Optimal surveillance of *SDHB* mutation carriers

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Background

Germline mutations of the gene encoding succinate dehydrogenase subunit B (*SDHB*) predispose to head and neck paraganglioma (HNPGL), sympathetic PGL, pheochromocytoma and renal cell carcinoma for which regular surveillance is required. *SDHB*-associated tumors harbor germline and somatic mutations, consistent with Knudson's two-hit hypothesis stating that the combination of an inactivating germline mutation as a first hit and somatic loss of function of the wild type allele as a second hit is essential for tumor development.

Objective

To assess the penetrance and optimal surveillance for different manifestations of *SDHB* mutation carriers.

Patients and Methods

This study included all *SDHB* mutation carriers who were followed at the department of Endocrinology at the University Medical Center of Groningen. Kaplan Meier curves were used to assess the penetrance. Poisson distribution model was used to calculate the hit rate and average time to detect manifestations, to assess the optimal age to start surveillance and intervals.

Results

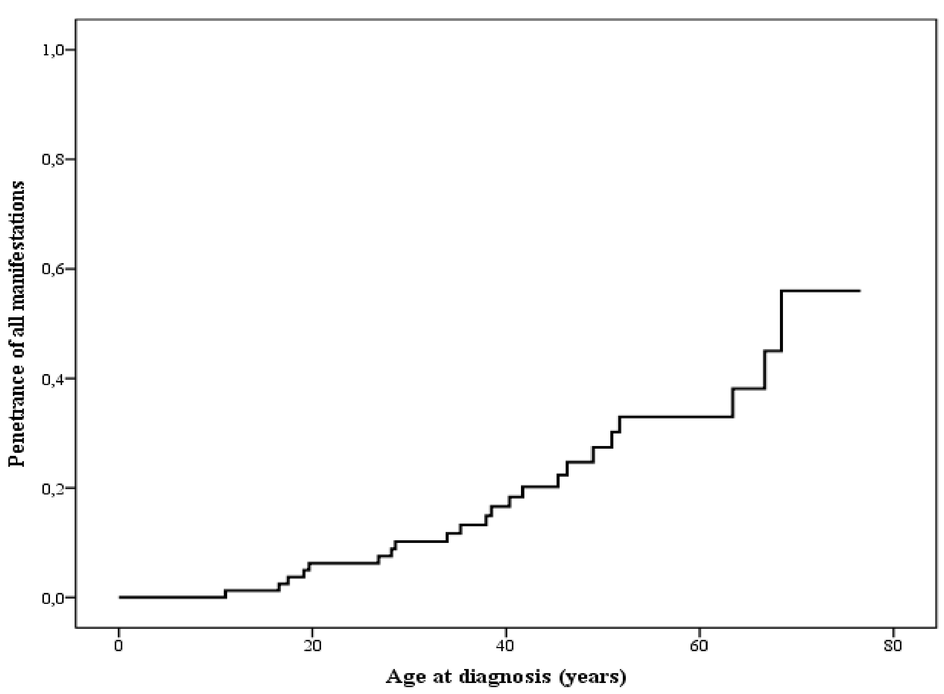

Figure 1. Age-related penetrance of all manifestations of the *SDHB*-gene (including HNPGL, PCC, and sPGL), including index cases.

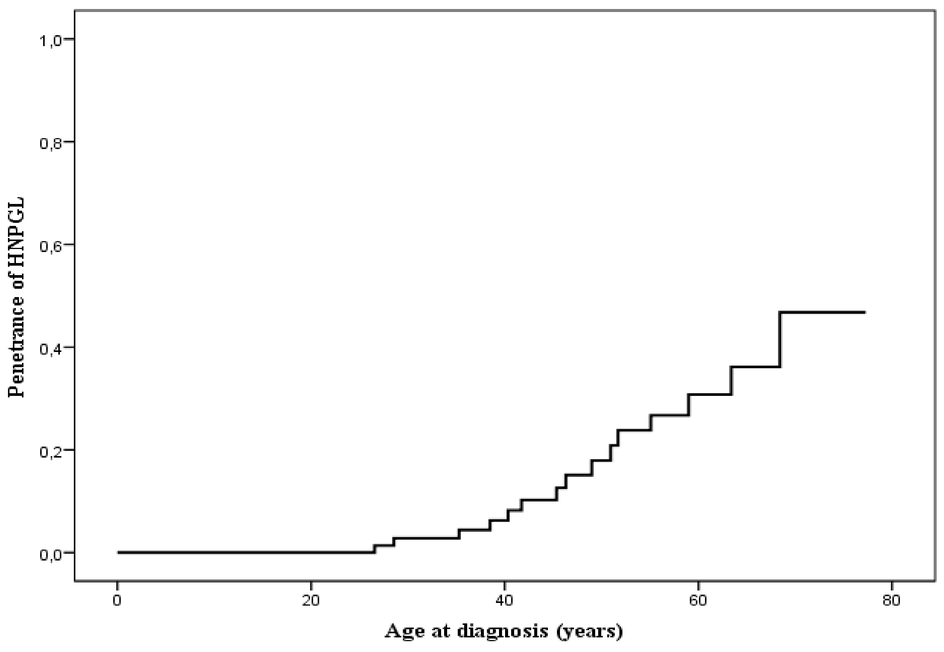

Figure 2. Age-related penetrance of *SDHB* mutation carriers with a HNPGL, including index cases.

Results

Table 1. Recommendations for surveillance of *SDHB* mutation carriers

	Age to start surveillance (years)	Surveillance program		
		Biochemical tests	Anatomical imaging	Functional imaging
Kirmani et al. 2012	10	Annual	Biennial CT/MRI of head and neck Quadrennial MRI of thorax-abdomen-pelvis	^{123}I-MIBG every 4 years
Benn et al. 2006	10	Annual	Biennial CT and/or MRI neck and thorax-abdomen-pelvis	Consider ^{18}F-DOPA-PET
Neumann et al. 2009	Not reported	Annual	Annual MRI of neck and thorax-abdomen-pelvis	Consider ^{18}F-DOPA-PET
Srirangalingam et al. 2008	5	Annual	Annual MRI of neck and thorax-abdomen-pelvis	
Dutch guideline	18	Annual	Biennial MRI of thorax-abdomen-pelvis Triennial MRI of head and neck	
Taïeb et. al. 2014	Not reported	Annual	Triennial MRI of head and neck	PET should be discussed on individual cases

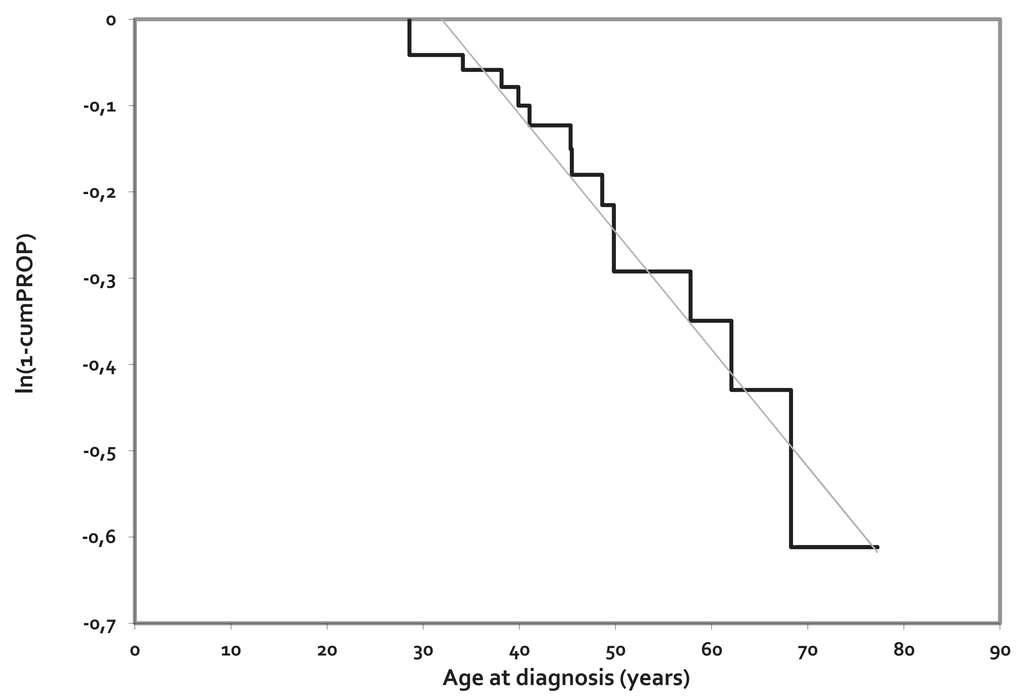

Figure 3. Natural logarithm of 1-cumulative proportion (ln(1-cumPROP) shown for *SDHB* mutation carriers with a HNPGL (black line), corresponding to Poisson distribution model (grey line).

Major findings

- Overall penetrance of 35% at age 60 years
- Penetrance for HNPGL 24% at age 60 years
- Optimal surveillance for HNPGL: start at age 24 years with an interval of 4 years

Conclusion and relevance

This study emphasizes a relatively low penetrance of disease in *SDHB* mutation carriers. Use of a Poisson distribution model provided a more accurate estimation of the age to initiate surveillance and subsequent intervals for HNPGL, suggesting that guideline recommendations regarding the screening of these mutation carriers might need to be revised.

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