The role of *AIP* mutations in pituitary adenomas: 10 years on

Adrian F. Daly¹ · Albert Beckers¹

Received: 25 November 2016 / Accepted: 30 November 2016 / Published online: 16 December 2016
© Springer Science+Business Media New York 2016

Pituitary adenomas causing clinical symptoms occur in about 1/1000 of the general population, making them one of the main tumors encountered by endocrinologists [1]. In practice, pituitary tumor etiology is rarely known, with 5% of cases having a genetic or hereditary background [2]. These include syndromes like multiple endocrine neoplasia (MEN) 1, familial isolated pituitary adenomas (FIPA), MEN4, Carney complex, McCune-Albright syndrome and X-linked acrogigantism (X-LAG), among others [3, 4].

Among the genetic causes, mutation of the *aryl hydrocarbon receptor interacting protein* (*AIP*) gene has received the most research interest in recent times. The publication by Ramírez-Rentería and colleagues in the current issue of *Endocrine* adds the Mexican experience to this body of work from around the world [5]. It is now the 10th anniversary of the discovery of *AIP* as a pituitary adenoma predisposition gene by Vierimaa et al. [6]. In that study germline *AIP* mutations led generally to the familial occurrence of acromegaly and prolactinomas. Primarily, that study was focused on large kindreds from Finland that had a p.Q14X *AIP* mutation, while other *AIP* mutations were also reported, including p.R304X in Italy. This latter mutation, present in the current Mexican cohort, has been shown to be the most frequently reported *AIP* mutation worldwide and founder mutations have been established in Italy and Northern Ireland [7, 8].

Over the last decade more than 150 publications have dealt with aspects of *AIP* function and its role in pituitary tumorigenesis [9]. From this body of work some characteristics of the role of *AIP* mutations in the clinical setting have emerged. While acromegaly and prolactinomas account for the vast majority of *AIP* mutation related pituitary adenomas, rare cases of non-functioning adenomas, Cushing's disease and TSH-secreting adenomas have been reported. In general pituitary adenomas associated with *AIP* mutations are more aggressive than non-mutated cases. They occur at a younger age and are larger at first symptoms and diagnosis. In the setting of acromegaly, this is also accompanied by a reduced responsiveness to somatostatin analogs, which complicates management [10]. While the mechanism behind this is still unclear, *AIP* staining intensity is now acknowledged as a marker of somatostatin analog responsiveness in acromegaly irrespective of *AIP* mutation status [11, 12]. Despite this profile, it remains uncertain if somatostatin analog resistance *per se* is a criterion for defining a suitable population for screening for *AIP* mutations.

Among FIPA kindreds about 15–20% are carriers of *AIP* mutations. Patients with sporadic pituitary macroadenomas that occur during childhood/adolescence and early adulthood also should be considered to be at risk for an *AIP* mutation (12–20%). The young age at onset and the propensity for causing somatotropinomas means that *AIP* mutations are strongly associated with pituitary gigantism and represent the single most frequent genetic cause of pituitary gigantism [13]. The study by Ramírez-Rentería et al. confirms that *AIP* mutations explain a small minority (7%) of sporadic acromegaly patients and that these patients exhibit aggressive features and an earlier age at onset than non-mutated cases. They also studied DNA extracted from a

✉ Adrian F. Daly
adrian.daly@ulg.ac.be
Albert Beckers
albert.beckers@chu.ulg.ac.be

¹ Department of Endocrinology, Centre Hospitalier Universitaire de Liège, University of Liège, Liège, Belgium

historic case of gigantism and identified an *AIP* variant that previously was reported as being non pathological. It may be that this gigantism case is part of the >50% of cases in which no known genetic cause has been found to date. It also raises the question of how we call an *AIP* variant as being non-pathological vs. a pathological mutation. This is a challenge in many genetic conditions, particularly with the routine use of next-generation sequencing and whole exome sequencing that provide rich datasets that are heavily laden with variants. While in silico models can help, they are often contradictory in their conclusions and no single model should be relied upon. There are now multiple in vitro models of *AIP* function, each of which appears to target a different pathway. While the results of these experiments can be persuasive, they raise an important issue. Although there is agreement that *AIP* mutations are associated with aggressive pituitary adenomas, there is still no consensus on how this occurs and whether *AIP* is always the primary driver of tumorigenesis. Should *AIP* have a multifaceted functionality in the pituitary (as suggested by the multiple in vitro models), it may be that *AIP* mutations could drive or facilitate tumor formation via a variety of routes. As more information accrues, variants that are considered as clinically pathological today could be reclassified as innocuous based on integrated analyses of in silico and in vitro models. The reverse would also be true. After the first decade of research on *AIP* in the pituitary we have a good understanding of what *AIP* mutations do in the clinical setting but we have a way to go before determining how they do it.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

References

1. A.F. Daly, M. Rixhon, C. Adam, A. Dempegioti, M.A. Tichomirowa, A. Beckers, High prevalence of pituitary adenomas: a cross-sectional study in the province of Liège, Belgium. *J. Clin. Endocrinol. Metab.* **91**, 4769–4775 (2006)
2. A.F. Daly, M.A. Tichomirowa, A. Beckers, Genetic, molecular and clinical features of familial isolated pituitary adenomas. *Horm. Res.* **71**, 116–122 (2009)
3. L. Rostomyan, A. Beckers, Screening for genetic causes of growth hormone hypersecretion. *Growth Horm. IGF Res.* (2016) Published online early on 12 Oct 2016. pii: S1096-6374(16)30062-4. (in press). doi:10.1016/j.ghir.2016.10.004. [Epub ahead of print]
4. A. Beckers, M.B. Lodish, G. Trivellin, L. Rostomyan, M. Lee, F. R. Faucz, B. Yuan, C.S. Choong, J.-H. Caberg, E. Verrua, L.A. Naves, T.D. Cheetham, J. Young, P.A. Lysy, P. Petrossians, A. Cotterill, N.S. Shah, D. Metzger, E. Castermans, M.R. Ambrosio, C. Villa, N. Strebkova, N. Mazerkina, S. Gaillard, G.B. Barra, L. A. Casulari, S.J. Neggers, R. Salvatori, M.-L. Jaffrain-Rea, M. Zacharin, B.L. Santamaria, S. Zacharieva, E.M. Lim, G. Mantovani, M.C. Zatelli, M.T. Collins, J.-F. Bonneville, M. Quezado, P. Chittiboina, E.H. Oldfield, V. Bours, P. Liu, W.W. De Herder, N. Pellegata, J.R. Lupski, A.F. Daly, C.A. Stratakis, X-linked acrogigantism syndrome: clinical profile and therapeutic responses. *Endocr. Relat. Cancer.* **22**, 353–367 (2015)
5. C. Ramírez-Rentería, L.C. Hernández-Ramírez, L. Portocarrero-Ortiz, G. Vargas, V. Melgar, E. Espinosa, A.L. Espinosa-de-Los-Monteros, E. Sosa, B. González, S. Zúñiga, M. Unterländer, J. Burger, K. Stals, A.-M.M. Bussell, S. Ellard, M. Dang, D. Iacovazzo, S. Kapur, P. Gabrovská, S. Radian, F. Roncaroli, M. Korbonits, M. Mercado, *AIP* mutations in young patients with acromegaly and the Tampico Giant: the Mexican experience. *Endocrine* **53**, 402–411 (2016)
6. O. Vierimaa, M. Georgitsi, R. Lehtonen, P. Vahteristo, A. Kokko, A. Raitila, K. Tuppurainen, T.M. Ebeling, P.I. Salmela, R. Paschke, S. Gundogdu, E. De Menis, M.J. Makinen, V. Launonen, A. Karhu, L.A. Aaltonen, Pituitary adenoma predisposition caused by germline mutations in the *AIP* gene. *Science* **312**, 1228–1230 (2006)
7. G. Occhi, M.L. Jaffrain-Rea, G. Trivellin, N. Albiger, F. Ceccato, E. De Menis, M. Angelini, S. Ferasin, A. Beckers, F. Mantero, C. Scaroni, The R304X mutation of the aryl hydrocarbon receptor interacting protein gene in familial isolated pituitary adenomas: mutational hot-spot or founder effect? *J. Endocrinol. Invest* **33**, 800–805 (2010)
8. H.S. Chahal, K. Stals, M. Unterlander, D.J. Balding, M.G. Thomas, A.V. Kumar, G.M. Besser, A.B. Atkinson, P.J. Morrison, T. A. Howlett, M.J. Levy, S.M. Orme, S.A. Akker, R.L. Abel, A.B. Grossman, J. Burger, S. Ellard, M. Korbonits, *AIP* mutation in pituitary adenomas in the 18th century and today. *N. Engl. J. Med.* **364**, 43–50 (2011)
9. A.F. Daly, A. Beckers, Familial Isolated Pituitary Adenomas (FIPA) and Mutations in the Aryl Hydrocarbon Receptor Interacting Protein (*AIP*) Gene. *Endocrinol. Metab. Clin. North Am.* **44**, 19–25 (2016)
10. A.F. Daly, M.A. Tichomirowa, P. Petrossians, E. Heliövaara, M.-L. Jaffrain-Rea, A. Barlier, L.A. Naves, T. Ebeling, A. Karhu, A. Raappana, L. Cazabat, E. De Menis, C.F. Montañana, G. Raverot, R.J. Weil, T. Sane, D. Maiter, S. Neggers, M. Yaneva, A. Tabarin, E. Verrua, E. Eloranta, A. Murat, O. Vierimaa, P.I. Salmela, P. Emy, R.A. Toledo, M.I. Sabaté, C. Villa, M. Popelier, R. Salvatori, J. Jennings, Á.F. Longás, J.I.L. Aizpún, M. Georgitsi, R. Paschke, C. Ronchi, M. Valimaki, C. Saloranta, W. De Herder, R. Cozzi, M. Guitelman, F. Magri, M.S. Lagonigro, G. Halaby, V. Corman, M.-T. Hagelstein, J.-F. Vanbellinchen, G.B. Barra, A.-P. Gimenez-Roqueplo, F.J. Cameron, F. Borson-Chazot, I. Holdaway, S.P.A. Toledo, G.K. Stalla, A. Spada, S. Zacharieva, J. Bertherat, T. Brue, V. Bours, P. Chanson, L.A. Aaltonen, A. Beckers, Clinical characteristics and therapeutic responses in patients with germ-line *AIP* mutations and pituitary adenomas: an international collaborative study. *J. Clin. Endocrinol. Metab.* **95**, E373–E383 (2010)
11. M.-L. Jaffrain-Rea, M. Angelini, D. Gargano, M.A. Tichomirowa, A.F. Daly, J.-F. Vanbellinchen, E. D'Innocenzo, A. Barlier, F. Giangaspero, V. Esposito, L. Ventura, A. Arcella, M. Theodoropoulou, L.A. Naves, C. Fajardo, S. Zacharieva, V. Rohmer, T. Brue, A. Gulino, G. Cantore, E. Alesse, A. Beckers, Expression of aryl hydrocarbon receptor (*AHR*) and *AHR*-interacting protein in pituitary adenomas: pathological and clinical implications. *Endocr. Relat. Cancer* **16**, 1029–1043 (2009)
12. L. Kasuki Jomori de Pinho, L. Vieira Neto, L.E. Armondi Wildemberg, E.L. Gasparetto, J. Marcondes, B. de Almeida Nunes, C. M. Takiya, M.R. Gadelha, Low aryl hydrocarbon receptor-interacting protein expression is a better marker of invasiveness in somatotropinomas than Ki-67 and p53. *Neuroendocrinology* **94**, 39–48 (2011)

13. L. Rostomyan, A.F. Daly, P. Petrossians, E. Nachev, A.R. Lila, A.-L. Lecoq, B. Lecumberri, G. Trivellin, R. Salvatori, A.G. Moraitis, I. Holdaway, D.J. Kranenburg-Van Klaveren, M.C. Zatelli, N. Palacios, C. Nozieres, M. Zacharin, T. Ebeling, M. Ojaniemi, L. Rozhinskaya, E. Verrua, M.-L. Jaffrain-Rea, S. Filipponi, D. Gusakova, V. Pronin, J. Bertherat, Z. Belaya, I. Ilovayskaya, M. Sahnoun-Fathallah, C. Sievers, G.K. Stalla, E. Castermans, J.-H. Caberg, E. Sorkina, R.S. Auriemma, S. Mittal, M. Kareva, P.A. Lysy, P. Emy, E. De Menis, C.S. Choong, G. Mantovani, V. Bours, W. De Herder, T. Brue, A. Barlier, S.J.C.M. M. Neggers, S. Zacharieva, P. Chanson, N.S. Shah, C.A. Stratakis, L.A. Naves, A. Beckers, Clinical and genetic characterization of pituitary gigantism: an international collaborative study in 208 patients. *Endocr. Relat. Cancer* **22**, 745–757 (2015)