caused EvC phenotype.
- *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