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## ORIGINAL ARTICLE

### PICOGEN: Five years experience with a genetic counselling program for dementia<sup>☆</sup>

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#### Abstract

**Introduction:** We describe the 5 year experience of a genetic counselling program for familial dementias (the PICOGEN program).

**Methods:** The neurologist selected the candidates for genetic testing in the screening visit based on family history and phenotype (Alzheimer disease-AD, frontotemporal lobar degeneration-FTLD, or prion disease). Asymptomatic subjects who decided to know their genetic status were evaluated within a structured protocol by the psychiatrist and psychologist prior to entering the program and followed up afterwards.

**Results:** A total of 87 patients from 72 families were candidates for the genetic study, 20 of the 72 families had a family history of autosomal dominant early-onset dementia (ADEOD). A pathogenic mutation was found in 22 patients (8 *PSEN1*, 1 *PSEN2*, 1 *APP*, 4 *MAPT*, 8 *PRNP*), 5 of which had not been previously described. All positive cases, except for 1 *PSEN1* (12.5%) and 4 *PRNP* (50%) showed ADEOD. In 3 ADEOD cases (15%) no pathogenic mutation was found. After individual genetic counselling, 24/ 54 asymptomatic subjects at risk decided to have the pre-symptomatic study, of whom 10 (42%) were carriers of the pathogenic mutation. In the follow up, no major psychiatric complication was observed. **Conclusions:** In our series, family history of ADEOD was a sensitive criterion for the detection of pathogenic mutations in AD and FTLD but not in prion diseases. No genetic

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**PALABRAS CLAVE**

Consejo genético;  
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Demencia familiar;  
Enfermedad de  
Alzheimer;  
Degeneración lobular  
frontotemporal;  
Enfermedades priónicas

anomalies were detected in 15% of the ADEOD cases using conventional diagnostic procedures, and 43% of pre-symptomatic subjects at risk who received individual genetic counselling decided to have the study. The pre-symptomatic diagnosis proved to be safe under these conditions

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## **PICOGEN: experiencia de 5 años de un programa de asesoramiento genético en demencia**

**Resumen**

**Introducción:** Describimos la experiencia del Programa de Información y Consejo Genético para demencias familiares (PICOGEN) en sus 5 años de funcionamiento.

**Métodos:** Todos los sujetos fueron asesorados por un neurólogo que seleccionó los candidatos a estudio genético según la historia familiar y el diagnóstico (enfermedad de Alzheimer [EA], degeneración lobular frontotemporal [DLFT] o enfermedad priónica). Los sujetos asintomáticos que decidieron conocer su estatus genético siguieron un protocolo estructurado de evaluación antes y después de la realización del test genético.

**Resultados:** Ochenta y siete pacientes de 72 familias fueron candidatos a estudio genético, 20 de 72 familias presentaban historia familiar autosómica dominante de inicio precoz (HADp). En 22 se detectó una mutación patogénica (8 *PSEN1*, 1 *PSEN2*, 1 *APP*, 4 *MAPT*, 8 *PRNP*), 5 no descritas previamente. Todos los casos con mutación, excepto uno *PSEN1* (12,5%) y 4 *PRNP* (50%) presentaban HADp. En 3 casos con HADp (15%) no se encontró ninguna mutación. 24 de 54 sujetos asintomáticos de familias con mutación conocida decidieron realizarse el estudio presintomático, 10 resultaron portadores. En el seguimiento de los sujetos que realizaron el estudio predictivo no se observó ninguna complicación psiquiátrica mayor.

**Conclusiones:** En nuestra serie la HADp resultó un criterio sensible para la detección de mutaciones patogénicas en EA y DLFT, pero no en enfermedades priónicas. Un 15% de los casos HADp no presentaron alteraciones genéticas causales en estudios diagnósticos convencionales. El 43% de los sujetos en riesgo que recibieron asesoramiento genético individual realizaron el estudio presintomático. El estudio presintomático resultó seguro en este contexto

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**Introduction**

Most cases of dementia present at late ages and are not genetically determined, although genetic factors may play a predisposing role. Fewer than 1% of the total number of cases of neurodegenerative dementia are genetically determined by the presence of a mutation in a gene implicated in the pathogenesis of the disease and are inherited with an autosomal dominant pattern.<sup>1</sup> Around 0.1% of cases of Alzheimer's Disease (AD) are caused by the presence of mutations in the presenilin 1 (*PSEN1*) or presenilin 2 (*PSEN2*) genes or in amyloid precursor protein (*APP*);<sup>2</sup> 5% to 10% of frontotemporal lobar degeneration (FTLD) cases are due to mutations in genes of tau protein (*MAPT*) or progranulin (*PGRN*) and 10% to 15% of prion disease are through mutations in the prion protein gene (*PRNP*).<sup>3-6</sup> The detection of a genetic cause in a patient has immediate repercussions on their direct relatives, placing them at risk of developing the disease themselves in future.

On the other hand, the implication of genetic factors in the pathogenesis of the disease, either as the determinant trigger, such as in genetic cases, or else as a predisposing element, such as genetic risk factors, has generated a demand among the population at risk of dementia for information generally not covered by the usual health-care devices.

In this sense, in order to offer genetic counselling to patients with dementia and their relatives, a Multidisciplinary Programme was implemented in 2001 at the Clinic Hospital in Barcelona for Genetic Information and Counselling on familial dementias, known as the PICOGEN programme, based on the available experience and on the clinical practice guidelines on genetic counselling in Huntington's disease.<sup>7</sup>

The aim of the present study is to describe the experience of the PICOGEN programme over its first 5 years of operation (October, 2001, to September, 2003, and July, 2006, to June, 2009).

## Patients and methods

At the Clinic Hospital in Barcelona, within the framework of the Unit for Alzheimer's Disease and other cognitive disorders, a specific genetic counselling clinic was set up in the field of neurodegenerative dementias (PICOGEN). The programme, approved by the hospital's Ethics Committee, helps patients with suspected AD, FTLT or genetically determined prion diseases and their relatives at risk of developing this condition. In an initial phase (October, 2001, to September, 2003), the project was funded through donations made by two private institutions (Caixa Catalunya Bank and the Editorial Planeta publishing firm). The dissemination of the programme among professionals in the field and associations of patients together with the need to continue helping families who had begun to be cared for during the first phase of the programme, as well as the interest aroused by the programme at both the clinical and research levels, meant that the programme was re-started in a clinical research-linked context in July, 2006.

In the first phase of the programme, the dissemination through the mass media led to many of the subjects visited requesting an interview for themselves, with the remainder coming from the Hospital's own unit or referrals from other centres. In the second phase of the programme the subjects visited came from the Hospital's own unit, from families already included in the programme during its first phase or referrals made by neurologists at other centres.

Subjects referred into the programme are evaluated at a first visit by the neurologist responsible for the programme (JLM in the first phase; RSV in the second phase), who examined the clinical phenotype of the affected subjects, the age at which their symptoms debuted, the familial transmission pattern and the possibility of obtaining biological samples from at least one person affected when the person attending the clinic is an asymptomatic subject at risk. Depending on these details, candidates were selected to carry out a genetic study.

The criteria used in the PICOGEN programme to perform genetic screening are:

1. AD phenotype:
  - a) Early-onset AD with a history of a first-degree relative with early-onset AD;
  - b) AD starting < 58 years of age when there is no reliable family history (for example early demise of parents or ignorance of biological parents)<sup>2</sup> or very early-onset AD (< 50 years) even in the absence of a family history;
  - c) Early-onset AD and neuropathological data suggesting a genetic origin of the AD (for example, cotton wool plaques).<sup>8</sup>

No genetic screening studies are carried out for diagnostic purposes in the event of a family history of senile AD.<sup>9</sup>
2. FTLT phenotype:
  - a) FTLT with a family history of a similar disease;
  - b) FTLT with autosomal dominant pattern of dementia in the family with scant clinical information;
  - c) FTLT regardless of the age at debut and neuropathological data suggesting a genetic origin (for example inclusions of intraneuronal ubiquitin).

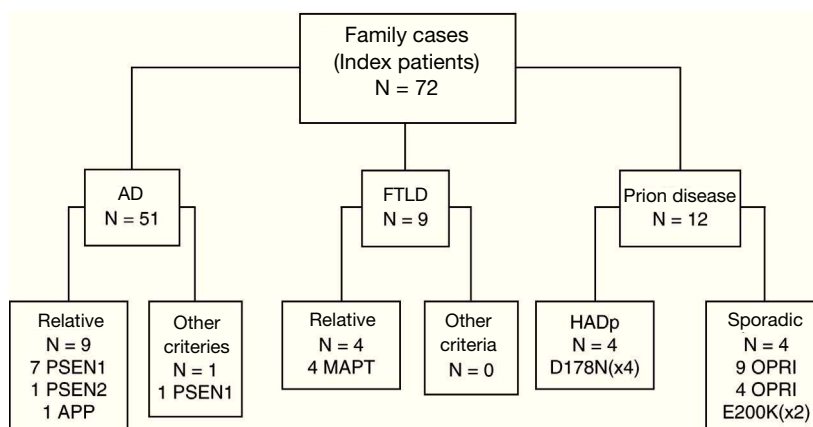
### 3. Phenotype for prion disease:

- a) Screening of causal mutations is performed regardless of age or family history.<sup>3</sup>

Those subjects not considered as candidates for a genetic screening study, either because they do not meet the required criteria, or else because there are no biological samples available from affected subjects on which to perform genetic screening, receive a general explanation about the genetic risk in their particular case and about the lack of indication for performing a specific study.

In candidates who are symptomatic patients, the genetic study is performed directly after obtaining consent in writing. Asymptomatic subjects at risk of being carriers of a known mutation and who express a desire to know their genetic status follow a specific assessment protocol prior to the test and post-test follow-up with different professionals (neurologists, psychiatrist, psychologist and geneticist). The multidisciplinary protocol is explained in detail in advance<sup>10</sup> with slight modifications and, in summary, comprises the following stages:

1. At a first visit with the neurologist to assess the presence or otherwise of symptoms, asymptomatic participants are informed about the risk and the study protocol should they decide to carry out the test.
2. After a period of reflection lasting for approximately three months, a structured clinical interview is scheduled with a psychiatrist and a psychological assessment, including anxiety and depression and quality of life scales, for those subjects who ratify their wish to know their genetic status.
3. After the psychiatric and psychological evaluation, a joint assessment is made of the risk-benefit balance of the pre-symptomatic study in the subject in question by the neurologist, the psychiatrist and the clinical psychologist. From this evaluation a recommendation is made to the subject by the team. In the event of a discrepancy, the psychiatric opinion prevails.
4. The subject is informed about the team's opinion about the safety of the test if applicable and, if he or she finally decides to have the study done, blood is drawn after the informed consent is signed.
5. The results are always delivered directly in person to the subject concerned in the presence of another trusted person accompanying him or her, with the recommendation that this person should not be another subject at risk.
6. Regardless of the test result, the subject is offered follow-up initially including a visit to the psychiatrist and the neurologist between two weeks and one month after the notification of the result. The need for pharmacological and/or psychological treatment and the frequency of subsequent visits to the neurologist and the psychiatrist are established in the light of the clinical criteria and depending on the subject's individual situation, having regard for such factors as their proximity to the theoretical age for onset of the symptoms, the psychological consequences of the result or the subject's wishes.
7. If prenatal counselling is requested, the subject is referred to a clinical geneticist.



**Figure 1** Summary of the index cases studied.

In patients with AD phenotype, candidates for a genetic study were screened for mutations using the *Single Strand Conformation Polymorphism* (SSCP) technique on exons 3-12 of the *PSEN1* and *PSEN2* genes and exons 16 and 17 of the *APP* gene during the first phase of the programme, and then by direct sequencing of the *PSEN1* and *APP* genes in the second phase of the programme. Since the sensitivity calculated for detection of mutations is 80% with the SSCP technique (Hayashi),<sup>11</sup> of the 7 subjects with ADEOD in whom no mutation had been detected with SSCP were subsequently studied using a direct sequencing technique.

Patients with the FTLD phenotype and genetic screening were studied using a direct sequencing technique for exons 1 and 9-13 of the *MAPT* gene and exons 0-12 and the adjacent intronic region of the *PGRN* gene. Where neuropathological data are available on any patient, the *MAPT* gene is studied only where deposits of tau protein are seen or for *PGRN* inclusions of intraneuronal ubiquitin are found.

In patients with suspected prion disease, a study of the complete *PRNP* encoding region is studied using direct sequencing.

The pathogenicity of mutations in genes related with AD not previously published was estimated on the basis of the probability criteria described by Guerreiro et al.<sup>12</sup>

The handling of the case reports was different for symptomatic and asymptomatic subjects. Documentation referring to symptomatic subjects is filed at the hospital's general archive. Although legally any kind of information contained in a case report is confidential and therefore both the centre and the professionals involved have a duty to protect this, in the case of asymptomatic subjects it was decided to adopt an extra security measure by keeping the documentation about genetic counselling separate from the patient's hospital reports and stored under lock and key in the office of the person responsible for the programme. On the other hand, information about asymptomatic subjects at risk was only reflected on the subject's own documentation, without any reference being made to the details of asymptomatic subjects in the documentation for other relatives.

## Results

In the 5 years the programme has been operating, 87 symptomatic subjects were identified, belonging to 72 different families, all candidates for a genetic screening test according to the criteria set out above (fig. 1). Of these, 9 presented FTLD phenotype, 12 prion disease phenotype and the remainder (51 patients) AD phenotype.

Among the 22 index patients, 13 different pathogenic mutations were detected: 6 in *PSEN1*: E120G,<sup>13</sup> M139T<sup>14</sup> in two different families, K239N,<sup>15</sup> P264L<sup>16</sup> in two different families, L286P,<sup>17</sup> L282R,<sup>18</sup> one in *PSEN2* (T430M),<sup>19</sup> one in *APP* (I716F),<sup>12</sup> one in *MAPT* (P301L) and 4 in *PRNP* (E200K in two families; D178N in 4 families; one insertion of 9 octapeptides and another of 4 octapeptides).<sup>3</sup> Five of these mutations had not previously been described and have recently been published (E120G,<sup>13</sup> K239N,<sup>15</sup> L286P<sup>17</sup> in *PSEN1*, T430M<sup>19</sup> in *PSEN2*, and I716F<sup>12</sup> in *APP*). All of them met the probable or definite pathogenicity criteria according to Guerreiro et al.<sup>12</sup>

The type of family history, the number of subjects affected in each family and the age ranges for debut in each of the families are described in table 1. Six of the symptomatic subjects studied (probands or secondary cases) presented a debut of the illness at ages over 65 years: 4 of them had a family history of ADEOD (AD, FTLD or prion disease) and 2 showed sporadic presentation (prion disease linked to mutation E200K).

Twenty of the 72 index patients studied presented a clear pattern of ADEOD, defined as more than three cases in two different generations of debut before 65 years of age (when a generation only had one member, 2 cases in 2 generations were considered to be ADD). A pathogenic mutation was found in 17 of the cases with ADEOD (85%). In 24% of the cases where a pathogenic mutation was detected, they presented with no pattern of ADD (one case of *PSEN1* and 4 cases of *PRNP*).

Pathogenic mutations were found in 9 of the 51 families studied with AD: 7 families (13 symptomatic subjects) presented mutations in the *PSEN1* gene, one family (2 symptomatic subjects) presented a mutation in the *PSEN2*

**Table 1** Summary of the main characteristics of each of the families with a detected mutation

Mutation	Gene	Phenotype	N° affected by ADD	Median age at debut (range)	Publication
E120G	PSEN1	AD	Yes (3)	40? (34-42?)	Ref. 13
M139T-1	PSEN1	AD	Yes (10)	46 (38-51)	Ref. 13
M139T-2	PSEN1	AD	Yes (2)	(47-50?)	Ref. 13
K239N	PSEN1	AD	Yes (7)	53 (43-71)	Ref. 15
P264L-1	PSEN1	AD	Yes (3)	45 (45-46)	Ref. 16
P264L-2	PSEN1	AD + sp	No (1)	53	Ref. 16
L282R	PSEN1	AD	Yes (8)	50 (?)	Ref. 18
L286P	PSEN1	AD	Yes (7)	40 (35-42)	Ref. 17
T430M	PSEN2	AD	Yes (4)	57 (45-64)	Ref. 19
I716F	APP	AD	Yes (2)	33.5 (31-36)	Ref. 12
P301L-1	MAPT	FTLD	Yes (3)	46 (46-48)	Ref. 22
P301L-2	MAPT	FTLD	Yes (6)	50 (?)	Ref. 22
P301L-3	MAPT	FTLD	Yes (4)	49 (46-57)	Ref. 22
P301L-4	MAPT	FTLD	Yes (5)	60 (51-69)	Ref. 22
D178N-1	PRNP	FFI	Yes (6)	50.5 (39-68)	Ref. 3
D178N-2	PRNP	FFI	Yes (4)	49 (40-56)	Ref. 3
D178N-3	PRNP	FFI	Yes (7)	42 (28-48)	Ref. 3
D178N-4	PRNP	FFI	Yes (3)	56.5 (50-63)	Ref. 3
9OPRI	PRNP	Dem + ataxia	No (1)	27	Ref. 20
4OPRI	PRNP	CJD	No (1)	39	Ref. 3
E200K-1	PRNP	CJD	No (1)	67	Ref. 3
E200K-2	PRNP	CJD	No (2)	72.5 (60-85)	Ref. 3

sp = spastic paraparesis.

gene (T430M)<sup>19</sup> and another in the *APP* gene (one symptomatic subject studied) (I716F).<sup>12</sup> ADEOD was present in 86% of the families with a detected mutation. In the only case with AD phenotype where a pathogenic mutation was detected without any family history, the genetic screening study was carried out because the neuropathological study revealed lesions suggesting a genetic origin of their disease (predominance of  $\beta$ -amyloid deposits in diffuse plaques, some of them cotton wool plaques).

Of the 9 families studied with FTLD, 4 (6 symptomatic subjects) presented a mutation (P301L) in the *MAPT* gene. All these cases presented an ADEOD pattern.

With respect to cases of prion disease, 2 of the 12 index patients studied presented the E200K mutation in the *PRNP* gene, 4 the D178N mutation and 2 repeat insertions of 9 and 4 octapeptides, respectively. Both of the patients with the E200K mutation and also the patients with octapeptide insertions lacked any family history of the disease. In the patient with a 9 octapeptide insertion, it was possible to show that the mutation had appeared *de novo* in this subject.<sup>20</sup> On the other hand, all the patients with a D178N mutation causing fatal familial insomnia presented ADEOD.

After the notification of the genetic diagnosis to the families were determining mutations were found, 54 asymptomatic subjects from these families came for individual genetic counselling. The number of subjects at risk per family who came to the programme varied greatly from one family to another (0-10 cases/ family). Of these 54 subjects, 24 expressed a desire to know if they carried the mutation. No cases were detected of opposition by relatives to the individual's decision to take the test, at least in the

3 cases of subjects who finally did not have the test done, their relatives felt that they should have had it. After the pre-test multidisciplinary evaluation, 23 asymptomatic subjects at risk took the pre-symptomatic study. Nine of the subjects (41%) taking the predictive study turned out to be carriers of the pathogenic mutation. Only one subject was recommended to defer the study until after the multidisciplinary assessment. This subject was very close to the median age for debut of the illness in the Ia family and, although the cognitive studies were still normal, already presented some complaints suggesting the start of the disease, as could be confirmed in later follow-up. In the post-test follow-up session, which varied from 2 to 90 months for subjects who were shown to be carriers, no catastrophic adverse event has been recorded (admission to hospital on psychiatric grounds or attempted self-harm) nor any radical changes in lifestyle, although there were frequent references to a discreet increase in immediate and transient stress levels. All subjects who were carriers ratified their decision to take the genetic test even though the result was unfavourable. Non-carrier subjects felt relieved when they were notified of the result and no feelings of "survivor guilt" were detected during the follow-up.

In addition to the information about the risk of transmitting the disease to offspring and the possibilities in our setting for avoiding this transmission offered to all the subjects at risk of carrying a pathogenic mutation, three couples came explicitly to the programme to request prenatal counselling. Two of these couples asked for chorionic biopsies to be performed for the purposes of

prenatal counselling. No couple has yet opted for the possibility of preimplantational embryo selection or the donation of gametes as part of our programme.

## Discussion

The present paper describes the experience of a specific pioneering genetic counselling programme aimed at patients and subjects at risk of suffering genetically determined dementias, the PICOGEN programme. Clinical guidelines for handling AD and other dementias, such as the guidance from the European Federation of Neurological Societies,<sup>21</sup> recommend conducting screening studies for pathogenic mutations in patients with familial dementia at specialist centres simultaneously offering genetic counselling for patients and their relatives. However, the normal health-care provision mechanisms, structured depending on the health-care needs for the most frequent late-onset sporadic forms,<sup>22</sup> do not usually contemplate this fact, since only a minority of the subjects affected with dementia are candidates for carrying out this kind of study. On the other hand, there is little information published about the clinical experience of genetic counselling units specializing in field of dementia through which to reach a consensus on handling symptomatic and asymptomatic subjects, and prenatal counselling.<sup>23</sup>

The first observation in our study is that the presence of a family history of ADEOD is a sensitive criterion for detecting a disease-determining mutation in the subject. In this way, overall, pathogenic mutations were identified in 80% of cases with a clear history of ADEOD. The rest of the criteria for conducting genetic studies, for example applying more lax inheritance criteria that included the remaining 52 index patients, presented low detection performance with regard to pathogenic mutations, especially if patients with prion disease are excluded. Thus, a pathogenic mutation was detected in only one (2.2%) of the 44 other index patients studied who did not present ADEOD. In this study we did not carry out any studies of the *APOE* gene for genetic counselling purposes in accordance with the clinical guidance recommendations<sup>9,21</sup> so we cannot distinguish whether this factor might have a role in the inheritance of cases of presenile AD with a family history but no ADEOD pattern.

We must also point out that, although all the cases of FTLD in which pathogenic mutation was detected presented ADEOD, our series only found cases with mutations in the *MAPT* gene. This fact might vary if mutations were detected in the *PGFIV* gene, where, according to the published data, the age at debut and the presence of a family history are much more variable.

Another element to be highlighted is the age at debut of the different mutations and in the different families. Although, as we said in the preceding paragraph, the ADEOD criterion was met by the vast majority of patients presenting a mutation, we should point out that 4 of the patients belonging to these families with a habitually presenile age at debut were all elderly when diagnosed. Thus, the subject's age should not be an exclusion criterion for participation in genetic counselling programmes if they present a family history of ADEOD. On the other hand,

subjects at risk are informed about the current impossibility of precisely predicting the age at debut of the disease in those subjects carrying the mutation and the existence of different age ranges for the debut in different families.

In addition, 3 families with ADEOD did not present any mutations in the genes studied, 2 of which presented an AD phenotype and one with FTLD phenotype. This datum can be explained in part by the fact that in 2 of the 7 probands the genetic study was carried out using SSCP with a calculated sensitivity of 80%<sup>1</sup> and it was not complemented by direct sequencing as no sample was available. Also, no duplication studies were done for *APP* or any other genes less frequently involved in FTLD (*VCP*, *CHMP2B*, *TDP43*)<sup>16</sup> in these subjects as the technique is not available at our centre at present. However, this datum is similar to that of other case series in which, despite complete studies, in as much as 11% of cases of AD with ADEOD<sup>24</sup> and in 37% of cases of FTLD,<sup>25</sup> it is not possible to detect any known genetic cause, suggesting that there might be mutations or gene dose alterations in other genes implicated in these genetic dementias still to be discovered. In any case, this fact is important and must be borne in mind when interpreting the negative result of a genetic study, as a normal outcome in the genetic studies carried out does not rule out a genetic origin.

Another observation, also in line with the published results of other series of subjects at risk for genetic dementia or Huntington's disease, is that only a minority of asymptomatic subjects at risk carry out the pre-symptomatic study.<sup>26-28</sup> In our series, 41% of the subjects attending genetic counselling sessions finally had the predictive test carried out. In this paper, unlike other published studies, we have calculated the subjects not on the basis of the number of subjects at risk calculated<sup>28</sup> or reported through a letter,<sup>27</sup> but in connection with the number of subjects attending the direct genetic counselling session. It is obvious that, when we compare percentages, the number of subjects at risk is much greater than the number of subjects attending the programme, and therefore the final percentage of tests carried out is lower. Nonetheless, we prefer to use this group of subjects for the calculation since, in our experience, we know that the information about genetic risks does not always correctly reach all the subjects when they are notified through relatives, either through desires to mollify or to offend some relatives, or else through the incorrect interpretation of the information, lack of contact with the relative, etc. On the other hand, unlike the experience reported by Riedijk et al,<sup>28</sup> we have not detected any opposition by family members regarding the use of the predictive test in any case.

Finally, in our series, in all but one of the subjects (95%) the study was considered safe for the subject in the pre-test multidisciplinary assessment. No case of catastrophic reaction<sup>29</sup> was detected after the genetic diagnosis.

A prior study described in detail the psychological motivations and reactions of the first 9 asymptomatic subjects who carried out the predictive study as part of the PICOGEN programme.<sup>10</sup> The longer-term follow-up of the subjects included in that paper and the rest of the subjects supports the fact that, within strict genetic counselling protocols, the predictive study can be considered safe and, in addition, it is perceived as beneficial by the subjects at risk.



To sum up, the experience of the PICOGEN programme suggests that ADEOD is a sensitive criterion for detecting pathogenic mutations in AD and FTLD, but not in prion diseases, although ADEOD could not be identified as a genetic cause of the disease in 20% of the cases. Even though the predictive study was safe in the context of a multidisciplinary assessment, fewer than half the subjects at risk attending the genetic counselling sessions decided to have the pre-symptomatic study done.

## Conflict of interest

The authors declare that they have no conflict of interest.

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