EVIDENCE FOR A FOUNDER EFFECT IN MULTIPLE ENDOCRINE NEOPLASIA 2

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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 GUIDELINES) [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]
- PowerPlex® Y32 System, Promega that detects 23 Y-STR loci
- Haplotypes predicted (Whit Atthey’s Haplogroup Predictor tool): Generates probabilities for assignment to one of the major Y-DNA haplogroups (Heraclides & Cariolou et al 2017 in PLoS ONE)

Results

Direct sequencing of the RET proto-oncogene

9 probands (69.2%): p.Cys618Arg (High risk-cysteine rich domain) △ MENZA

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) △ MENZA

1 patient (7.7%): somatic deleL632-L633 (High risk-cysteine rich domain) △ MENZA

2 patients (15.4%): p.Met198Thr (Highest risk for aggressive MTC – tyrosine domain) △ MENZA

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.
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- Six microsatellite STR genetic markers covering the RET gene & neighbouring regions.
- GRS3.8.17: NC_000010.11: STR1 (4307034-4307065 bp), STR2 (4306640-4306634 bp) and STR3 (4314363-4314364 bp all located upstream of the RET gene & STRA (4305158-4305161 bp), D10S681 (42897871-43143640 bp and D10S681 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

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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REFERENCES