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A heritable predisposition to pituitary tumors

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Abstract

Pituitary tumors are prevalent in the general population, with a frequency of nearly 1 in 5. The cause of most pituitary tumors remains unknown, although a genetic contribution is recognized for some. We analyzed the Utah Population Data Base (UPDB), a resource combining a computerized genealogy of the Utah population with a statewide tumor registry, to investigate familial clustering of pituitary tumors. We analyzed the genetic relationships among 741 individuals diagnosed with benign or malignant pituitary tumors who had Utah genealogy data. To test for evidence of genetic contribution to predisposition, we compared average relatedness between all pairs of individuals with pituitary tumors with the expected relatedness in this population. We also estimated relative risks (RRs) for pituitary tumors in close and distant relatives of cases by comparing observed and expected numbers of cases among relatives. Relative risks for first- and third-degree relatives were significantly elevated (RR = 2.83 and 1.63, respectively), while relative risk for second-degree relatives was not significantly different from 1.0 (RR = 0.83). The average pairwise relatedness of pituitary tumor cases was significantly higher than expected, even when close relationships were ignored. The significantly elevated risks to relatives as well as the significant excess distant relatedness observed in cases provide strong support for a genetic contribution to predisposition to pituitary tumors. Multiple high-risk pedigrees can be identified in the UPDB, and study of such pedigrees might allow identification of the gene(s) responsible for our observations. Recognizing genetic contribution to the disease may also help with counseling family members of affected individuals.

Keywords

Pituitary tumor; Genetic predisposition; UPDB

Introduction

Pituitary tumors are common tumors, estimated to be present (but not always detected) in 16.7% of the population [22]. Individuals with a family history of multiple endocrine neoplasia type 1 (MEN1) and the Carney complex have an increased risk of pituitary tumors [55]; however, these heritable disorders are responsible for only a minority of patients with pituitary tumors. More recently, non-MEN/Carney complex pituitary tumors, known as familial isolated pituitary adenomas, have been described. It has previously been estimated that about 5% of

cases occur in a familial setting [51,53]. In other pituitary tumors, a common genetic link has not yet been demonstrated.

The Utah Population Data Base (UPDB) has previously been analyzed to show the familial clustering of many different cancer sites [2,9–11,13,26,39,50]. Other studies using genealogical data linked to Utah death certificates have demonstrated heritable predisposition to aneurysms, heart disease, asthma, and influenza mortality [1,12,30,31,49]. Most recently, genealogical data linked to diagnosis data from a single Utah health care provider serving 20% of the state has demonstrated a heritable contribution to predisposition to rotator cuff disease [48].

The UPDB is a computerized data resource consisting of genealogical and demographic data representing the Utah population [46]. Genealogy data for individuals who were born, married, or died in Utah or along the pioneer trail from the east, and for their Utah descendants, was computerized to create a genealogy of 1.6 million individuals representing up to 7 generations of families. State vital records (birth, marriage, death) have been used to extend the genealogical data to current birth cohorts; some pedigrees now extend to 11 generations. Currently, over 2.5 million individuals with at least 3 generations of genealogical data linking back to the Utah pioneers are included. These pedigrees were primarily founded by pioneers who emigrated from Northern Europe in the mid-1800s. The Utah population is genetically representative of Northern Europe, where the founding population originated, and has low inbreeding levels, similar to other areas of the United States [35,40].

The genealogical data in the UPDB has been record-linked to other statewide data resources, including the Utah Cancer Registry (UCR), which has collected cancer data statewide since 1966 and has been a National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry since 1973. All cancers occurring in the state are reportable by law. Only independent malignant primary cancers in the UCR data are record-linked to the UPDB genealogy data annually. Since the majority of pituitary tumors are benign, analysis of pituitary tumors has not been previously performed (although data on benign pituitary tumors has been collected by the UCR since it began in 1966). Using the data available in the UPDB and the UCR, we analyzed the genetic relationships among individuals diagnosed with benign or malignant pituitary tumors in Utah to investigate whether there is evidence for a heritable contribution to the disease.

Methods

We identified individuals with pituitary tumors from the UCR data collection who linked to genealogy data in the UPDB for this analysis. The use of these data resources for this study was approved by the University of Utah Institutional Review Board and by the Utah Resource for Genetic and Epidemiology Research.

To study the familial clustering of pituitary tumors, we used two different methods. First, we compared the average relatedness of all patients with pituitary tumors to the expected relatedness in this population using the genealogical index of familiarity (GIF). We also estimated the relative risk (RR) for pituitary tumors in the relatives of patients with diagnosed pituitary tumors.

Genealogical index of familiarity

The GIF statistic was designed to study familial aggregation of cancer within the Utah genealogy [29] and has been used in previous studies of familiarity [1,2,11,12,30,31,39,50]. An analysis similar to the GIF statistic has been used with the extended Iceland genealogies [3,27,34,47]. An advantage to the GIF statistic over other methods is that it takes into account

all genetic relationships between all cases. The Malécot coefficient of kinship was used to measure the relatedness between all possible pairs of diagnosed pituitary tumor cases. The coefficient of kinship is the probability that randomly selected homologous genes from two individuals are identical by descent from a common ancestor [38]. The coefficient for parent–offspring pairs is $\frac{1}{2}$, for grandparent/grandchild or sibling pairs is $(\frac{1}{2})^2$, for avuncular pairs is $(\frac{1}{2})^3$, and for first-cousin pairs is $(\frac{1}{2})^4$, and so forth. The case GIF is calculated as the mean of all coefficients of kinship between all possible pairs of cases. The case GIF is multiplied by 10^5 for ease of presentation.

We tested the hypothesis that there was no excess relatedness among pituitary tumor cases by comparison of the case average relatedness to the expected relatedness as observed for 1,000 sets of cohort-matched controls. For each case, a control individual was selected at random from the genealogy resource, matched on sex, 5-year birth cohort, and place of birth (in or out of Utah), resulting in a control set of the same size as the case set. The matching strategy is employed to account for potential differences in kinship based on matching characteristics. One thousand independent control sets were selected, and the GIF was measured for each set. The hypothesis of no excess relatedness of the pituitary tumor cases was tested empirically by comparing the case GIF to the distribution of the 1,000 control GIFs.

The degree of shared genetic composition between pairs of cases representing different genetic distances can be quantified with GIF analysis. When an excess of close genetic relationships is observed for cases compared with controls, it is difficult to identify whether the excess familiarity is due to shared environment or shared genetic composition, or a combination of both. If, however, close relationships are ignored and a significant excess of relationships for cases compared with controls is observed, then this observed excess familiarity among cases strongly supports a genetic contribution.

We compared contributions to the GIF statistic for cases and controls across close and distant relationships, measured by genetic distance between pairs of individuals. In the GIF analysis, genetic distance is approximated by path length between individuals in a pair. For example, a parent and a child are assigned a genetic distance of one, siblings are assigned a genetic distance of two, an aunt and a niece are assigned a genetic distance of three, and so forth. The empirical significance of the GIF test tells us whether overall excess familiarity is observed. We also performed this same test ignoring all close relationships (genetic distance <4) to determine whether the excess familiarity is also significant when ignoring all close relationships. We call this statistic the Distant GIF and also tested it empirically.

Relative risk

Estimation of relative risks in relatives is an alternative approach to testing the hypothesis of a genetic contribution to disease. Whereas the GIF analysis uses all relationships between all cases regardless of genetic distance, the relative risk analysis typically relies on comparisons in close relatives only. The relative risk approach compares the observed rate of disease (in this case, pituitary tumor) in relatives of probands (cases) with the expected rates of disease in relatives. All individuals in the UPDB with genealogy were used to estimate cohort-specific expected pituitary tumor rates in the UPDB.

We estimated relative risk as follows. All 2.5 million individuals in the UPDB with data linking to the original Utah genealogy were assigned to one of 132 cohorts based on birthplace (in or out of Utah), sex, and 5-year birth cohorts. For each cohort, internal cohort-specific pituitary tumor rates were calculated by summing the number of individuals in each cohort with pituitary tumor, and dividing by the number of individuals in the cohort. The expected number of pituitary tumors among first-degree relatives of patients with pituitary tumor was calculated by multiplying the number of first-degree relatives of patients with pituitary tumor (in each

cohort) by the cohort-specific internal rate of pituitary tumors, and then summing over all cohorts.

The first-degree relative risk is estimated as the ratio of the number of observed pituitary tumor cases among first-degree relatives of patients with pituitary tumors to the number of expected pituitary tumor cases among first-degree relatives. The relative risk was similarly estimated for second- and third-degree relatives. The relative risk is assumed to follow a Poisson distribution, with the mean value equal to the number of expected pituitary tumor cases among relatives of probands. The Poisson distribution is an approximation to a sum of multiple binomial distributions, representing the number of expected tumors in each cohort. This Poisson approximation is appropriate for both rare and common phenotypes, being more conservative for common diseases. Probability values for one-sided tests of significance and 95% CIs for the relative risk statistic can be calculated for the Poisson distribution under the null hypothesis that the relative risk is equal to unity. While significantly elevated risks in first-degree relatives are suggestive of a genetic contribution to disease, they may also result from shared environment. Significantly elevated risks for second- or third-degree relatives, however, are strongly suggestive that a heritable component also exists.

Results

Patient population

Twenty-one individuals with a malignant pituitary tumor and 720 individuals with a benign pituitary tumor were recorded in the UCR since 1966 and also had Utah genealogy data. Thus, 741 individuals with either a malignant or benign pituitary tumor who also had Utah genealogy were included in the study population. Men comprised 384 of the pituitary tumor cases, while 357 of the cases were women.

Statistical results

Our analysis of the GIF and the Distant GIF tests of hypothesis for no excess relatedness for all pituitary tumor cases showed that the pituitary cases did have a higher average relatedness than expected. The case GIF statistic was 3.51, the mean control GIF statistic from 1,000 control sets was 2.68, and the empirical significance for the overall GIF statistic was $p < 0.001$. The average relatedness of all pituitary tumor cases was also significantly higher than expected when all relationships closer than third degree were ignored (empirical $p < 0.001$).

Figure 1 shows the distribution of contribution to the GIF statistic (y axis), for cases versus controls, by the pairwise genetic distance (x axis). The pairwise genetic distance represents the relationship between the pair of individuals; a genetic distance of 1 represents parent/offspring, 2 represents siblings or grandparent/child, 3 represents avuncular relatives, and so forth. The more distant the genetic relationship, the larger the genetic distance. As seen in the figure, there is an excess of case relationships out to a genetic distance of 8 (representing third cousins), except at a genetic distances of 3 (representing primarily avuncular relatives). Genetic distance 3 represents individuals who are in different generations; the observation of fewer than expected such relationships among cases may simply indicate that relationships that cross generations were not as frequently observed with a window of view to only 40+ years of diagnoses (from 1966 until the present).

Table 1 shows the estimated relative risks for first-, second-, and third-degree relatives of pituitary tumor cases. First- and third-degree risks were significantly greater than 1 (2.83 and 1.63, respectively); however, second-degree relative risks (primarily genetic distance = 3) were not significantly different from 1.0. These results agree with the GIF results, for which we noted no excess for genetic distance = 3. Again, because we only have a narrow window of

pituitary tumors, we are less likely to observe relationships that cross generations, but relationships that do not cross generations, such as siblings (genetic distance = 2) or first cousins (genetic distance = 4), are more likely to be observed.

Discussion

Familiality of pituitary adenomas

Using a unique population-based genealogical resource for the state of Utah, we analyzed clinically significant benign and malignant pituitary tumors (defined by presence of a report in a statewide tumor registry from 1966 to present). We found strong evidence for a genetic contribution to predisposition to symptomatic pituitary tumors using two different analyses. The significantly elevated risk to first- and third-degree relatives as well as the significant excess distant relatedness observed in cases provides strong support for a genetic contribution to predisposition to symptomatic pituitary tumors. Multiple high-risk pedigrees can be identified in the UPDB, and study of such pedigrees might allow identification of the gene(s) responsible for our observations.

Molecular genetics and epigenetic alterations

Previous studies, using X-chromosome inactivation, have demonstrated that pituitary adenomas are monoclonal tumors [32]. Most known genetic abnormalities in pituitary tumors relate to dysregulation of hormone signaling, dysregulation of growth-factor signaling, dysregulation of signaling proteins, or cell cycle control. For example, Carney complex is an inherited syndrome in which growth hormone-producing tumors are seen in approximately 10% of patients [55]. Recent studies have shown that knockout of the gene *PRKAr1a* (dysregulation of Protein Kinase A, as signaling protein) in a rodent model was sufficient to produce growth hormone-secreting pituitary tumors, in analogy to human patients with Carney complex [55]. The autosomal dominant syndrome MEN1 is caused by germline mutations of the *MEN1* tumor-suppressor gene on chromosome 11q13, with loss of heterozygosity inactivating the normal allele. However, while reduced expression of *MEN1* in sporadic adenomas might indicate that this protein functions as a tumor suppressor, *MEN1* mRNA is not down-regulated in sporadic adenomas.

Pituitary tumor-transforming gene (*Pttg*) was originally isolated from pituitary tumor cells [43] and is overexpressed in pituitary tumors [56]. *Pttg* overexpression causes cell transformation and promotes tumor formation in nude mice and activates angiogenesis [28]. Conversely, *Pttg* deletion in a murine model results in pituitary-specific senescent features including increased levels of p53 and cyclin-dependent kinase inhibitors, overexpression of cyclin D1, and elevated senescence-associated β -galactosidase expression. Senescence provoked by *Pttg* deletion facilitates pituitary gland hypoplasia and senescence independent of telomeric shortening and was protective of pituitary tumor development [15]. In recent work in human tumors, Chesnokova et al. [16] noted that among 72 human pituitary adenomas of various phenotypes, strong coexpression of *Pttg* and p21 was noted in 56 specimens. These authors put forth evidence supporting their hypothesis that *Pttg*, functioning as an oncogene, acts proximally in tumor formation, and, as a result of aneuploidy and DNA damage, p21 appears later to restrain subsequent tumor growth and malignant transformation.

Local production of cytokines within the pituitary gland may act in an autocrine or paracrine manner. Changes in the levels of cytokines contribute to endocrine homeostasis of the pituitary and have been implicated in the pituitary adenomas (reviewed in [7]). For example, bone morphogenetic protein-4 (BMP-4), a member of the transforming growth factor- β (TGF- β) family, plays a crucial role in pituitary development [52], is overexpressed in animal models of prolactinoma, and appears to promote prolactinoma development [42] while it inhibits

ACTH-secreting tumor development [25]. The cytokine interleukin 6 (IL-6) participates in the development of the pituitary and has the distinct capacity to inhibit normal pituitary cells on one hand, yet promote tumor growth on the other [4]. That IL-6 is growth-stimulatory in many pituitary adenomas indicates an important role in autocrine/paracrine stimulation of adenoma progression [5,6]. In this regard, it has more recently been identified to have a role in oncogene-induced senescence, a mechanism whereby small benign tumors may develop in many tissues, and oncogenic signaling may paradoxically produce a growth arrest response [45]. Recent work by Kuilman et al. [36] has elegantly demonstrated a role in the induction and maintenance of oncogene-induced senescence by using short inhibitory RNA; their work also demonstrated a shared role of IL-8 in this process.

Recent descriptions of familial isolated pituitary adenomas (non-MEN/Carney complex pituitary tumors) indicate that clinical features differ from those of sporadic pituitary adenomas, as patients with familial isolated pituitary adenoma present at a younger age at diagnosis with larger tumors. About 15% of patients with familial isolated pituitary adenoma have mutations in the aryl hydrocarbon receptor-interacting protein (AIP) gene, which indicates that familial isolated pituitary adenoma may have a diverse genetic pathophysiology. Over 90 familial isolated pituitary adenoma kindreds have been described [19]. In familial isolated pituitary adenoma, both homogeneous and heterogeneous pituitary adenoma phenotypes can occur within families, and virtually all familial isolated pituitary adenoma kindreds contain at least one prolactinoma or somatotropinoma. The familial isolated pituitary adenoma cohort differs from MEN1 in having a lower proportion of prolactinomas and more frequent somatotropinomas [8,18,19].

Much recent work has focused also on epigenetic events in the pathogenesis and growth regulation of pituitary tumor cells. “Epigenetic” refers to a process by which heritability may influence the expression of a particular gene without genetic change to the underlying DNA sequence [33]. The first gene identified in sporadic pituitary tumors to be subjected to epigenetic change (gene silencing by methylation) was the tumor suppressor gene p16 [54], which has been confirmed in other studies (reviewed in [23]). Since then, many other genes, including cell cycle regulators, other tumor suppressor genes, and genes with roles in apoptosis, invasion, and metastasis, have been identified to be silenced by DNA methylation-mediation. These have been identified using candidate gene approaches, differential display approaches, and genome-wide DNA approaches (recently reviewed in [21]). Epigenomics research is a current fertile ground for investigators interested in mechanisms of pituitary tumorigenesis. Therefore, while much information is emerging regarding specific gene alterations noted in subtypes of pituitary tumors and specific epigenetic changes, it has become increasingly evident that no single gene mutation or epigenetic alteration can be implicated in the pathogenesis of most pituitary tumors.

Prevalence and incidence of pituitary tumors

Pituitary tumors accounted for 6.6% of primary brain and central nervous system tumors by histology (among a study group of 37,788) in a recent report from the Central Brain Tumor Registry of the US, which provides population-based incidence rate data concerning all brain tumors [14]. A meta-analysis estimated the prevalence of pituitary adenomas to be 16.7% in the general population; separate analyses of postmortem and radiologic data produced estimated prevalence rates of 14.4 and 22.5%, respectively [22]. These figures indicate that pituitary tumors are remarkably common in the general population. Most of these tumors are likely to represent incidental, asymptomatic microadenomas. With macroadenomas (tumors ≥ 10 mm) occurring at a rate of 1 in 600 persons, there also are likely many persons with unrecognized macroadenomas. Given that pituitary tumors are common in the general population, the incidental nature of these lesions and the underdiagnosis of some is the likely

reason that the number of pituitary tumors reported to registries such as the UCR may not equal the estimated prevalence. Here we report on the subset of clinically significant pituitary tumors diagnosed in Utah from 1966 to present. There were 741 tumors identified in the database comprising approximately 1.6 million people, equating to a prevalence of 46 individuals/100,000 population. This is less than the recent estimate of 77 pituitary adenomas/100,000 inhabitants noted by Fernandez et al. [24] in a well-defined population study performed in Banbury, Oxfordshire, United Kingdom, but more than the 25 per 100,000 prevalence described in data from the Central Brain Tumor Registry of the United States in a study by Davis et al. [20]. The prevalence of such tumors indicates some variation in reported prevalence and the possibility of underdiagnosis in some populations and an overall significant burden on the health care system [24].

Symptoms of pituitary tumors

Pituitary adenomas cause symptoms by producing endocrinopathy (either hypersecretion in functional secreting adenomas, or so-called “stalk effect” resulting in hyper-prolactinemia, or hyposecretion from compression of the normal gland), or by direct mass effect on surrounding structures, such as the optic chiasm, commonly producing visual loss [17]. Despite the high prevalence of adenomas, only a minority present with symptoms that require treatment. As a significant percentage of these tumors stain positively for prolactin, however, it is possible that some may be producing insidious or mild symptoms of hypogonadism that are under-recognized clinically. In addition, some tumors may be producing general hypopituitarism because of compressive effects on the native pituitary gland. The authors of a Swedish epidemiologic study of pituitary adenomas evaluated the records of 2,279 of 3,321 patients with pituitary adenomas in the Swedish Cancer Registry between 1958 and 1991 [41]. They found that in the 33-year study period the annual incidence of pituitary adenoma increased from approximately 6 per million to 11 per million, with a significant increase in overall mortality noted in patients with pituitary adenomas, primarily as a result of cardiovascular disease. In a study of patients with hypopituitarism in Spain, Regal et al. [44] noted that those with pituitary tumor-induced hypopituitarism showed a tendency to suffer growth hormone deficiency more frequently than those with hypopituitarism due to nontumor causes. They suggested that the mortality rate, especially from atherosclerosis, may be increased among adults with hypopituitarism receiving conventional pituitary hormone replacement (cortisol, thyroid, and sex hormone) other than growth hormone, from associated lipid abnormalities.

Conclusion

From this study, the significantly elevated risk to relatives as well as the significant excess distant relatedness observed in cases provides strong support for a genetic contribution to predisposition to clinically significant pituitary tumors. The relative risk for the development of a symptomatic pituitary tumor was significantly elevated in first- and third-degree relatives of affected individuals. Such information is valuable for counseling family members of patients treated for pituitary adenomas and for raising a higher index of suspicion for the detection of a symptomatic pituitary tumor in such individuals. The cost-effectiveness of screening close relatives for pituitary tumors using magnetic resonance imaging and endocrine studies in these relatives remains to be determined. In this regard, genetic testing identifies patients harboring an MEN1 mutation before the development of clinical signs or symptoms of endocrine disease [37]. In this population, genetically positive patients are carefully studied prospectively for the presence of hypercalcemia, as biochemical evidence of neoplasia can be detected an average of 10 years before clinically evident disease, allowing for early surgical intervention. It is possible that the early identification of at-risk relatives with pituitary adenomas will facilitate early treatment prior to the onset of endocrinopathy or neurological deficit. Furthermore, the study of high-risk genetic pedigrees from the UPDB should facilitate identification of the gene(s) involved in the genesis of these tumors.

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References

1. Albright FS, Orlando P, Pavia AT, Jackson GG, Cannon Albright LA. Evidence for a heritable predisposition to death due to influenza. *J Infect Dis* 2008;197:18–24. [PubMed: 18171280]
2. Allen-Brady K, Camp NJ, Ward JH, Cannon-Albright LA. Lobular breast cancer: excess familiarity observed in the Utah Population Database. *Int J Cancer* 2005;117:655–661. [PubMed: 15929077]
3. Arnar DO, Thorvaldsson S, Manolio TA, Thorgeirsson G, Kristjansson K, Hakonarson H, Stefansson K. Familial aggregation of atrial fibrillation in Iceland. *Eur Heart J* 2006;27:708–712. [PubMed: 16428254]
4. Arzt E, Buric R, Stelzer G, Stalla J, Sauer J, Renner U, Stalla GK. Interleukin involvement in anterior pituitary cell growth regulation: effects of IL-2 and IL-6. *Endocrinology* 1993;132:459–467. [PubMed: 8419142]
5. Arzt E, Pereda MP, Castro CP, Pagotto U, Renner U, Stalla GK. Pathophysiological role of the cytokine network in the anterior pituitary gland. *Front Neuroendocrinol* 1999;20:71–95. [PubMed: 9882537]
6. Arzt E. gp130 cytokine signaling in the pituitary gland: a paradigm for cytokine-neuro-endocrine pathways. *J Clin Invest* 2001;108:1729–1733. [PubMed: 11748253]
7. Arzt E, Chesnokova V, Stalla GK, Melmed S. Pituitary adenoma growth: a model for cellular senescence and cytokine action. *Cell Cycle* 2009;8:677–678. [PubMed: 19223763]
8. Barlier A, Vanbellinghen JF, Daly AF, Silvy M, Jaffrain-Rea ML, Trouillas J, Tamagno G, Cazabat L, Bours V, Brue T, Enjalbert A, Beckers A. Mutations in the aryl hydrocarbon receptor interacting protein gene are not highly prevalent among subjects with sporadic pituitary adenomas. *J Clin Endocrinol Metab* 2007;92:1952–1955. [PubMed: 17299063]
9. Bishop DT, Skolnick MH. Genetic epidemiology of cancer in Utah genealogies: a prelude to the molecular genetics of common cancers. *J Cell Physiol* 1984;63–77.
10. Burt RW, Bishop DT, Cannon LA, Dowdle MA, Lee RG, Skolnick MH. Dominant inheritance of adenomatous colonic polyps and colorectal cancer. *N Engl J Med* 1985;312:1540–1544. [PubMed: 4000184]
11. Cannon-Albright LA, Thomas A, Goldgar DE, Gholami K, Rowe K, Jacobsen M, McWhorter WP, Skolnick MH. Familiality of cancer in Utah. *Cancer Res* 1994;54:2378–2385. [PubMed: 8162584]
12. Cannon Albright LA, Camp NJ, Farnham JM, MacDonald J, Abtin K, Rowe KG. A genealogical assessment of heritable predisposition to aneurysms. *J Neurosurg* 2003;99:637–643. [PubMed: 14567597]
13. Cannon LA, Bishop DT, Skolnick M, Hunt SC, Lyon JL, Smart C. Genetic epidemiology of prostate cancer in the Utah Mormon genealogy. *Cancer Surv* 1982;1:48–69.
14. CBTRUS. Statistical report: primary brain tumors in the United States, 1995–1999. Central Brain Tumor Registry of the United States; Hinsdale: 2002.
15. Chesnokova V, Zonis S, Rubinek T, Yu R, Ben-Shlomo A, Kovacs K, Wawrowsky K, Melmed S. Senescence mediates pituitary hypoplasia and restrains pituitary tumor growth. *Cancer Res* 2007;67:10564–10572. [PubMed: 17975001]
16. Chesnokova V, Zonis S, Kovacs K, Ben-Shlomo A, Wawrowsky K, Bannykh S, Melmed S. p21 (Cip1) restrains pituitary tumor growth. *Proc Natl Acad Sci USA* 2008;105:17498–17503. [PubMed: 18981426]
17. Couldwell WT. Transsphenoidal and transcranial surgery for pituitary adenomas. *J Neurooncol* 2004;69:237–256. [PubMed: 15527094]
18. Daly AF, Jaffrain-Rea ML, Ciccarelli A, Valdes-Socin H, Rohmer V, Tamburrano G, Borson-Chazot C, Estour B, Ciccarelli E, Brue T, Ferolla P, Emy P, Colao A, De Menis E, Lecomte P, Penfornis F,

- Delemer B, Bertherat J, Wemeau JL, De Herder W, Archambeaud F, Stevenaert A, Calender A, Murat A, Cavagnini F, Beckers A. Clinical characterization of familial isolated pituitary adenomas. *J Clin Endocrinol Metab* 2006;91:3316–3323. [PubMed: 16787992]
19. Daly AF, Vanbellinthen JF, Khoo SK, Jaffrain-Rea ML, Naves LA, Guitelman MA, Murat A, Emy P, Gimenez-Roqueplo AP, Tamburrano G, Raverot G, Barlier A, De Herder W, Penfornis A, Ciccirelli E, Estour B, Lecomte P, Gatta B, Chabre O, Sabate MI, Bertagna X, Garcia Basavilbaso N, Stalldecker G, Colao A, Ferolla P, Wemeau JL, Caron P, Sadoul JL, Oneto A, Archambeaud F, Calender A, Sinilnikova O, Montanana CF, Cavagnini F, Hana V, Solano A, Deleltieres D, Luccio-Camelo DC, Basso A, Rohmer V, Brue T, Bours V, Teh BT, Beckers A. Aryl hydrocarbon receptor-interacting protein gene mutations in familial isolated pituitary adenomas: analysis in 73 families. *J Clin Endocrinol Metab* 2007;92:1891–1896. [PubMed: 17244780]
20. Davis FG, Kupelian V, Freels S, McCarthy B, Surawicz T. Prevalence estimates for primary brain tumors in the United States by behavior and major histology groups. *Neuro Oncol* 2001;3:152–158. [PubMed: 11465395]
21. Dudley KJ, Revill K, Clayton RN, Farrell WE. Pituitary tumours: all silent on the epigenetics front. *J Mol Endocrinol* 2009;42:461–468. [PubMed: 19208779]
22. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004;101:613–619. [PubMed: 15274075]
23. Farrell WE. Epigenetic mechanisms of tumorigenesis. *Horm Metab Res* 2005;37:361–368. [PubMed: 16001328]
24. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)*. 2009 July 24;2009 Epub ahead of print.
25. Giacomini D, Paez-Pereda M, Theodoropoulou M, Labeur M, Refojo D, Gerez J, Chervin A, Berner S, Losa M, Buchfelder M, Renner U, Stalla GK, Arzt E. Bone morphogenetic protein-4 inhibits corticotroph tumor cells: involvement in the retinoic acid inhibitory action. *Endocrinology* 2006;147:247–256. [PubMed: 16195406]
26. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. *J Natl Cancer Inst* 1994;86:1600–1608. [PubMed: 7932824]
27. Gulcher J, Stefansson K. Population genomics: laying the groundwork for genetic disease modeling and targeting. *Clin Chem Lab Med* 1998;36:523–527. [PubMed: 9806453]
28. Heaney AP, Horwitz GA, Wang Z, Singson R, Melmed S. Early involvement of estrogen-induced pituitary tumor transforming gene and fibroblast growth factor expression in prolactinoma pathogenesis. *Nat Med* 1999;5:1317–1321. [PubMed: 10546001]
29. Hill, J. A survey of cancer sites by kinship in the Utah Mormon population. In: Cairns, J.; Lyon, JL.; Skolnick, M., editors. Banbury Report No 4 Cancer incidence in defined populations. Cold Spring Harbor Laboratory; Cold Spring Harbor: 1980.
30. Horne BD, Camp NJ, Muhlestein JB, Cannon-Albright LA. Evidence for a heritable component in death resulting from aortic and mitral valve diseases. *Circulation* 2004;110:3143–3148. [PubMed: 15520309]
31. Horne BD, Camp NJ, Muhlestein JB, Cannon-Albright LA. Identification of excess clustering of coronary heart diseases among extended pedigrees in a genealogical population database. *Am Heart J* 2006;152:305–311. [PubMed: 16875915]
32. Jacoby LB, Hedley-Whyte ET, Pulaski K, Seizinger BR, Martuza RL. Clonal origin of pituitary adenomas. *J Neurosurg* 1990;73:731–735. [PubMed: 2213163]
33. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nat Genet* 2003;33:245–254. [PubMed: 12610534]
34. Jonsson H, Manolescu I, Stefansson SE, Ingvarsson T, Jonsson HH, Manolescu A, Gulcher J, Stefansson K. The inheritance of hand osteoarthritis in Iceland. *Arthritis Rheum* 2003;48:391–395. [PubMed: 12571848]
35. Jorde LB. Inbreeding in the Utah Mormons: an evaluation of estimates based on pedigrees, isonymy, and migration matrices. *Ann Hum Genet* 1989;53:339–355. [PubMed: 2624429]

36. Kuilman T, Michaloglou C, Vredeveld LC, Douma S, van Doorn R, Desmet CJ, Aarden LA, Mooi WJ, Peeper DS. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. *Cell* 2008;133:1019–1031. [PubMed: 18555778]
37. Lairmore TC, Piersall LD, DeBenedetti MK, Dilley WG, Mutch MG, Whelan AJ, Zehnbauser B. Clinical genetic testing and early surgical intervention in patients with multiple endocrine neoplasia type 1 (MEN 1). *Ann Surg* 2004;239:637–645. Discussion 645–637. [PubMed: 15082967]
38. Malécot, G. Les mathématiques de l'hérédité. Masson; Paris: 1948.
39. Maul JS, Burt RW, Cannon-Albright LA. A familial component to human rectal cancer, independent of colon cancer risk. *Clin Gastroenterol Hepatol* 2007;5:1080–1084. [PubMed: 17625976]
40. McLellan T, Jorde LB, Skolnick MH. Genetic distances between the Utah Mormons and related populations. *Am J Hum Genet* 1984;36:836–857. [PubMed: 6591796]
41. Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B. Pituitary adenomas in Sweden between 1958 and 1991: incidence, survival, and mortality. *J Clin Endocrinol Metab* 2000;85:1420–1425. [PubMed: 10770176]
42. Paez-Pereda M, Giacomini D, Refojo D, Nagashima AC, Hopfner U, Grubler Y, Chervin A, Goldberg V, Goya R, Hentges ST, Low MJ, Holsboer F, Stalla GK, Arzt E. Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk. *Proc Natl Acad Sci USA* 2003;100:1034–1039. [PubMed: 12552124]
43. Pei L, Melmed S. Isolation and characterization of a pituitary tumor-transforming gene (PTTG). *Mol Endocrinol* 1997;11:433–441. [PubMed: 9092795]
44. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. *Clin Endocrinol (Oxf)* 2001;55:735–740. [PubMed: 11895214]
45. Serrano M, Lin AW, McCurrach ME, Beach D, Lowe SW. Oncogenic ras provokes premature cell senescence associated with accumulation of p53 and p16INK4a. *Cell* 1997;88:593–602. [PubMed: 9054499]
46. Skolnick, M. The Utah genealogical database: a resource for genetic epidemiology. In: Cairns, J.; Lyon, JL.; Skolnick, M., editors. Banbury Report No 4 Cancer incidence in defined populations. Cold Spring Harbor Laboratory; Cold Spring Harbor: 1980.
47. Sveinbjornsdottir S, Hicks AA, Jonsson T, Petursson H, Gugmundsson G, Frigge ML, Kong A, Gulcher JR, Stefansson K. Familial aggregation of Parkinson's disease in Iceland. *N Engl J Med* 2000;343:1765–1770. [PubMed: 11114315]
48. Tashjian RZ, Farnham JM, Albright FS, Teerlink CC, Cannon-Albright L. Evidence for an inherited predisposition contributing to risk for rotator disease. *J Bone Joint Surg* 2009;91:1136–1142. [PubMed: 19411462]
49. Teerlink CC, Hegewald MJ, Cannon-Albright LA. A genealogical assessment of heritable predisposition to asthma mortality. *Am J Respir Crit Care Med* 2007;176:865–870. [PubMed: 17690335]
50. Thomas A, Cannon-Albright L, Bansal A, Skolnick MH. Familial associations between cancer sites. *Comput Biomed Res* 1999;32:517–529. [PubMed: 10587469]
51. Tichomirowa MA, Daly AF, Beckers A. Familial pituitary adenomas. *J Intern Med* 2009;266:5–18. [PubMed: 19522822]
52. Treier M, Gleiberman AS, O'Connell SM, Szeto DP, McMahon JA, McMahon AP, Rosenfeld MG. Multistep signaling requirements for pituitary organogenesis in vivo. *Genes Dev* 1998;12:1691–1704. [PubMed: 9620855]
53. Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, Gundogdu S, De Menis E, Makinen MJ, Launonen V, Karhu A, Aaltonen LA. Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006;312:1228–1230. [PubMed: 16728643]
54. Woloschak M, Yu A, Post KD. Frequent inactivation of the p16 gene in human pituitary tumors by gene methylation. *Mol Carcinog* 1997;19:221–224. [PubMed: 9290697]
55. Yin Z, Williams-Simons L, Parlow AF, Asa S, Kirschner LS. Pituitary-specific knockout of the Carney complex gene *Prkar1a* leads to pituitary tumorigenesis. *Mol Endocrinol* 2008;22:380–387. [PubMed: 17975024]

56. Zhang X, Horwitz GA, Heaney AP, Nakashima M, Prezant TR, Bronstein MD, Melmed S. Pituitary tumor transforming gene (PTTG) expression in pituitary adenomas. *J Clin Endocrinol Metab* 1999;84:761–767. [PubMed: 10022450]

Fig. 1.
GIF statistic for 741 pituitary tumor cases shown by genetic distance between pairs of cases versus controls

Table 1

Estimated relative risks in first-, second-, and third-degree relatives of 741 pituitary tumor cases

Relatedness	Number of relatives	Observed/expected number of cases	Relative risk (95% CI)
First degree	6,338	10/3.5	2.83 (1.36, 5.21)
Second degree	20,112	6/7.2	0.83 (0.30, 1.80)
Third degree	51,595	31/19.0	1.63 (1.11, 2.32)