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Uncommon manifestations in type 4 familial paraganglioma syndrome – A large cohort of patients harbouring the *SDHB* p.Q214Ter variant

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Background:

- Familial paraganglioma type 4 syndrome (PPGL4) is caused by a germline pathogenic variant (PV) in the *SDHB* gene
- Patients harbouring germline SDHB PV have a higher risk of developing paragangliomas and pheochromocytomas (PPGL)
- Penetrance in PPGL4 is 22-42% by the age of 60 and 25-65% by the age of 80
- Patients with PPGL4 also have a higher-risk for aggressive, and metastatic, abdominal-thoracic paragangliomas compared with other familial paraganglioma syndromes
- This syndrome confers increased mortality compared to other familial paraganglioma syndromes

Aim:

Describe the largest cohort of patients with the pathogenic variant (PV) *SDHB* c.640C>T p.Q214Ter

Methods:

- Three index patients referred to our clinic due to PPGL underwent germline DNA isolation and sequencing
- All three harbored the same *SDHB* PV (c.640C>T p.Q214Ter) and reside in the same district
- Family members also underwent genetic evaluation (Sanger sequencing for the PV)
- Patients harbouring the PV underwent clinical evaluation, and blood pressure measurements and were referred for catecholamine quantification and neck, chest, abdomen, and pelvic imaging

Results:

- The cohort includes 114 patients (44.2% females) from three kindreds (A, B &C)
- Genetic evaluation was performed in 45/50, 16/28, and 25/36 in kindreds A, B, and C, respectively
- The *SDHB* PV was identified in 50 patients (total: 58.1%, and 68.9%, 56.2%, and 40.0%, in kindreds A, B, and C, respectively)
- Figure 1 shows the results of the genetic evaluation
- Eight patients had paraganglioma (metastatic in 4/8), and three had pheochromocytoma
- Penetrance was 22%, and metastatic rate 36%
- The table below shows tumor characteristics, with one testicular, one urinary bladder PPGL and two head and neck paragangliomas

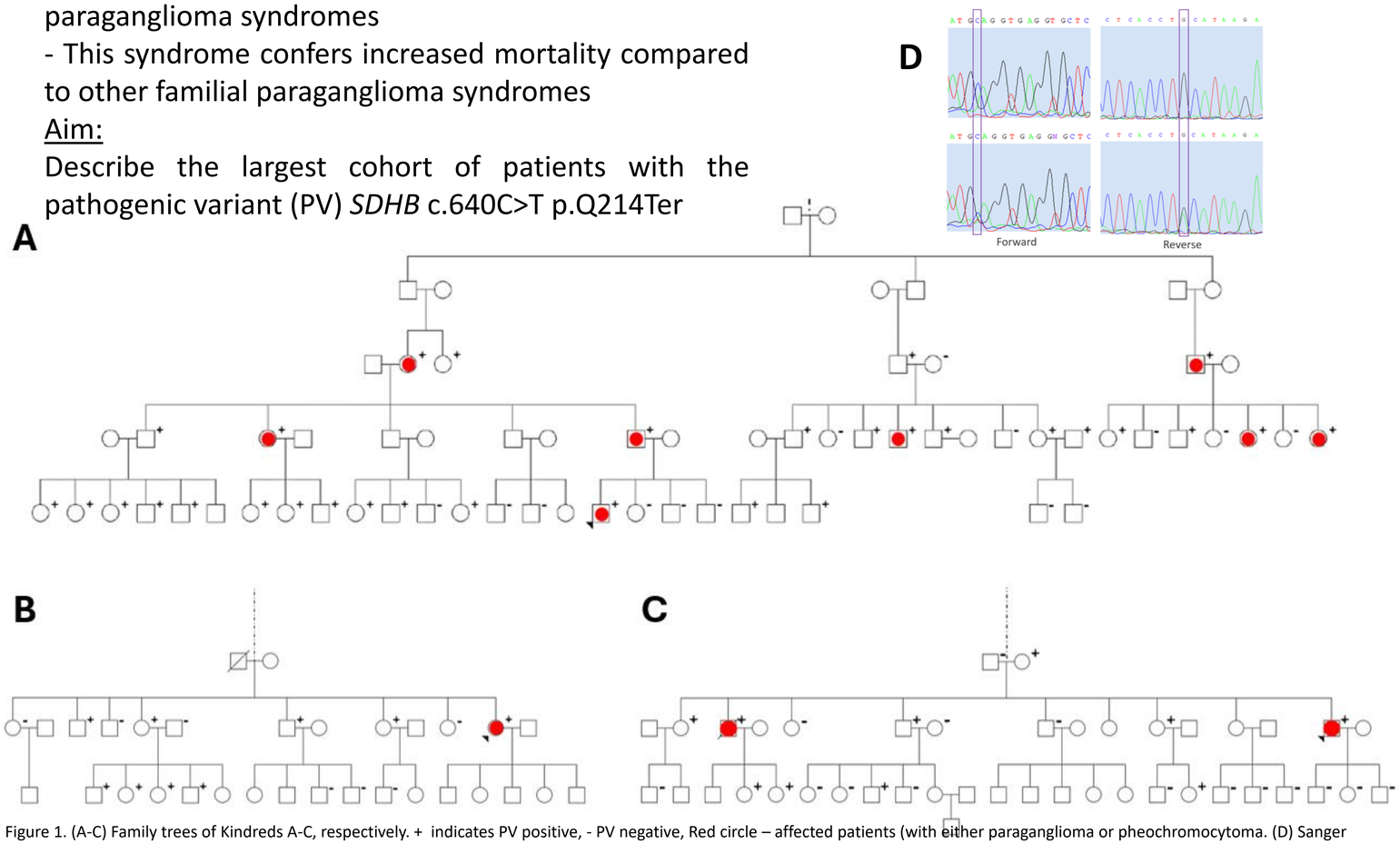

Figure 1. (A-C) Family trees of Kindreds A-C, respectively. + indicates PV positive, - PV negative, Red circle – affected patients (with either paraganglioma or pheochromocytoma. (D) Sanger sequencing, top – a patients with no PV, bottom – a patient with PV

Kindred	Assessment age (years)	Sex	Clinical manifestation (age [years])	Notes	Treatment
A	40	M	Pheo	Functional	Surgery
A	20	F	Urinary bladder PPGL (7)	Metastatic Functional	Surgery, SSA, PRRT
A	12	F	Abd PPGL		
A	15	M	Testicular PPGL (13), Thoracic PPGL (13)	Non-functional	Surgery
A		M	CBT (27), Abd PPGL (27)		
A	58	F	Pheo (22)	Functional	Surgery
A	19	M	Pheo (19)		Surgery
A		F	HN PPGL (NA)		
B	30	F	Abd PPGL (26)	Metastatic	Surgery, SSA
C	41	M	Abd PPGL (38)	Metastatic	CVD, SSA
C		M	Abd PPGL (NA)	Metastatic	

To conclude, this is one of the largest PPGL4 kindred described, with similar penetrance of metastatic rate to that describe in the literature. However, patients also harbored uncommon PPGL locations, warranting through evaluation.

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