Acquired prosopagnosia (PA) is a rare condition after, for example, a stroke or brain injury. The congenital form of PA is generally considered to be even less common. Beside a few single case reports and anecdotal mentioning of familial cases no data on the epidemiology exists. Following a questionnaire-based screening in local secondary schools and at our medical faculty, candidates suspicious for PA underwent a semi-structured interview followed by examinations of first degree relatives. Among 689 local pupils and medical students of our university we found 17 with congenital PA. This corresponds to a prevalence rate of 2.47% (95% CI 1.31–3.63). The frequency is among the highest known for a monogenic disorder. All those index subjects (n = 14) of the target group who agreed to further examinations of their family members had other first degree relatives with the same cognitive disorder. This study provides epidemiological evidence that congenital PA is a very common cognitive disorder which almost always runs in families. The segregation pattern of this hereditary prosopagnosia (HPA) is fully compatible with autosomal dominant inheritance.

Key words: prosopagnosia; face blindness; hereditary prosopagnosia; congenital prosopagnosia; non-syndromic; prevalence; Caucasian

INTRODUCTION

Prosopagnosia (PA) is a selective impairment in visual learning and recognition of faces. Acquired PA is known to be associated with right or bilateral and temporal lobe damage. Congenital PA without any known insult, traumatic or toxic event were reported rarely, mostly as single case reports [Kress and Daum, 2003; Behrmann and Avidan, 2005]. The first hint of possible familial transmission from mother to daughter was published by McConachie [1976] (Fig. 1A). The index proposita as well as her mother claimed that they had never been able to recognize faces except the most familiar one. The girl learned to recognize her classmates at a school of gifted children only after 1 or 2 months. Both mother and daughter have overcome their handicap by using voice recognition or by memorizing clothing. There are only two later reports of a familial history of inborn PA. De Haan [1999] describes PA in a father and two daughters (and probably one son; Fig. 1B). The index subject complained that she had never been able to recognize familiar people in a reliable manner. It soon transpired that her father, her brother, and her middle sister also complained about making face recognition mistakes in daily life. This was obviously an accepted occurrence in the family. She recalled that, as children, her mother used to instruct them beforehand as to who was coming to visit that day. Galaburda and Duchaine [2003] found familial recurrence in four generations including father-to-son transmission. It was not until the index subject in this report entered the army that he realized his problem. In his case he could not differentiate his fellow servicemen in their uniforms (Fig. 1C). To date, no systematic investigations of formal genetic basis of congenital PA has taken place.


There is no generally accepted standard for the designation of different types of PA. The terms “congenital,” “developmental,” and “childhood PA” were used differently in the past. However, these terms just regard the time of onset such as “congenital PA” [Ariel and Sadeh, 1996; Hasson et al., 2003; Behrmann and Avidan, 2005], or “childhood PA” [Young and Ellis, 1989], the pathogenesis such as “developmental prosopagnosia” [McConachie, 1976; de Haan and Campbell, 1991; Temple, 1992; Bentin et al., 1999; de Haan, 1999; de Gelder and Rouw, 2000; Jones and Tranel, 2001; Nunn et al., 2001; Kress and Daum, 2003; Duchaine et al., 2003a], or the consequence of brain injury or encephalitis, such as “acquired prosopagnosia.” The term “congenital” only means present at birth; it defines the time of onset but not the etiology which could be hereditary (ab ovo) or acquired during delivery (e.g., perinatal asphyxia). The same is true for “developmental or childhood prosopagnosia” which may also be hereditary or acquired.

A critical review of the literature on congenital/developmental PA [Kennerknecht et al., 2002; Grueter et al., 2006], indicate that there are two main types: (a) cases of the acquired form and (b) hereditary cases of PA. The latter might be monosymptomatic (i.e., non-syndromal) or syndromal with concurrent neurodevelopmental disorders such as Asperger syndrome [Kracke, 1994; Pietz et al., 2003; Duchaine et al., 2003b; Ellis et al., 2005]. The congenital type is defined on the basis of familial recurrence which we therefore called hereditary prosopagnosia (HPA) [Kennerknecht et al., 2002; Grueter et al., 2006]. From a formal genetic point of view the hereditary type can also be a single case in a family, for example, due to a de novo mutation or an “isolated familial” case. However, no systematic investigations have been reported. The acquired and hereditary types can have a very early onset (i.e., congenital) or in childhood (i.e., developmental). We assume that a late-onset PA represents only the acquired type.

Meanwhile we are aware of more than 200 persons with PA and more than 40 families. They were ascertained by personal acquaintance, by providing an internet portal and further by response to reports of our project in mass media. In a pilot study we found among 90 sibs, from 6 unrelated families, 31 had PA (20 females, 11 males) [Grueter, 2004]. There is always vertical segregation, involving both sexes and father-to-son transmissions and no skipping of generations which is compatible with autosomal dominant inheritance (e.g., Fig. 1D). In order to assess the diagnoses more objectively we extended our studies. Eight out of thirty-eight with HPA, from seven different families, agreed to in-depth testing. The testing included the Warrington Recognition Memory Test forFaces (RMF) [Warrington, 1984], famous and family faces tests, learning tests for internal and external facial features, and a measure of mental imagery for face and non-face images. The results of these tests supported the data of the individual interviews as was true with the respective familial segregation data. Thus since the eight tested individuals were randomly chosen, it is likely that the others with HPA may show a similar pattern of face recognition ability [Grueter et al., 2006].

In previous studies those diagnosed with PA were ascertained by chance. This is the first reported systematic search done in circumspective collections. Here, we present evidence that HPA is a common cognitive dysfunction and one of the most frequent monogenic disorders in humans.

MATERIALS AND METHODS

Subject Selection and Questionnaire Administration

This study was conducted with ethical committee approval from the University of Münster, protocol No 3XKenn2, “Genotype/phenotype correlation of PA (syn. face blindness).” Subjects were recruited, with informed consent, by questionnaire-based screening in three local secondary schools (final
2 years) and among first year medical students from our university. Only after completing the questionnaire did the pupils and students get more detailed information on the project. The same questionnaire was subsequently sent to family members of the index subjects (Survey instrument, in German, available from author on request). All of those highly suspicious for PA from the screening results were asked if they were willing to undergo a semi-structured interview (at least 1 hr) in person or by phone.

### Data Analysis

The following questionnaire data were collected: integrity of visual input; frequency of contact with other people; sense of orientation in cities, buildings, and nature; differentiation of common animal and plant species (inter/intra class object differentiation); recognition of other persons in a variety of situations; behavior in meetings with known and unknown people.

“Highly suspicious” was assumed if the questionnaire documented: (1) anamnestic data excluding any event of brain damage (perinatal asphyxia, epileptic attack, meningitis, injuries, brain surgery) or neurological or psychiatric disorders; (2) severe problems recognizing familiar faces or of faces outside of the normal context, for example, a colleague in a restaurant in the evening or a neighbor at the station; (3) inability to decide whether a face is familiar, including false positive and negative decisions, for example, that a stranger is falsely recognized as familiar, and that a familiar person was classified as unknown. In general, we find that those with PA suffer from a felt uncertainty of face recognition. They have trouble reaching a sufficient level of confidence in the known/unknown decision. (4) Prolonged decision time for recognition seems to be a consequence of the lack of face recognition confidence, as is (5) poor face memory after brief contact. (6) Development of adaptive strategies appears common: for example, not going to places where other people could be met unexpectedly, or being first to an appointment, or the habit of appearing absent-minded or looking to the ground when walking down the street; (7) as well as heavily relying on non-facial features for person recognition like voice, gait, accessories, hair, haircut etc., and (8) a family history of at least one affected first degree relative. Diagnosis was established by a semi-structured diagnostic interview (at least 1 hr).

### RESULTS

Screening questionnaires were completed by 689 out of approximately 750 apparently unrelated subjects (return rate 92%; Table I). Sixty-five persons were rated “highly suspicious,” forty-three were available for an in-depth interview. The diagnosis of PA was established in 17 individuals (6 males and 11 females). The prevalence of PA is 2.47% (95% CI 1.31–3.63). The frequency—at least in this population—is among the highest known for a monogenic disorder. The probability that subjects with the acquired form of PA were included coincidentally was minimized by assessing at least one first degree relative in all 14 out of 17 index subjects who allowed further interrogations.

Table II shows the characteristic symptoms of hereditary PA. Our interviews documented a variety of impressive qualitative differences. All affected persons have a similar, characteristic pattern of symptoms. Therefore, we assume that HPA is a single, well-defined entity. Nearly all affected persons report a problem in deciding immediately, whether a face is known. In many cases, they cannot decide this question at all and report an agonizing uncertainty in social situations which require visual recognition of faces in the absence of other clues. Many complain about a lack of or presence of coarse mental images of persons, animals, and objects. They cannot image the faces of close relatives, and cannot recall mental images of trees, leaves, or birds. Many also complain of problems in following TV programs or movies, because they cannot tell similar actors apart. However, most affected persons report no problems with the assessment of facial expressions. Quite notably, most persons with PA do not feel the need or even the inclination to look into the face of people they talk with. Some state that they have taken up this habit deliberately, because they learned that other people expected it from them. None of those with PA showed signs of an “autism spectrum disorder.”

We found secondary behavioral adaptations in all affected persons. A detailed analysis showed three distinct strategies: a compensation strategy, an

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**TABLE I. Synopsis of the Questionnaire-Based Screening and Semi-Structured Interviews for Prosopagnosia in a Caucasian Population**

<table>
<thead>
<tr>
<th>Questionnaires completed</th>
<th>Highly suspicious for prosopagnosia by questionnaire-based screening</th>
<th>Subjects agreeing to an interview</th>
<th>Diagnosis of prosopagnosia established by successive semi-structured interview (for details see Table II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (N)</td>
<td>Female (N)</td>
<td>Total (N)</td>
<td>Male (N)</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>266</td>
<td>423</td>
<td>689</td>
<td>25</td>
</tr>
</tbody>
</table>

Around 750 questionnaires were distributed. The return rate was 689 (92%).
explanation strategy, and an avoidance strategy. We define compensational behavior as the attempt to recognize people by means other than their face. Most affected persons name voice, gait, bearing, favorite clothing, hair color, and style, accessories such as earrings or glasses as their favorite means of recognition. Others include the laugh, teeth, shoes, or the typical facial expression. People with HPA recognize other people readily in their usual settings, because they expect to meet them there. Explanatory strategies are defined as excuses or explanations for a socially inadequate behavior caused by HPA. Most affected persons have a ready set of excuses for not recognizing someone in the street, like being deep in thought, needing new glasses, being tired or distracted, or suffering from a bad headache. We define an avoidance strategy as behavior intended to avoid situations where the HPA can cause affected persons to behave in a socially inadequate or unacceptable way. Affected persons, therefore, avoid going to large functions without company, or meeting others in crowded places. All affected persons stated that they suffered from their disability to some extent, though none of them saw a doctor about it. All affected persons seem to be well integrated into society.

These behavioral adaptations are present in all affected persons studied. The exact severity of the individual cases of HPA is difficult to assess, because the adaptive behavior balances the deficit to an unknown extent. Still, our in-depth assessment showed that the underlying disorder always was fully expressed; we did not see intermediate forms. The impairments in additional family members—exclusively seen in an autosomal dominant pattern—further assists in the diagnosis of PA and especially of the hereditary form rather than the acquired form.

TABLE II. Test Items Assessed by Questionnaire-Based Screening and Individual Interviews Regarding Facial Recognition and Object Recognition

<table>
<thead>
<tr>
<th>Test Items Assessed by Questionnaire-Based Screening and Individual Interviews Regarding Facial Recognition and Object Recognition</th>
<th>Target group N = 17 6 males/11 females</th>
<th>Controls N = 26 13 males/13 females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target group N = 17 6 males/11 females</td>
<td>Controls N = 26 13 males/13 females</td>
<td></td>
</tr>
<tr>
<td>mean age</td>
<td>19.6 years SD ± 3.5 years</td>
<td>mean age</td>
</tr>
<tr>
<td>Key manifestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>False negative and false positive recognition events</td>
<td>17/17</td>
<td>1/26</td>
</tr>
<tr>
<td>Prolonged face recognition time</td>
<td>17/17</td>
<td>4/26</td>
</tr>
<tr>
<td>Prolonged face learning time</td>
<td>17/17</td>
<td>5/26</td>
</tr>
<tr>
<td>Development of adaptive behavior</td>
<td>17/17</td>
<td>0/25</td>
</tr>
<tr>
<td>Use of explicit learning strategies for visual person recognition</td>
<td>15/15</td>
<td>0/25</td>
</tr>
<tr>
<td>Early onset (congenital)</td>
<td>17/17</td>
<td>0/26</td>
</tr>
<tr>
<td>Affected first degree relatives</td>
<td>14/14</td>
<td>0/26</td>
</tr>
<tr>
<td>Facultative symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No gaze contact necessary</td>
<td>6/17</td>
<td>4/26</td>
</tr>
<tr>
<td>Impaired visual recognition of objects and scenes</td>
<td>9/15</td>
<td>2/26</td>
</tr>
<tr>
<td>Poor orientation in unknown environments</td>
<td>12/17</td>
<td>7/26</td>
</tr>
<tr>
<td>Unimpaired functions in those with prosopagnosia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recognition of facial emotions</td>
<td>15/16</td>
<td>26/26</td>
</tr>
<tr>
<td>Judgment of facial attractiveness</td>
<td>14/14</td>
<td>24/25</td>
</tr>
<tr>
<td>Recognition of gender from faces</td>
<td>12/12</td>
<td>23/25</td>
</tr>
<tr>
<td>Recognition of persons from non-facial clues</td>
<td>17/17</td>
<td>24/24</td>
</tr>
</tbody>
</table>

Total frequencies of less than 17 or 26, denotes that we have information on this topic from only less than the total study group, respectively.

DISCUSSION

Many published reports deal with acquired PA, a few with developmental and childhood PA, and recently in an increasing number with congenital PA. Subjects with acquired PA are more easily assessed because of the sudden loss of a socially important function. Those with the congenital type have been conditionally instructed from the very beginning with compensatory strategies. Many of them had not realized that they were dealing with a specific dysfunction. They have learned to recognize people from voice, gait, habits, gestalt, clothing, accessories, name, and other non-facial cues. This could explain why this kind of cognitive impairment is largely unknown to lay persons or even to physicians other than neurologists and psychiatrists.

The crucial point is the diagnosis of congenital PA. Despite a variety of face recognition tests, there are no established diagnostic tools for PA. Some tests such as the Benton Facial Recognition Test (BFRT) [Benton et al., 1983], have been shown to be insufficiently face specific [Duchaine and Weidenfeld, 2003]. In a first case study with in-depth-testing of eight subjects with hereditary PA (with at least one first-degree prosopagnosic relative) we could show that they were impaired on one or more of the following tests: Warrington Recognition Memory Test for Faces (RMF) [Warrington, 1984], famous and family faces tests, learning tests for internal and external facial features (Cardiff Repeated Recognition Test for Faces), and a modified version of the Marks Vividness of Visual Imagery Questionnaire (VVIQ) as a measure of mental imagery for face and non-face images [Grueter et al., 2006]. However, these time-consuming tests are not suitable for large scale screening for the prevalence of PA. As these functional tests supported all our primary diagnoses.
derived by a questionnaire-based screening of subjects and a successive semi-structured interview, we used the latter approach to estimate the prevalence of congenital PA. As we only interviewed participants who were rated “highly suspicious” from their screening questionnaires, there may be more participants with PA. Our data, therefore, documented only the minimal prevalence. Prima vista, we are not aware of a selection bias as questionnaires were distributed to all pupils/students of the same school year/semester. However, we do not know the rate of PA in those who refused to fill in the questionnaire. Even if there would be a positive or negative selection bias this would rather increase than significantly decrease the frequency: this is based on the assumption that those with PA might be afraid of being detected. It should be noted that a questionnaire by itself is not valid for diagnosing congenital PA, because it is not evaluated by interviews of the total collection. The diagnosis must also be based on the semi-structured interview, which must cover all important aspects of the disorder presented above.

McConachie stated [1976]: “Perhaps the condition is more common than is presently thought.” Our recent collection of families indicates that congenital PA seems to be a very common inherited cognitive disorder [Kennerknecht et al., 2002; Grueter et al., 2006]. Although agnostic impairment forms a central aspect in affected relatives, familial occurrence is not obviously registered among family members with PA. Whenever family members were available for interviews we always found one or more affected relatives. There is no pointer to an incomplete penetrance. Hence, admixture of sporadic cases (acquired PA) is obviously not significant as the sporadic cases (non-hereditary or new mutations/isolated familial) can easily be discerned because both parents are unaffected.

The simple familial segregation pattern of HPA is surprising with respect to the complex organization of the visual cortex. It is generally thought that functional maps are formed during development and are refined by individual visual experience [Crowley and Katz, 2000]. It could be shown that not only global morphometric brain measures such as total gray and white matter as in NMR studies on humans [Baare et al., 2001] but also visual fine structures as in 2-deoxyglucose autoradiographs of cat brains [Kaschube et al., 2002] can be under substantial genetic control.

Whether PA is a single trait or a cluster of related subtypes with distinct etiologies remains an open question. The subjects show very similar symptoms, but we are aware of some intra—and interfamilial variability. Whether this is due to their individual history with, for example, different avoidance or compensation strategies is unknown. Genetic dissection will show whether the suggested phenotypic variability is due to pleiotropic and/or heterogenic gene effects. Hence, those with isolated congenital PA, where only the module for face recognition is deleted, will be of high interest for providing insight into the process of face recognition and may serve for further detailed molecular genetic and neurophysiological studies (i.e., phenotype–genotype correlation) as well as for computational modeling of improved face recognition models and computer-based face recognition.

In congenital PA, individual face recognition is strongly affected, while the processing of other facial information like gender, age, and emotional expression are much less reduced of at all. This supports the “classical” theory of face recognition [Bruce and Young, 1986; Ellis and Lewis, 2001] which postulates that facial information like identity, gender, age, and emotional expression are processed independently of one another.

Congenital PA is the only known monogenic dysfunction of a higher cognitive visual skill. Among more than 90 different cognitive functions (e.g., musical mind, absolute pitch) and dysfunctions (e.g., agraphia, dyscalculia, dyslexia) related to specific cognitive behavioral and neurological disorders we could only find a few monosymptomatic conditions in the OMIM database (http://www.ncbi.nlm.nih.gov/Omim/) with proven or suggested heredity: perfect musical pitch, syn. absolute pitch [OMIM 6159300]; specific language impairment (SLI) [OMIM 602081]; specific dyslexia, syn. word-blindness (DYX1, [OMIM 127700], DYX2 [OMIM 600202], DYX3 [OMIM 604254], DYX5 [OMIM 606896]; DYX6 [OMIM 606616], DYX8 [OMIM 608995], DYX9 [OMIM 300509]), familial developmental dysphasia [OMIM 60017], tune deafness, syn. dysmelodopa [OMIM 191200]; congenital anosmia; syn. odor blindness [OMIM 107200]; inability to smell musk [OMIM 254150]; hereditary whispering dysphonia [OMIM 193680]; indifference to pain, syn. congenital analgesia [OMIM 243000]. Gene mapping was successful, in one disorder [OMIM 602081], a single but large family in which half of the members had orofacial dyspraxia and severe speech and language impairment. A point mutation was found in the FOXP2 (forkhead box protein 2) gene co-segregating with the disorder [Lai et al., 2001]. There are several susceptibility genes described in the heterogeneous group of dyslexia with regular segregation. The resulting phenotypes do not represent this in any case.

CONCLUSIONS

Congenital PA is a very common nevertheless largely unknown dysfunction almost always running in families in a regular segregation pattern. The designation “hereditary” can be used synonymously. The affected persons are only occasionally aware of
others with the same dysfunction even in very close relatives. Other non-facial object agnosias do not belong to this entity. It is known that face recognition is independent from all object recognition in many ways. Neurophysiological studies of people with this highly selective dysfunction might fundamentally improve our understanding of face recognition. As soon as gene mapping/mutation mapping will be successful the genotype/phenotype correlations should widen our knowledge of the development of higher cerebral functions.

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We would like to thank the pupils and students who participated in this study especially the index persons for their valuable help in recruiting other family members. The commitment of the teachers in the co-operating secondary schools in the area of Münster is highly appreciated. Especially, we would like to thank Dr. Linß, Mrs. Guthberlet, Gymnasium Arnoldinum, D-48565 Steinfurt; Mrs. Wulfekammer, Johann-Conrad-Schlaun Schule, D-59394 Nordkirchen; and Mrs. Hesse, Marienschule, D-48151 Münster.

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