EVIDENCE FOR A FOUNDER EFFECT IN MULTIPLE ENDOCRINE NEOPLASIA 2

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57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

September 27, 2018
Rapid Free communication 5 (RFC5.5)

THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS

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METHODS & PATIENTS

Study included a Cohort of patients with MTC between 2002-2017

- 40 patients from 11 apparently unrelated Cypriot families and two non-familial sporadic cases diagnosed with familial medullary thyroid carcinoma (MTC)
- Patients underwent *RET* testing by Sanger sequencing of exons 10–11 and 13–16 (BEST PRACTICE QUIDELINES) [**Revised American Thyroid Association (ATA) Guidelines for the Management of Medullary Thyroid Carcinoma, Thyroid, vol. 25 (6), 567-610, 2015. https://doi.org/10.1089/thy.2014.0335**]

RESULTS

Direct sequencing of the *RET* proto-oncogene

9 probands (69.2%): **p.Cys618Arg** (**High risk**-cysteine rich domain) ∴ **MEN2A**

Mean age at MTC diagnosis : 36.8±14.2 yrs

Age of pheo at diagnosis 26-43 yrs & simultaneously with MTC in 5/36 (13.9%) cases

1 patient (7.7%): **p.Cys634Phe** (**High risk**-cysteine rich domain) ∴ **MEN2A**

1 patient (7.7%): **somatic delE632-L633**(**High risk**-cysteine rich domain)∴ **MEN2A**

2 patients (15.4%): **p.Met918Thr (Highest risk for aggressive MTC – tyrosine domain)** ∴ **MEN2B**

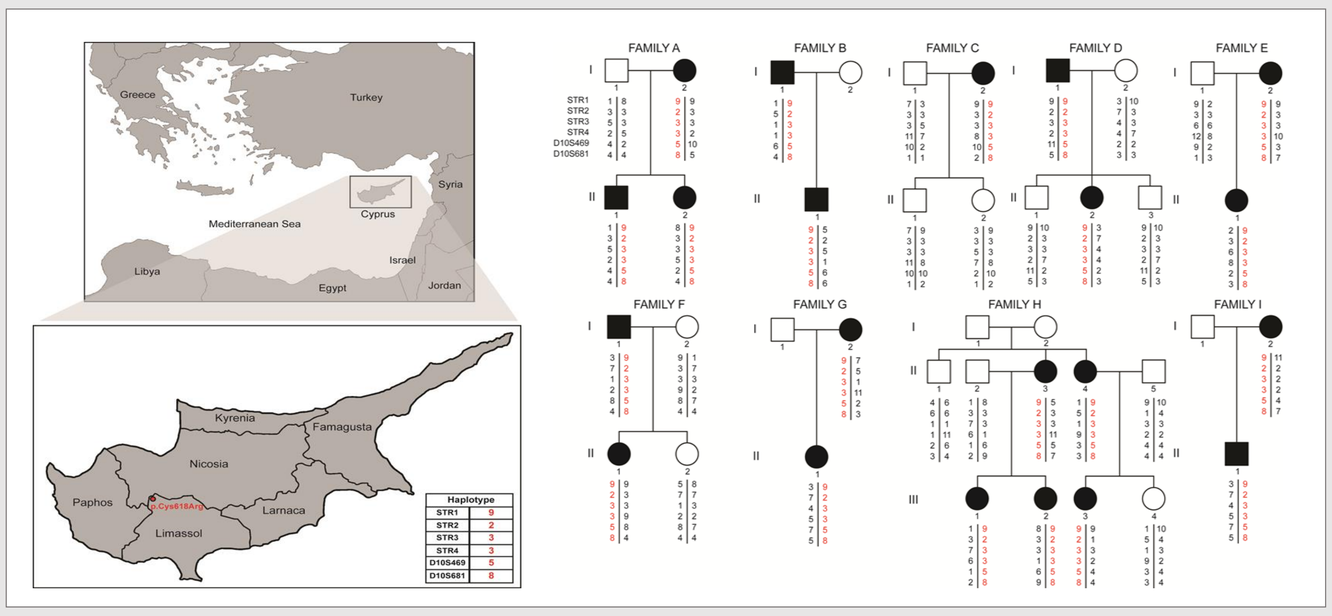
The high frequency of the p.Cys618Arg mutation suggested a possible ancestral mutational event

Haplotype analysis in families with and without p.Cys618Arg

- Six microsatellite STR genetic markers covering the *RET* gene & neighbouring regions.

GRCh38.p7: NC_000010.11 : STR1 (43207304-43207530 bp), STR2 (43664013-43664241 bp) and STR3 (43143426-43143640 bp) all located upstream of the *RET* gene & STR4 (43015181-43015361 bp), D10S469 (43445299-43445435 bp) and D10S681 (42897992-42897871 bp) all located downstream of the *RET* gene

One core haplotype associated with all patients carrying p.Cys618Arg -Possible founder effect Phenomenon!



- A village at the north-western end of the Limassol province was listed as property of the *Venetian Government – 15th century*
  - ✓ *According to the historian deadly disease plunged the village and the nearby areas during that period*
  - ✓ *People left the area and spread all over the island*
- We speculate that the reported disease of that time was the result of a founder mutation such as p.Cys618Arg
- Likely introduced to the locals by an *invader* or a *settler*
  - ✓ during the *Venetian era* between 1489-1570
  - ✓ or during the Crusades and the *Lusignan* Period between 1191–1489

Y-STR haplogroup assignment for all male (#10) patients with p.Cys618Arg

- PowerPlex® Y23 System, Promega that detects 23 Y-STR loci
- Haplotypes predicted (Whit Athey's Haplogroup Predictor tool): Generates probabilities for assignment to one of the major Y-DNA haplogroups (Heraclides & Cariolou *et al* 2017 in *PLoS ONE*)

Y-haplogroup assignment – Findings

- 7 major Y-haplogroups (G2a, J1, R1b, R1a, I2a, E1b1a, J2b) were predicted
- Most frequent Y-haplogroup: G2a (40%)
- Followed by J1, R1b, R1a, I2a, E1b1a and J2b at 10%, each

CONCLUSIONS

- p.Cys618Arg of the RET proto-oncogene is by far the most prevalent mutation in Cyprus
- Molecular data provides evidence for p.Cys618Arg mutation as an ancestral mutation that has spread due to a possible founder effect
- This founder mutation was likely introduced to the locals by an *invader* or a *settler* during the *Venetian era* between 1489-1570 or prior to that period during the Crusades and the *Lusignan* Period 1191–1489

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Acknowledgements:
This work was supported by the A.G. Leventis Foundation with a grant to LAP

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Competing Interests: The authors declare no competing interests.