[Frontiers in Bioscience 13, 3150-3158, January 1, 2008]

Congenital prosopagnosia – a common hereditary cognitive dysfunction in humans

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1. ABSTRACT

The apparent selectivity of agnosia for faces is termed prosopagnosia or face blindness. This cognitive dysfunction can be seen after traumatic events - involving at least the right occipital temporal region – or very frequently congenital in the absence of any detectable lesions. The familiarity of congenital prosopagnosia was studied in two independently ascertained collections of subjects with prosopagnosia. One was an unselected group of pupils and students who underwent a questionnaire based screening. The others were self reported subjects after having heard for the first time about the phenomenon of prosopagnosia from mass media citing our studies and/or from our homepage (www.prosopagnosia.de). Those who agreed with consecutive studies of their family members had mostly one or more prosopagnosic first degree relatives. The segregation patterns derived from 39 families are compatible with autosomal dominant inheritance. Hence, mutation(s) in one gene are sufficient for manifestation of the phenotype. Still fitting the concept of autosomal dominant inheritance, we have evidence for a slightly reduced penetrance (4 normal transmitters from distinct families) and one or two *de novo* mutations.

2. INTRODUCTION

The term *prosopagnosia* (PA) was first introduced by Bodamer (1947) by assimilating the Greek words *prosopon* for “face” and *agnosia* for “not knowing”. People with prosopagnosia or face blindness cannot easily tell faces apart even if they belong to close friends or family members. The selectivity of face recognition is still debated. Some researchers document a double dissociation between subjects impaired with object agnosia but not prosopagnosia and vice versa (1, 2, 3) whereas others see no such clear dissociation in their tests (4). Other aspects of face processing apart from recognizing facial identity may be relatively intact, such as facial recognition of gender, and age (5). Basic facial expression seems to be rather unimpaired in those with the congenital form (6, 7) whereas individuals with the acquired form may have problems (8). Moreover, a subject who acquired PA after a stroke can perfectly recognize all his sheep individually (2), and Jane Goodall (9) - having congenital PA like her sister - can easily individualize her chimpanzees. Yet, by what cues e.g. by face, fur, and/or gestalt is not known. On the other hand an ornithologist with acquired prosopagnosia after suffering from an insult was also not able to distinguish

birds of different species (10), the same was true for a stockfarmer also with acquired prosopagnosia and zooagnosia for cows and calves who lost the ability to differ his own cows (11, 12).

Whereas Bodamer´s term *prosopagnosia* (13) implicates a visual agnosia others viewed it as a deficit of memory (14) or a disconnection between face perception and face memory (15). Since the first linear hierarchic cognitive model of face processing (16), box-and-arrow diagrams (17), and neuronal-network models (18, 19) have been constructed to allow more explicit predictions. But what exactly constitutes face recognition is subject of an ongoing debate. Nevertheless, face recognition is distinct from object recognition in many ways. Cortical neurons can be selectively sensitive to faces (20). This does not implicate that they are necessary for individualizing a face. By removing bilaterally the face cell area at the superior temporal sulcus in macaque monkeys it could be shown that face recognition was not significantly impaired (21). Face recognition is a very quick function of the brain. Using magneto-encephalography (MEG) after as early as 100 – 120 ms there is a response to emotional faces or face categorization and after approximately 170 ms (N170) there is a wave associated only with face recognition (22, 23).

This gives evidence that the human brain has evolved special neuronal pathways for visual recognition of faces. A region in the mid-fusiform gyrus known as the fusiform face area (FFA) is especially activated when seeing a face and when impaired by e.g. traumatic events it is associated with prosopagnosia. Another region in the inferior occipital gyrus (IOG) (24) also responds more strongly to facial than to non-facial objects (25). Also the amygdala is suspected but data are lacking (26). That the fusiform face area is rather a part of a cascade/network and not solely dedicated to processing of faces is partially supported by functional neuroimaging studies of face perception of subjects with congenital prosopagnosia showing normal activation profiles (27, 28) whereas others saw a reduced activation in the fusiform area (29, 30). By conventional structural MRI Jones and Tranel (31) found no anatomical alteration whereas Behrman *et al.* (26) report a volumetric reduction in the anterior fusiform gyrus and Bentin *et al.* (32) in the right temporal lobe.

Whether the brain represents and processes face recognition in a modular or a distributed fashion is still unclear. Both aspects are well supported. Downing *et al.* (33) provide evidence in favour of a distinct cortical region in humans that responds selectively to images of the human body but not to a variety of control stimuli. Haxby *et al.* (34) also found a distinct pattern of response while subjects viewed faces, cats or man-made objects. But the respective response in the ventral temporal cortex was widely distributed and overlapping. Quiroga *et al.* (20) could even show a memory-based visual representation by single neurons in the human medial temporal lobe responding to complex images such as individual faces. The consistency of responses to e.g. different images of the same famous actor is very striking. However, this is also the case when showing the written name of the same actor. Hence, these findings say less about visual representation as such than they do about memory and maximal compact or sparse coding (35). This might also be true in some way for honey bees - having less than 1 million neurons or 0.01% of the number of neurons of the humans - which can recognize not only the faces of conspecifics but also individual human faces (36). Most probably they process these information very different to sheep (and humans) which also can individualize other sheep faces and human faces (37).

In principal, faces are recognized by featural processing by making use of the shape of the individual features as well as by configural processing – the spacing of features. It was shown that early deprivation of visual input in humans born with a dense central cataract of both eyes results in permanent deficits in configural (holistic) face processing (38). A configural impairment may affect other visual stimuli too but is thought to be particularly devastating for face processing (39). This also implies that brain plasticity is limited and that to a large extent face processing is experience-dependent. It is clear that both mechanisms feature-based and configuration-based identification play a role in face recognition. Prosopagnosics show a good recognition performance on external face features test but a poor performance on the internal features tests (40). Yet, external features on which prosopagnosics rely, like hairstyle or beard, or face-related properties like age are not robust for recognition. It has been argued that the differences between recognition of upright and inverted faces (41) (i.e. a general phenomenon which was introduced by Thompson (42) as "Thatcher effect") are mainly due to changes in the configuration of internal features. Prosopagnosics do not show this difference. Thus, despite the dominance of internal, configural information in face processing, prosopagnosics do rely on external, changeable aspects of faces for recognition and do not make use of internal, configural information (43, 44).

Lissauer (45) differentiated an apperceptive visual deficit and an associative visual deficit with impaired perceptual processing, respectively, and an associative visual deficit with impaired access to memory in the presence of intact perception. Using this classification some congenital prosopagnosics were addressed as apperceptive whereas others as associatively (31, 46, 47, 48).

It could be first shown by Bauer (49) that some prosopagnosics – despite the absence of conscious (overt) face recognition - have covert signs of individual face recognition. This can be measured by skin conductance response event related potentials (ERP), P300 evoked potential (50) or behaviourals measures such as covert "priming". When a semantic cue of the name of the individual face is provided prosopagnosics are better at learning to associate, e.g. a famous face with a correct name, than with an incorrect one (51, 52, 53).

Prosopagnosia was also suggested to be a symptom of Capgras syndrome (54, 55, 56) but there is

evidence that facial recognition impairment itself is not the underlying key factor and is unlikely to explain the Capgras syndrome (57). Njiokiktjien *et al.* (58) found obviously prosopagnosia in three otherwise high functioning boys who met the criteria of Asperger syndrome. In one boy perinatal asphyxia is reported whereas in the other two boys lack of traumatic events might be compatible with a congenital form of prosopagnosia, yet family data are not presented.

It is thought that prosopagnosia is rare and almost always acquired after traumatic events, encephalitis, cerebral stroke or atrophy of at least the right occipito-temporal region. Only a few reports dealt with an inborn form (27, 46, 59), the pathogenesis such as "developmental prosopagnosia" (5, 6, 31, 32, 60, 61, 62, 63, 64) and familial recurrences was only mentioned anecdotally in three families (60, 62, 65).

Recently, we could show that - in contrast to the rare acquired form – the congenital form is among the most common anomalies in humans with a prevalence of 2.5% and most amazingly that it runs in a regular autosomal dominant pattern (66). We therefore coined the term hereditary prosopagnosia (HPA) (40, 66, 67, OMIM 610382). This is not only true in the Caucasian population but also in other ethnicities (67). Here we present a largely extended collection of pedigree data either from subjects ascertained by a questionnaire based screening or by self report when learning from our topic by mass media.

3. MATERIAL AND METHODS

Subjects were recruited from two sources. Once by a systematic population based screening, the other by self report when being aware of this dysfunction by information about our project in press media, broadcasting and/or our homepage www.prosopagnosia.de. All the participants gave their written consent. The study was approved by the ethical committee of the University of Muenster, Germany, protocol No 3XKenn2, "Genotype/phenotype correlation of prosopagnosia (syn. *face blindness*)".

3.1. Questionnaire based population screening

A questionnaire was administered to students at our university to screen for those with suspected prosopagnosia. Initially a 4-page long-form was used in establishing the prevalence among pupils from local secondary schools and medical students from our university (66). Based on these experiences the number of questions was significantly reduced to just 15 and further simplified by using a 5-point rating scale (67).

3.2. Self reported subjects

There was a high interest by local, national and international mass media including a press release by the American Journal of Medical Genetics, June 2006. This gave rise to feedback by subjects who identified themselves to be prosopagnosics.

3.3 Semi-structured diagnostic interview

Diagnosis of prosopagnosia was made by a semi-structured interview of about 90 minutes. We first excluded other causes for degraded face recognition such as poor eyesight, or earlier brain damage (head injury, encephalitis/meningitis, cerebral anoxia/hypoxia, cerebral malformation). We asked for judgement of gender, attractiveness or emotional information in faces. We further asked for a history of psychiatric diseases which could be accompanied by agnosias, e.g. Asperger syndrome. In addition, we asked for other associated cognitive and behavioural deficits, such as sense of orientation, hints to object agnosias, differentiation of inter and intra class objects e.g., plants/tree species or animals/birds species; colour blindness, social skills, e.g. number of friends, eye contact.

We interviewed all available subjects individually. Additionally we asked the third-person perspectives of all family members.

3.4. Final diagnostic assessment

A list of diagnostic criteria which proved to be robust over the time was described recently (40, 66, 67). In short, after having excluded concomitant visual agnosias and (familial) psychiatric diseases, the following criteria were considered to be obligate:

(1) Uncertainty in face recognition: Not recognizing familiar people unexpectedly or in crowed places, confusing unknown persons with familiar persons. Only anecdotic mentioning of not recognizing people is not taken as a positive criterion.

(2) Prolonged recognition time for faces (meant in terms of a socially accepted span of time).

(3) Development of compensatory strategies as sign of a longstanding frequent problem: (i) adaptive behaviour: Prosopagnosics rely heavily upon other personal characteristics like voice, gait, clothing etc.. (ii) Avoidance behaviour: e.g. they do not go to places where they could meet other people unexpectedly, or they aim to be first to an appointment in a restaurant, or they have a habit of looking absent minded whenever they walk in the street.

(4) Surprising anecdotal stories: e.g. they should have typically problems in following the actors in a movie especially when the scenes change frequently or the characters are similar (e.g., mixing up different inspectors in detective/crime films).

(5) A family history of at least one affected first degree relative makes the diagnosis of hereditary prosopagnosia more likely.

3.5. Assessment of pedigree data

Every sibship was ascertained by only one proband. As soon as the diagnosis of prosopagnosia was established in the first subject we extended the study to all available family members. We did this in the same way by successive individual diagnostic interviews and also by asking everyone within the family for hints to other prosopagnosics.

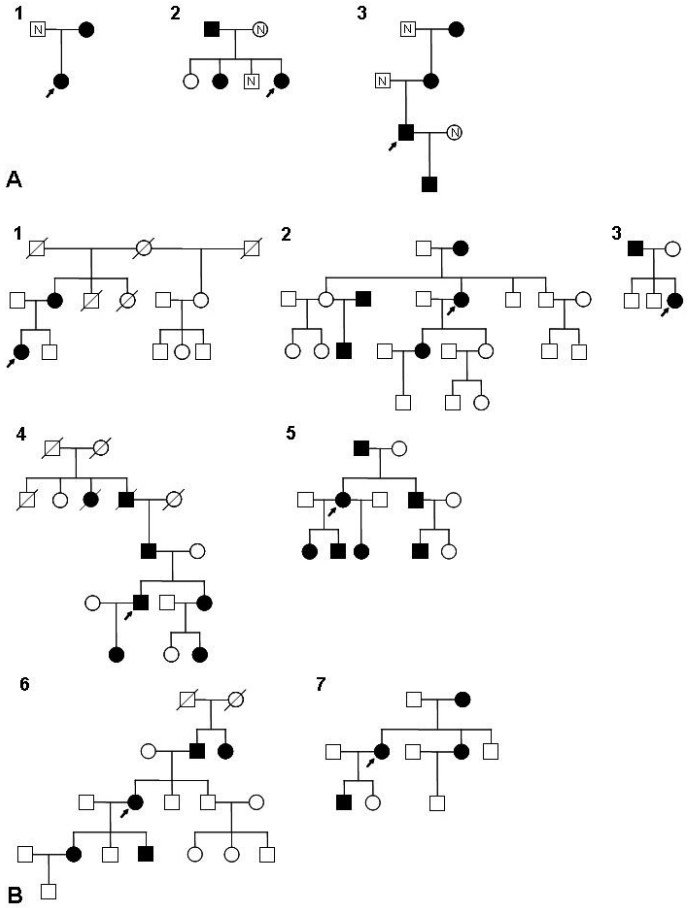

Figure 1. Pedigrees being fully compatible with autosomal dominant inheritance and complete penetrance. *Filled symbols* prosopagnosia, *arrow* indicates the index subject. A: Pedigree 1–3 are constructed by Kennerknecht *et al.* (66) from literature data (60, 62, 65). B: Pedigrees 1–7 are from a pilot study of us (40).

4. RESULTS AND DISCUSSION

4.1 Diagnostic considerations

The crucial point is the diagnostic assessment. As these criteria are mainly based on introspection a feedback to the validity of this procedure is given by in-depth testing of a sub-collection of eight prosopagnosics with (i) a battery of commonly used face tests (68), famous and family faces tests, learning tests for internal and external facial features (40), (ii) standardized test batteries, tailor-made experimental paradigms and clinical questionnaires in three of them (69), and (iii) by studies of gaze behaviour in four of these hereditary prosopagnosics from the same pool (70). These studies allowed to differentiate between the group of hereditary prosopagnosics and control participants. Eye tracking studies could further differentiate subjects with autism and schizophrenia and hereditary prosopagnosia, respectively. In contrast to autism and schizophrenics, prosopagnosics do not avoid looking at central features. Rather in addition they have a more dispersal gaze and also fixate external facial features. The data derived by these tests in favour of prosopagnosia are highly compatible with our semi-structural interview results. Moreover, we also had the intrafamilial controls with clearly distinct discrimination within a family. Further and best evidence we got from striking "qualitatively" differences including anecdotal stories and the presence/development of strategies which one will not find to that extent even in very "low functioning" normals. The clearly distinct phenotypes of prosopagnosics and controls in regard to the development of strategies and by the number of reported false negative and false positive recognition events is always surprising to those we could demonstrate this phenomenon for the first time.

Whether there is a phenotypic heterogeneity of the disorder still remains an open question. If so, it could be due to individual development of a more or less effective strategy and/or clinical distinct severity of symptoms and/or be in part due to varying methods of assessment. Yet, delineation of a putative phenotypic variability is not the aim of the present study as is in-depth testing for associated object agnosia. So far, with our approach we found no evidence for profound difficulties in object recognition. We further asked for mental images which were impaired in almost all prosopagnosics for objects and especially for faces.

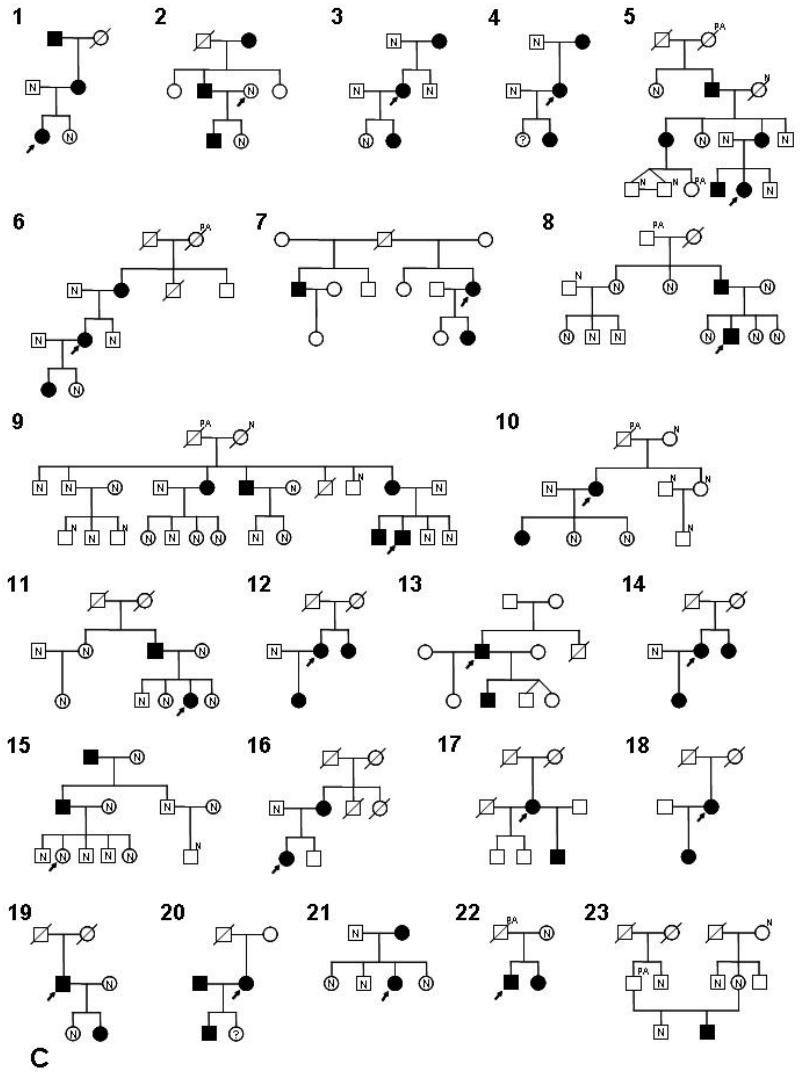

Figure 2. Hitherto unpublished pedigrees. *N* (= normal phenotype) within a symbol denotes a normal phenotype which was explicitly tested by one of us, whereas *N* and *PA* (= prosopagnosia) outside a symbol is based on plausible suggestions made by other family members. Empty symbols and no annotations denote subjects which could not be tested at all.

We also have a large family with cosegregation of prosopagnosia and a psychiatric disorder. This family was not included as we only selected - from a clinical point of view - monosymptomatic/non-syndromic prosopagnosics.

4.2. Empirical family data

Three pedigrees with familial recurrence were constructed by literature data (66). In all these cases familiarity was only mentioned anecdotally (Figure 1A 1 (60), 1A 2 (62), 1A 3 (65)). In a pilot study seven pedigrees were collected systematically (Figure 1B, (40)). In the present study another 27 families are evaluated (Figure 2, Figure 3). All together we have now data from 39 families with segregation of prosopagnosia in two to four generations.

As shown in Figure 1 the phenotype prosopagnosia segregates vertically with complete penetrance including male to male transmission which supports the concept of simple autosomal dominant inheritance. A first hint of reduced penetrance is given by Grueter *et al.* (40) (Figure 3A 1) obviously showing a normal female transmitter. Meanwhile we have found another three families with normal transmitters - still fitting the concept of autosomal dominant inheritance (Figure 3A). At present an estimate of the percentage of penetrance is not possible as data acquisition of three-generation families is still incomplete (Figure 1). Whether admixture of sporadic cases might be relevant remains an open question. Only in conditions with complete dominance the sporadic cases can easily be discovered because both parents are unaffected. In general, whenever we had the chance to test

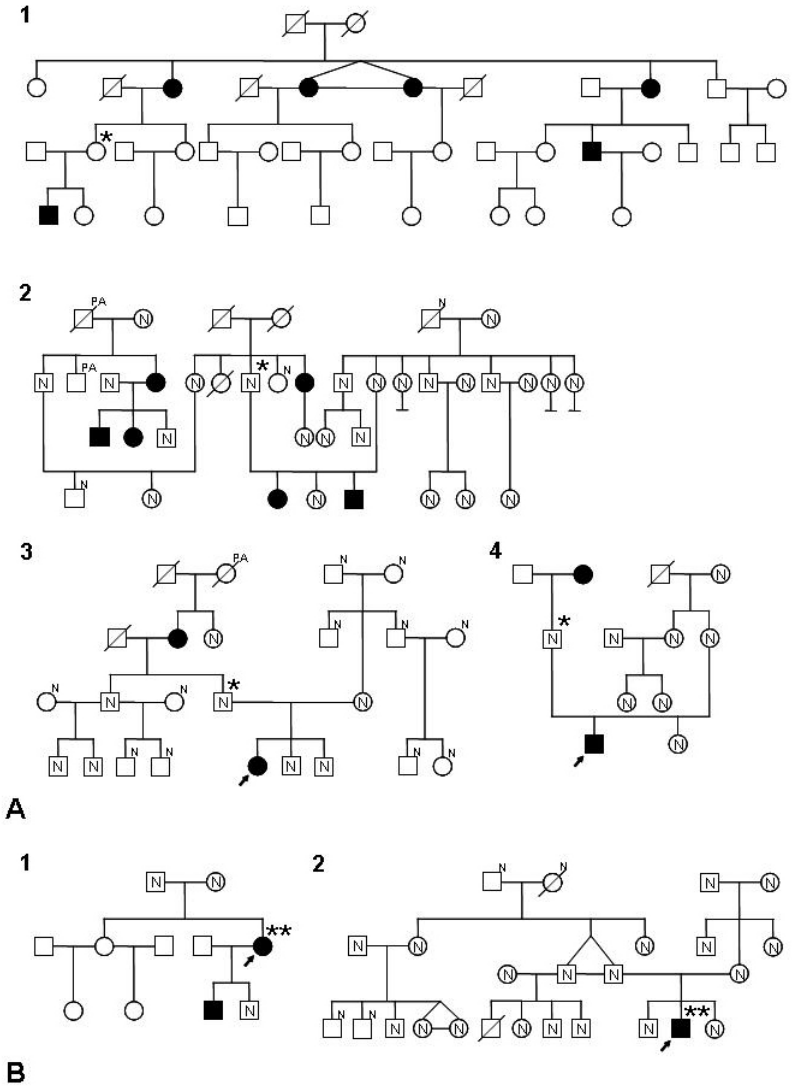

Figure 3. A: Pedigrees with reduced penetrance and B: with most probably new mutations for prosopagnosia. All pedigrees are still compatible with the concept of autosomal dominant inheritance. Pedigree A1 is derived from the pilot study by Grueter *et al.* (40) whereas all others are hitherto unpublished. For other symbols and abbreviations see Figure 1, * denotes a normal transmitter, ** suggestive of a new mutation. Pedigree B1: The index subject might have a new mutation. However, it cannot definitely be excluded that one of the parents might be a normal transmitter. In pedigree B2 a new mutation is very plausible as there are no hints to a traumatic event which might have lead to an acquired form of prosopagnosia.

the parents of an index subject one parent (and in one family both parents) was a prosopagnosic (Figure 2).

In family of Figure 3B 1 both parents of the index subject are unimpaired. As long as the grandparents are not studied by molecular genetics it remains unclear whether one (or both) of them are normal transmitters or whether the index subject has a de novo mutation. As his son is also prosopagnosic, hereditary prosopagnosia is most probably the underlying phenotype.

In family of Figure 3B 2 we have strong evidence for a sporadic or isolated case of congenital prosopagnosia. There is no history of any traumatic event during delivery or early childhood, and both parents and all grandparents are not prosopagnosics. Nevertheless, an acquired form of prosopagnosia cannot be excluded at the moment.

4.3 Genetic considerations

The segregation pattern of prosopagnosia as documented in Figures 1-3 is in consideration of a monogenic dysfunction best described by autosomal dominant inheritance with slightly reduced penetrance. Hence, one mutated gene should be enough for the manifestation of the phenotype. Incomplete penetrance in an otherwise autosomal dominant disorder does not allow to differ by formal genetic considerations whether a mutation is present in one of the parents (but did not

manifest itself) and the real sporadic cases with genotypically normal parents, i.e. new mutations. The high prevalence of prosopagnosia which is also found in other ethnicities (67) might point to a founder mutation. Yet, the most probably isolated familial case of prosopagnosia in pedigree of Figure 3B 2 is highly suggestive of a new mutation. As long as molecular genetic data are not available it remains open whether there are private mutations pointing to a high mutation rate and/or genetic heterogeneity with a variety of different genes leading to the same phenotype when mutated, respectively.

There are only a few monosymptomatic conditions related to cognitive functions and dysfunctions found in the OMIM database (http://www.ncbi.nlm.nih.gov/Omim/) with proven or suggested heredity. Only in the heterogeneous group of dyslexia and the language associated gene FOXP2 (71) regular cosegregation with the disorder is observed.

4.4 Conclusions

Face recognition and it´s counterpart prosopagnosia are peculiar in many ways. There is clear evidence that they are highly specific. A different psychological/physiological behaviour can be detected when facial and non-facial objects are presented. The complex network of visual processing from eye to brain is under genetic control. There should be many genes but as shown by familial segregation data one autosomal dominant gene mutation is enough to manifest the clinical phenotype of prosopagnosia. Future genetic dissection will show whether there is rather a founder effect or a high genetic heterogeneity (including private mutations) and whether other traits such as polygenic or multifactorial inheritance might also play a role in some families.

5. ACKNOWLEDGEMENTS

We would like to thank all subjects who participated in this study. The help of the index persons in recruiting other family members is highly appreciated. We also want to thank Rainer Stollhoff, Max Planck Institute for Mathematics in the Sciences, Leipzig for helpful comments.

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Abbreviations: PA prosopagnosia, HPA hereditary prosopagnosia

Key Words: Prosopagnosia, Face Blind, Congenital, Hereditary, Familial Recurrence, Monogenic, Autosomal Dominant, Incomplete Penetrance

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