

Hereditary Endocrine Cancer Group



Mercedes Robledo

Group Leader

Born in Madrid, Mercedes studied at the *Universidad Autónoma de Madrid* where she graduated in Biology in 1987. She then joined the Genetic Department of the same University supervised by J. Fernández-Piqueras, working on the cytogenetic and molecular characterisation of heterochromatin. In 1989, under the supervision of J. Benítez, she studied the characterisation of chromosomal and molecular alterations of lymphomas for which she was awarded her PhD.

In 1995 she was appointed as staff member of the Genetics Service of the *Fundación Jiménez Díaz* (Madrid). Since 1996 she has been working on the characterisation of hereditary endocrine cancer. Robledo moved to the CNIO in 2000 where her work continues to focus on these types of familial syndromes and on the identification of molecular predictor markers of clinical course, of new loci responsible for familial forms, and different altered pathways depending on individual genetic background.

She has authored more than 100 articles on genetic characterisation of hereditary diseases as well as seven books on molecular diagnosis in medical genetics and the use of SNP arrays in the identification of low penetrance genes. She plays a key role in the genetics of rare endocrine tumour diseases, leads Spanish Collaborative Groups and participates in International Consortia. She has made major contributions to the field of pheochromocytomas and paragangliomas as well as genetic risk factors related to thyroid cancer susceptibility. She has supervised seven doctoral theses.

Mercedes is an Honorary Lecturer at the *Universidad Autónoma de Madrid* and a member of the Spanish Society of Human Genetics.

Summary

Our Group is interested in identifying high and low genetic risk factors involved in endocrine tumour susceptibility and in revealing differences between tumour transcriptomes, microRNomes, methylomes and chromosomal gains and losses according to the different individual genetic backgrounds. Such comprehensive characterisation allows us to define diagnostic and prognostic markers associated to these tumours. We have therefore obtained a large collection of endocrine tumours from patients with germline mutations in most of the known major susceptibility genes related to these diseases as well as sporadic cases.

We are also interested in defining genetic markers associated with differences in anticancer drug responses. These efforts will collectively increase our genetic and molecular knowledge about these tumours and improve the diagnosis, prognosis and treatment of patients.

Strategic Goals

- Identify new major susceptibility genes related to endocrine cancer
- Elucidate the role of low penetrance genes related to sporadic endocrine tumour susceptibility as modifier genes in familial forms
- Identify genetic factors responsible for efficacy and toxicity of treatments used for endocrine tumours
- Recognise specific altered pathways differentially involved in endocrine tumours according to the individual genetic characteristics, searching for future specific therapeutic targets



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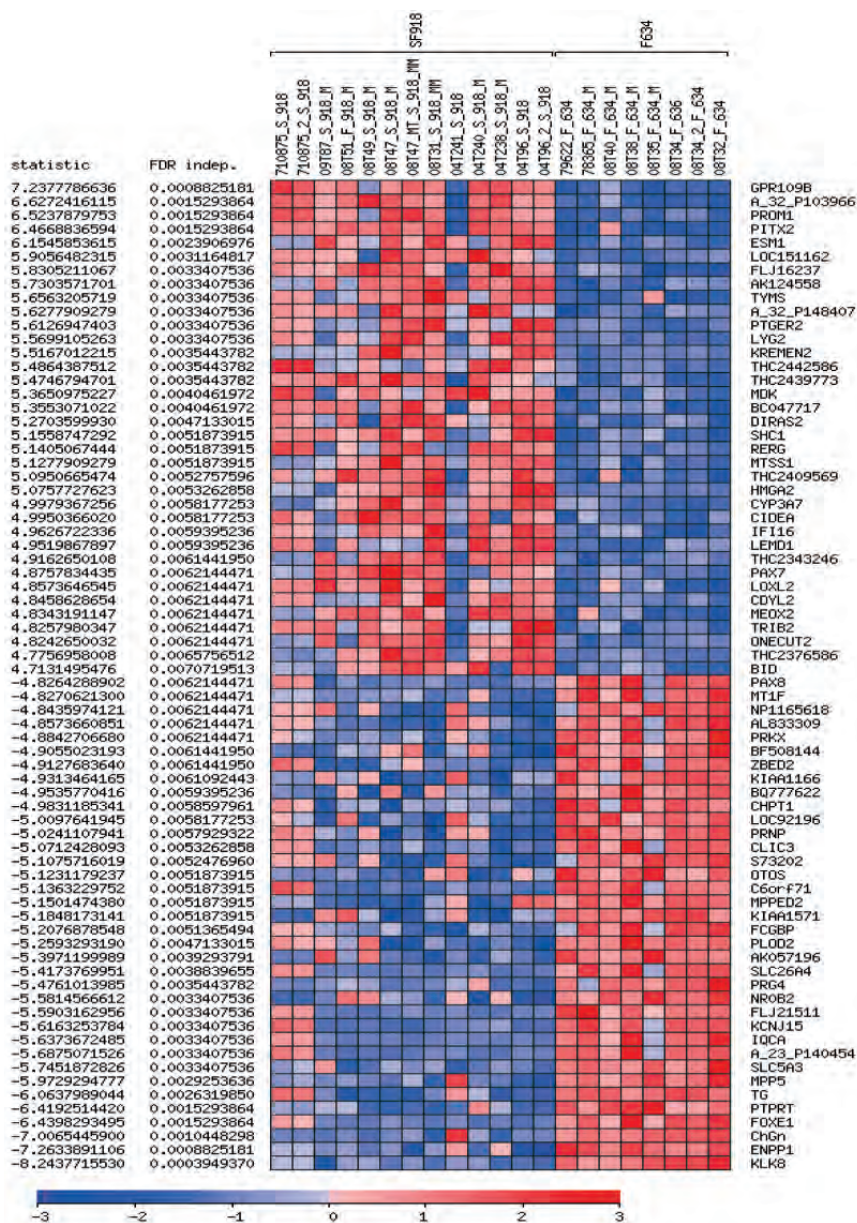
Highlights

SDHAF2: a new high susceptibility gene related to familial head and neck paraganglioma involved in specific clinical presentations

Paragangliomas and pheochromocytomas are neuroendocrine tumours frequently associated with germline mutations in *RET*, *VHL*, *SDHD*, *SDHC*, and *SDHB*, and more rarely in *MEN1*, *NF1* or *KIF1B*. This list of genes, responsible for the disease, has very recently increased through the addition of three newly identified genes whose function still needs to be established.

One of these new genes, *SDHAF2* (formerly known as *PGL2* or *SDH5*), encodes succinate dehydrogenase complex assembly factor 2, a highly evolutionarily conserved cofactor of flavin adenine dinucleotide (FAD). *SDHAF2* plays a role in the flavination of *SDHA* (one of the new genes recently involved in the susceptibility of pheochromocytoma/paraganglioma), essential for a fully functional succinate dehydrogenase complex. Loss of *SDHAF2* results in loss-of-function of succinate dehydrogenase and a reduction in stability of the enzyme complex, leading to diminished amounts of all subunits.

Figure 1: Transcriptional profiling in a series of medullary thyroid carcinomas. The figure shows a representative of the top differentially over- and under-expressed genes according to specific *RET* mutations in the comparison of familial and sporadic cases (FDR value <0.05).



A large cohort of patients were comprehensively characterised for *SDHAF2* alterations through an international multicentre collaborative study. Conclusions revealed that neither germline nor somatic *SDHAF2* mutations lead to development of pheochromocytoma. Although *SDHAF2* mutations are a rare cause of head and neck paraganglioma, the genetic analysis of *SDHAF2* should be considered in head and neck paraganglioma patients with familial predisposition and in individuals with a young age-of-onset and no mutations in *SDHD*, *SDHC*, or *SDHB*.

Transcriptome of sporadic and familial MTCs reveals *PROM-1* overexpression

PROM-1 overexpression as a specific marker of sporadic tumours harbouring *RET*⁹¹⁸ mutation that could be related to treatment resistance. Medullary thyroid carcinoma (MTC) arises from neural crest-derived parafollicular C cells and accounts for 2-5% of all thyroid malignancies. Around 75% of MTCs are sporadic, whereas the remaining 25% of cases are inherited and form part of the MEN2 (multiple endocrine neoplasia type 2) syndrome. Although a genotype-phenotype correlation has been well established for MEN2 patients, there is little knowledge about molecular

alterations specifically associated with each mutation as well as those involved in non-*RET* mutated sporadic MTC.

We used transcriptional profiling to gain insight into signalling pathways specifically related to familial and sporadic MTC. Among the whole list of genes differentially expressed between the two compared genetic classes (Figure 1), *PROM-1* (CD133) was one of the top over-expressed genes in those sporadic tumours specifically associated with *RET*⁹¹⁸ mutation. CD133 has very recently been described as a molecular marker for neural crest-derived stem cells. Its over-expression has also been shown in thyroid carcinoma cell lines harbouring *RET*⁹¹⁸ mutations and could be related to resistance to treatment and recurrence exhibited by this tumour.

Pharmacogenomics of microtubule-targeting drugs: SNPs in *CYP* genes influence the risk of paclitaxel toxicity

Microtubule-targeting drugs are cytotoxic agents used widely for the treatment of a variety of tumour types. Their mechanism of action consists of the alteration of cellular microtubule dynamics through β -tubulin binding. These drugs still present

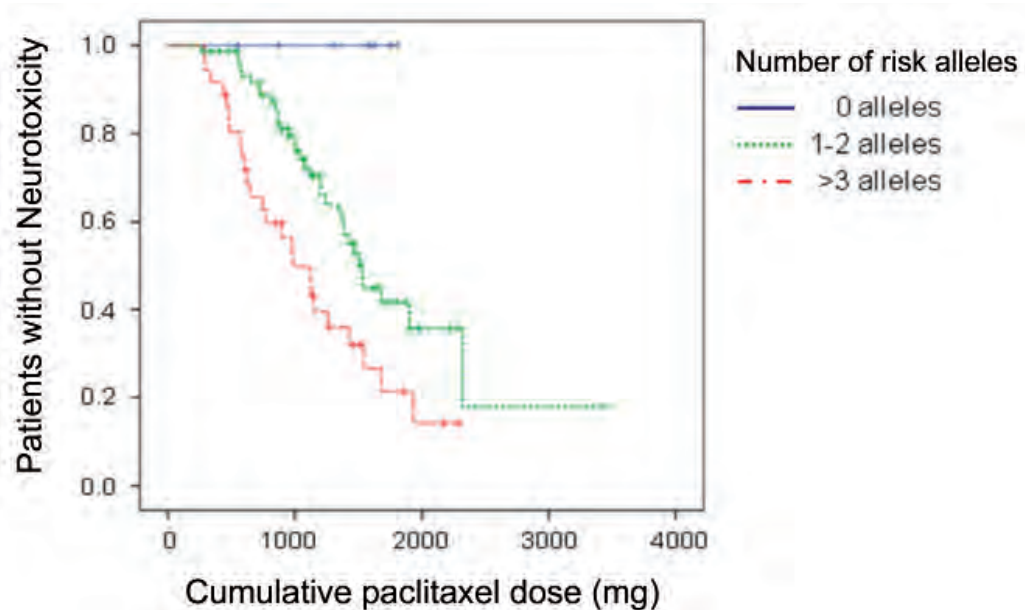


Figure 2: Proposed model for the risk of paclitaxel neurotoxicity including the 3 identified polymorphisms. Patients were classified into three groups according to the number of risk alleles (0 to 5). Kaplan-Meier analysis shows the comparisons of cumulative doses of paclitaxel up to the development of grade 2 neurotoxicity by the number of risk alleles: rs11572080A, rs1113129G and rs776746G.

unresolved safety and resistance issues and require the identification of treatment markers to improve therapy.

We have identified three common functional polymorphisms altering cytochrome P450 activity that influence paclitaxel neurotoxicity (HR=1.64; per allele, P=0.0003) (Figure 2). These markers may provide the basis for an individualised paclitaxel pharmacotherapy that could benefit a large number of cancer patients. With respect to microtubule-binding drug targets, we have characterised the tumoural and tissue-specific expression of the major human β -tubulin isotypes and showed complex expression patterns

of these isotypes that could be of crucial importance for therapy outcome. These findings could also facilitate the design of novel and more specific microtubule-binding drugs.

Publications

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