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Spanish Molecular Registry of Pituitary Adenomas (REMAH): A multicenter, translational approach aimed at improving patient management

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Introduction

Pituitary adenomas are heterogeneous, rare tumors, that present with a variety of clinical endocrine manifestations, and their prevalence has been largely underestimated (one case per ~1000 general population). In order to advance in the tools for the diagnosis/management of different types of pituitary adenomas, a multicenter, multidisciplinary clinical-basic strategy has been developed by combining clinical/pathological/molecular information at 6 Spanish regional nodes covering all reference centers for pituitary pathology:

1. Córdoba/Andalucía
2. Alicante/Levante
3. Madrid
4. Barcelona
5. Bilbao
6. Santiago de Compostela

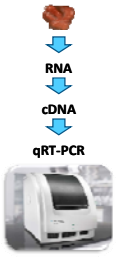
This unique coordinated, translational network initiative, named Spanish Molecular Registry of Pituitary Adenomas (**REMAH**), was developed in 2010 by the ***Sociedad Andaluza de Endocrinología y Nutrición***, and further endorsed by the ***Sociedad Española de Endocrinología y Nutrición***, and supported by ***Novartis***.

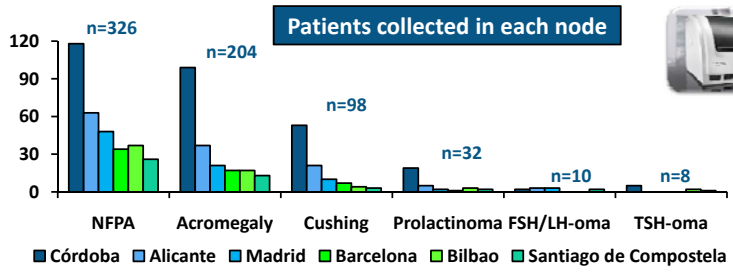
Materials & methods

To develop a shared database registering clinical, pathological and molecular information for each patient and to minimize inter-center variability, common protocols and methods were set up for tissue collection, and for clinical, pathological and molecular data analysis (including total RNA extraction, RNA quantification, retrotranscription, quantitative real-time RT-PCR) and registry. To date, the clinical, pathological and molecular data of 678 patients are being registered in a shared database (**http://www.remahnacional.com**) and the number continues growing.

A standardized system for adenoma molecular phenotyping was developed and validated. Specifically, 26 genes have been originally evaluated by quantitative real-time-PCR:

- All pituitary hormones: GH, PRL, POMC, βFSH, βLH, βTSH, αSUBUNIT
- Somatostatin receptors: SSTR1, SSTR2, SSTR3, SSTR5
- Dopamine receptors: DR1, DR2 [total (DR2T) and long isoform (DR2L)], DR4, DR5
- Hormone receptors: GHRH-R, GnRH-R, CRH-R1, AVPR1b, GHS-R1a
- Selected markers: Ki-67, PTTG-1
- Housekeeping genes for normalization: Beta-actin, HPRT, GAPDH



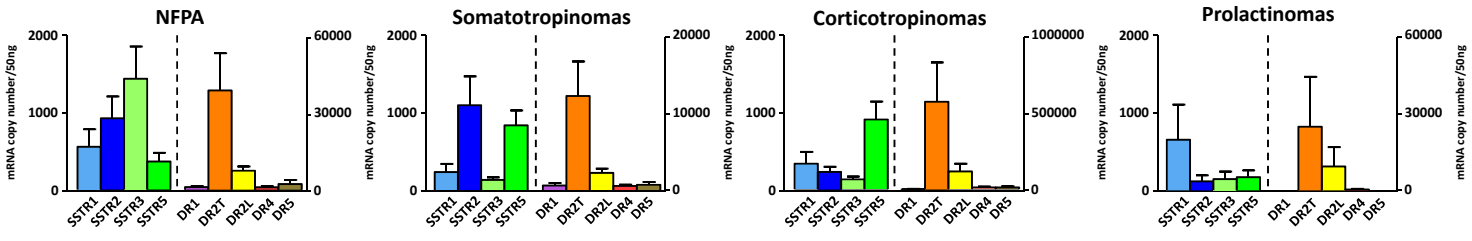


Results

Molecular information has been initially obtained on 250 tumors, out of 678 patients registered until April 2013. Specifically, 100 non-functioning pituitary adenomas (NFPA), 89 somatotropinomas, 44 corticotropinomas, 12 prolactinomas, 5 thyrotropinomas and 3 follicle-stimulating hormone secreting adenomas were analyzed. The expression levels of somatostatin receptors (SSTR) and dopamine receptors (DR) subtypes, the main two targets for medical treatment of pituitary adenomas, were found to be as follows:

1) NFPA: SSTR3 is the predominant SSTR receptor followed by SSTR2>SSTR1>SSTR5. DR2 is the most abundant DR-subtype followed by DR5≥DR1=DR4;
2) Somatotropinomas: SSTR2 and SSTR5 are present at the highest levels followed by SSTR1>SSTR3 . DR2 is the predominant DR subtype followed by DR5≥DR4≥DR1;
3) Corticotropinomas: SSTR5 is the predominant receptor followed by SSTR1≥SSTR2≥SSTR3. DR2 was the most abundant DR-subtype followed by DR5≥DR4>DR1;
4) Prolactinomas: SSTR1 is present at the highest levels followed by SSTR5≥SSTR3≥SSTR2 . DR2 is also the predominant DR subtype followed by DR4.

Results on somatostatin/dopamine receptor expression



Concluding remarks and future perspectives

1) **Initial analysis indicates a close parallelism of the molecular profile of the adenoma subtypes with previously reported data and with the clinical phenotype of the patients, and also provide additional information on specific receptors known as drug-targets.**
2) **REMAH is a unique, country-wide, multi-centric, multi-disciplinary network of expertise supported on a shared database enabling a translational, more powerful approach to the management of pituitary adenomas, paving the way for innovative clinical-basic studies with large numbers of patients of these rare pathologies.**
3) **Future studies using the REMAH database will be focused on determining whether a detailed knowledge of the adenoma molecular phenotyping profile could help to predict the hormonal response to therapy in order to improve the management of patients with different types of pituitary pathologies.**

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