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## Introduction

- Ellis-van Creveld syndrome (EvC) is an autosomal recessive chondro-ectodermal dysplasia, characterised by short ribs, short limbs, postaxial polydactyly (Figure 1), dysplastic nails and teeth and a range of dental anomalies. Congenital heart defects occur in 60% of cases.
- EvC is caused by mutations in *EVC* (21 exons) and *EVC2* (22 exons) at 4p16. These genes are highly polymorphic and are arranged in a divergent orientation separated by 2.6kb. EvC results from loss-of function mutations in *EVC* or *EVC2*. The majority of previously reported mutations introduce a premature termination codon.
- EvC is a rare disorder most prevalent in the USA Amish population. The birth prevalence in non-Amish is estimated as 0.7/100,000. Consanguinity is reported in 30% of cases (Ulucan *et al.* 2008).
- Weyer's Acrodistal Dysostosis is an allelic autosomal dominant disorder also caused by mutations in *EVC* or *EVC2*.
- The Bristol Genetics Laboratory have offered a testing service since September 2010 following acceptance of a UKGTN gene dossier.

## Method

A new UKGTN service for Ellis-van Creveld has been established using high throughput semi-automated bidirectional sequencing of 44 fragments (*EVC* 21, *EVC2* 23) followed by analysis using Mutation Surveyor (SoftGenetics). Both genes are sequenced simultaneously as the phenotype associated with mutations in *EVC/EVC2* is indistinguishable. Sequencing of *EVC/EVC2* is expected to detect approximately 69% of EvC cases (Tompson *et al.* 2007), it is therefore possible that there is further genetic heterogeneity. The service was validated using 17 EvC samples kindly provided through collaboration with the Institute of Human Genetics, Newcastle.

## Results

- In the first 6 months 10 probands were tested and 2 carrier tests performed.
- Four patients had a positive genetic diagnosis.
- Table 1 gives a table of results to date.

### Figure 1

Postaxial polydactyly and short distal phalanges. Image from Ruiz-Perez and Goodship, 2009.

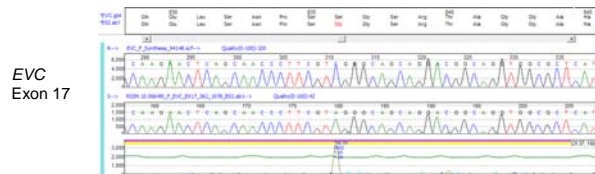


Table 1 Results to date

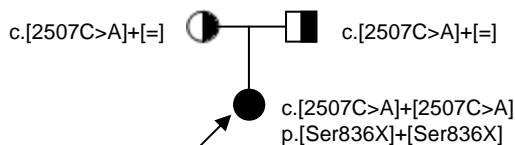
Case	Result	Referring Centre
1	c.[2507C>A]+[2507C>A]	TDL
2	c.[451-1_452delGTA] + [451-1_452delGTA]	Cambridge
3	3 novel heterozygous <i>EVC2</i> variants and 1 <i>EVC</i> variant - ?all non-pathogenic	Bristol
4	c.[1369G>A] + [=] - ?non-pathogenic	Bristol
5	N/N	Bristol
6	N/N	Newcastle
7	N/N	Australia
8 Investigation ongoing	? Homozygous LINE-1 mediated deletion of <i>EVC2</i> and <i>EVC</i> exons 1-11.	Dublin
9	c.[2326G>A] + [=] - ?non-pathogenic	Glasgow
10	c.[1700G>A]+[1700G>A]	St George's

## Case 1

- The proband is a 3 year old female of arabic origin.
- She presented with:
  - Short ribs with narrow thorax
  - Mesomelic shortening of the upper and lower limbs
  - Postaxial polysyndactyly
  - Fusion of carpal bones
- Sequence analysis identified a novel homozygous variant c.2507C>A, p.Ser836X; this results in a premature STOP codon in exon 17 of *EVC*.

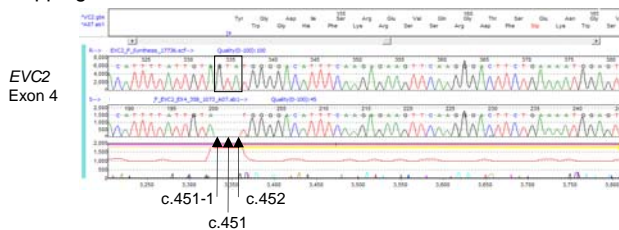


- Parental samples were tested to confirm carrier status and also to exclude the possibility of a large deletion of this region (The possibility of consanguinity has not been excluded).



## Case 2

- One year old female patient of consanguineous parents with an antenatal diagnosis of EvC.
- She presented with:
  - Large AVSD
  - Bilateral postaxial polydactyly of hands
  - Short ribs
  - Short long bones
- Sequence analysis identified a novel homozygous variant c.451-1\_452del in *EVC2*.
- This deletion at the intron-exon boundary of exon 4 is predicted by informatics analysis to alter the acceptor splice site, resulting in skipping of *EVC2* exon 4.



- Genetics analysis confirmed a diagnosis of EvC in this patient and allows the parents to consider prenatal diagnosis following carrier testing.

## Discussion

- The Bristol Genetics Laboratory has offered a UKGTN diagnostic testing service for Ellis-van Creveld syndrome since September 2010.
- Initial service difficulties presented due to the highly polymorphic nature of *EVC* and *EVC2*, over 60 variants were detected and determined to be benign polymorphisms.
- All of the mutations identified to date introduce a premature termination, either directly or as a result of a splicing defect. The presence of one or a combination of missense variants poses a reporting challenge, particularly with regards to pathogenicity.

## References

- Tompson SWJ. *et al.* (2007) Sequencing *EVC* and *EVC2* identifies mutations in two-thirds of Ellis-van Creveld syndrome patients. *Hum Genet.* **120**:663–670.
- Ulucan H. *et al.* (2008) Extending the spectrum of Ellis van Creveld syndrome: a large family with a mild mutation in the *EVC* gene. *BMC Medical Genetics.* **9**:92.
- Ruiz-Perez VL and Goodship JA. 2009. Ellis-van Creveld syndrome and Weyers acrodistal dysostosis are caused by cilia-mediated diminished response to hedgehog ligands. *Am J Med Genet Part C Semin Med Genet* **151C**:341–351.