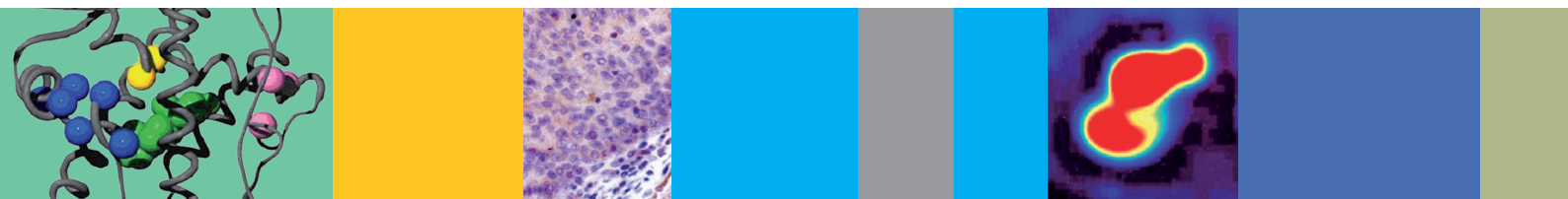


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Heterogeneous genetic background of Hungarian patients with pheochromocytoma/paraganglioma requires gene panel testingBalázs Sarkadi¹, Sára Zakariás¹, István Likó², Vince Kornél Grolmusz^{1,2}, Henriett Butz^{1,2,3}, Miklós Tóth¹, Nikolette Szücs¹, Péter Igaz⁴ & Attila Patócs^{2,3,4}¹2nd Department of Medicine, Semmelweis University, Budapest, Hungary; ²“Lendület” Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary; ³Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary; ⁴Molecular Medicine Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary.**Introduction**

Pheochromocytomas and paragangliomas (Pheo/PGL) are rare neuroendocrine tumours arising from the adrenal medulla or the sympathetic paraganglia, respectively. Germline mutations are present in ~40% of the patients. To date, at least 16 genes have been demonstrated to be involved in the genetic background of Pheo/PGL. Prioritization in order of genes tested can be applied, but if the probability of a disease-associated germline mutation exceeds 10% the testing of all susceptibility genes is recommended. Using next generation sequencing (NGS) based methods for genetic testing of Pheo/PGL associated genes progressively becomes part of the routine diagnostics.

Objective

To assess the genetic background of Hungarian patients with Pheo/PGL and to develop a NGS based gene panel assay for analysis of Pheo/PGL susceptibility genes.

Methods

We examined 131 patients with the diagnosis of Pheo/PGL diagnosed and nursed at the 2nd Department of Medicine, Semmelweis University. The prevalence of the germline mutations of Pheo/PGL genes was determined using conventional methods. Genotype-phenotype correlations were evaluated. A gene panel covering 15 genes (*RET*, *VHL*, *NF1*, *EPAS*, *EGLN1*, *KIF1B*, *SDHA*, *SDHB*, *SDHAF2*, *SDHC*, *SDHD*, *FH*, *MAX*, *TMEM127*, *MEN1*) was developed and analytical sensitivity was evaluated on 36 patients with known genetic background. Library preparation was performed using SeqCapEZ capture platform with our probe design. Illumina MiSeq instrument was used for sequencing. Sequencing data were analysed with GATK workflow. Variant annotation was performed with SNPeff.

Results

Germline mutations of Pheo/PGL genes were present in at 34% of the patients: 10 (7.6%) *SDHB*, 9 (6.9%) *RET*, 5 (3.8%) *VHL*, *TMEM127*, *MDH2*, 4 (3%) *NF1*, 3 (2.3%) *SDHD*, 2 (1.5%) *SDHC* and *KIF1B*. 5 of 10 *SDHB* mutation carriers developed malignant disease. Homozygous form of a *MDH2* variant was associated with malignancy. Among the 10 patients with bilateral adrenal Pheo 4 *RET*, 2 *TMEM127* and 1 *VHL* mutations were identified. The coverage of genes in our panel was higher than 150 reads in all regions and all known mutations were correctly identified.

Discussion

Our findings regarding the prevalence of germline mutations in the development of Pheo/PGL are in accordance with the literature. No founder mutation occurred in our population as we could detect mutations in 9 genes, underlining the need of novel methods for mutation analysis in everyday clinical practice. Our NGS-based gene panel performed accurately, however two recently identified genes (*MDH2*, *GOT2*) were not covered.

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Gastroenteropancreatic neuroendocrine tumors are predictive for a positive MEN1 germline mutation test: evidence from Hungarian MEN1 cohortAnnamária Kövesdi^{1,2}, Katalin Balogh¹, Miklós Tóth¹, Nikolette Szücs¹, Beatrix Sárman¹, Péter Pusztai¹, Péter Reismann¹, Anikó Somogyi¹, Katalin Borka³, Annamária Erdei⁴, Veronika Deák⁵, Zsuzsanna Valkusz⁶, Péter Igaz^{1,7}, Attila Patócs^{2,7,8} & Vince Kornél Grolmusz^{1,2}¹2nd Department of Medicine, Semmelweis University, Budapest, Hungary; ²“Lendület” Hereditary Endocrine Tumours Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary; ³2nd Department of Pathology, Semmelweis University, Budapest, Hungary; ⁴1st Department of Medicine, University of Debrecen, Debrecen, Hungary; ⁵Kaposi Mór County Hospital, Kaposvár, Hungary; ⁶1st Department of Medicine, University of Szeged, Szeged, Hungary; ⁷Molecular Medicine Research Group, Hungarian Academy of Sciences – Semmelweis University, Budapest, Hungary; ⁸Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary.**Objective**

Multiple endocrine neoplasia type 1 (MEN1) is a rare heritable tumor syndrome caused by germline mutations of *MEN1* gene affecting mainly the parathyroid, pituitary and pancreas. Phenotype varies widely, even in first-degree relatives. Recently it has been shown that functionally active gastroenteropancreatic neuroendocrine tumors (GEP-NETs), initially frequently diagnosed as sporadic cases, lead to MEN1 diagnosis. Non-functioning tumors are increasingly recognised due to advanced imaging modalities such as endoscopic ultrasound and thus became the most common GEP-NET in MEN1 patients. Contrary to sporadic GEP-NETs, MEN1-associated cases are diagnosed 10 years earlier and their penetrance is as high as 80-90%, reaching nearly that of the parathyroid adenomas. Mutation analysis enables early tumor detection, thus the possibility to prevent serious, even life-threatening morbidities associated with malignant GEP-NET. Our aim was to identify phenotype features predictive for a positive *MEN1* genetic test, and by comparing mutation-positive and mutation-negative patients to evaluate the role of *MEN1* mutations in phenotype modulation.

Design and methods

Of the 104 probands who fulfilled the criteria of *MEN1* mutation analysis, 36 patients with GEP-NET were enrolled in this study. Mutation screening of the *MEN1* gene by Sanger sequencing was performed at our national reference laboratory. Clinical data were studied together with laboratory, imaging and histological results. Multiple ligation probe amplification analysis of *MEN1* gene and Sanger sequencing of *CDKN1B* were carried out in clinically suspicious but *MEN1*-negative cases.

Results

Of 36 GEP-NET patients mutation analysis demonstrated disease-causing mutation in 19 patients. GEP-NET developed significantly earlier in mutation-positive patients; more than half of them appeared under 30 years of age. The prevalence of GEP-NET was also significantly higher at initial presentation in mutation carriers compared to mutation negative patients. The presence of GEP-NET under 30 years best predicted a positive *MEN1* genetic test. Its prevalence remained significantly higher among mutation carriers during the follow-up. In addition, probands with high-impact mutations (frameshift, nonsense, large deletions), predicted to affect menin function significantly, developed GEP-NETs more frequently compared to low-impact (inframe and missense) mutation carriers.

Conclusions

GEP-NETs appear significantly earlier and more frequently in *MEN1*-positive patients and best predicted a positive genetic test. MEN1 patients with high-impact mutations were more likely to develop GEP-NETs, revealing a possibly important prognostic consequences regarding genetic counseling.

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P127

Adrenocortical cancer – the effectiveness of mitotane therapy depending on the time of therapy and the therapeutic dose

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Introduction

Mitotane-o’p-DDD belongs to insecticides (DDT pesticide contamination), it is the only drug registered by the FDA in treatment in adrenocortical carcinoma (ACC). Treatment effect is controlled by mitotane concentration in the blood.

Aim

The aim of the study is to evaluate the effectiveness of mitotane treatment in patients with adrenocortical cancer.

Material and methods

We retrospectively reviewed data on ACC patients ($n=204$) treated with o,p’DDD ($n=117$) between 2002 and 2017. Finally, a total number of 55 patients was included in the study. In these patients, we analysed a graph of mitotane concentrations during the course of therapy. Therapeutic window of mitotane was set according to the characteristics of the medicinal product (FDA) at 14-20 mg/l. Patients were divided into two groups. For the study group, the inclusion criterion was to maintain the concentration window of mitotane in the plasma least at 50% of the treatment time. The study group included 17 people (31% of patients). The comparative group consisted of those who did not reach the therapeutic window, 38 patients (69%). We observed patients from both groups in time one year intervals after the inclusion of mitotane therapy. In the evaluation of the effectiveness of the therapy, we based on the comparison of subsequent CT and MR results according to RECIST criteria. Average duration of treatment was up to 40 months in the first group of patients. Average duration was of treatment was up to 28 months in the second group of patients.