CANCER

PDE11A—a phenotype modifier in Carney complex

Carney complex—an autosomal dominant multiple neoplasia that consists of myxomas of the soft tissues; spotty skin pigmentation; tumors of the adrenal gland, pituitary gland and testicle; and schwannomas of peripheral nerves—is predominantly caused by inactivating mutations of *PRKARIA*, a key component of the cAMP signaling pathway. A second component of this pathway, phosphodiesterase 11A (*PDE11A*), is encoded by a gene involved in isolated primary pigmented nodular adrenocortical disease, the main endocrine manifestation of the Carney complex. This gene is highly expressed in the adrenal gland and testes.

“Our previous finding of more frequent inactivating *PDE11A* variants in different types of tumors, such as adrenal and testicular tumors, led us to consider *PDE11A* as a genetic predisposition factor,” recalls senior investigator Jerome Bertherat (Hôpital Cochin, Paris, France). In other words, Bertherat and co-workers hypothesized that in patients who already carry *PRKARIA* mutations, *PDE11A* variants could contribute to the genetic predisposition for adrenal and testicular tumors.

An additional factor supporting this hypothesis was the emerging recognition of polygenic models for susceptibility, especially in endocrine disease, such as hypogonadotropic hypogonadism or testicular germ cell tumors.

The investigators selected 150 patients with inactivating *PRKARIA* mutations and sequenced the coding regions of the *PDE11A* gene in these individuals. “Further, we sequenced the coding parts of *PDE11A* in 279 healthy individuals, specifically tested and proven to be negative for signs, symptoms or history of any endocrine disorder,” recounts Bertherat. “Then we correlated the genetic data to the phenotype and performed a statistical analysis, comparing the patients to age-matched and sex-matched controls.”

Consistent with previous work on the role of *PDE11A* in adrenocortical and testicular tumors, the results showed that patients with Carney complex have a higher frequency of *PDE11A* variants than controls and that *PDE11A* plays a part in the pathogenesis of adrenal and testicular tumors.

To demonstrate a synergy between *PRKARIA* and *PDE11A*, functional studies of simultaneous inactivating

mutations of both genes are planned by Bertherat, who is also considering a high-throughput sequencing approach of the genes involved in the cAMP signaling pathway to identify other genetic factors.

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Original article Libé, R. *et al.* Frequent phosphodiesterase 11A gene (*PDE11A*) defects in patients with Carney complex (CNC) caused by *PRKARIA* mutations: *PDE11A* may contribute to adrenal and testicular tumors in CNC as a modifier of the phenotype. *J. Clin. Endocrinol. Metab.* doi:10.1210/jc.2010-1704