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Investigation

Human genetics of face recognition: discovery of *MCTP2* mutations in humans with face blindness (congenital prosopagnosia)

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Face recognition is important for both visual and social cognition. While prosopagnosia or face blindness has been known for seven decades and face-specific neurons for half a century, the molecular genetic mechanism is not clear. Here we report results after 17 years of research with classic genetics and modern genomics. From a large family with 18 congenital prosopagnosia (CP) members with obvious difficulties in face recognition in daily life, we uncovered a fully cosegregating private mutation in the *MCTP2* gene which encodes a calcium binding transmembrane protein expressed in the brain. After screening through cohorts of 6589, we found more CPs and their families, allowing detection of more CP associated mutations in *MCTP2*. Face recognition differences were detected between 14 carriers with the frameshift mutation S80fs in *MCTP2* and 19 noncarrying volunteers. Six families including one with 10 members showed the S80fs-CP correlation. Functional magnetic resonance imaging found association of impaired recognition of individual faces by *MCTP2* mutant CPs with reduced repetition suppression to repeated facial identities in the right fusiform face area. Our results have revealed genetic predisposition of *MCTP2* mutations in CP, 76 years after the initial report of prosopagnosia and 47 years after the report of the first CP. This is the first time a gene required for a higher form of visual social cognition was found in humans.

Keywords: cognitive genetics; face recognition; genomics; human genetics; prosopagnosia

Introduction

Although human cognition is fascinating, molecular studies of human cognition are rare. Often, genes were first identified in animals before their studies in humans were undertaken. This approach limits the phenotypes to those present in animals, often lower animals because it is difficult to uncover genes by function in nonhuman primates. Thus, molecular research on cognition existing only in humans or those not present in lower animals lags far-behind simpler behaviors.

However, genetic studies of human diseases have been highly successful (Schrott *et al.* 1972; Gusella *et al.* 1983; Tsui *et al.* 1985). It is unnecessary to assume that human cognition is fundamentally different from diseases with regard to their amenability to genetic studies. Genetics provides a noninvasive approach to study human cognition. Over the last decade, we have carried out several genome-wide association studies (GWAS) of human cognition from memory, social conformity to perceptual switching and top-down control in visual cognition (Zhu *et al.* 2016, 2018, 2019; Zhu, Chen *et al.* 2021; Chen, Zhu, Na *et al.* 2018; Chen, Zhu, Wang *et al.* 2018). Although we found associated markers, we do not know whether the genes harboring or around the markers are causally linked. Genetically, linkage analyses in large families have succeeded in identifying genetic mutations in human diseases. We have undertaken this approach to investigate the molecular genetic basis of face recognition and results are presented here.

Face recognition, one of the most sophisticated forms of visual cognition, is essential for social cognition, usually but not always in higher species (Bruce and Young 1986; Grill-Spector and Malach 2004; Tsao and Livingstone 2008; Freiwald *et al.* 2016). Neurons responding specifically to the face have been discovered in the inferotemporal cortex (IT) (Gross *et al.* 1972; Desimone *et al.* 1984; Rolls 1984; Yamane *et al.* 1988) and the superior temporal sulcus (STS) (Bruce *et al.* 1981; Perrett *et al.* 1982, 1984, 1985, 1987; Rolls 1984, 1985; Baylis *et al.* 1985; Chitty *et al.* 1985; Saito *et al.* 1986) of monkeys for half a century. Electric stimulation in monkeys has functionally implicated neurons in face recognition (Afraz *et al.* 2006; Moeller *et al.* 2017). Face-specific responses in neurons have also been detected by event-related potentials (Allison *et al.* 1999; McCarthy *et al.* 1999; Puce *et al.* 1999) or direct electrophysiological

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recordings (Kreiman et al. 2000) in humans. Face specifically responding brain areas in the occipital and temporal lobes have been detected in humans with positron emission tomography (PET) (Sergent et al. 1992; Haxby et al. 1994) and functional magnetic resonance imaging (fMRI) (Malach et al. 1995; Clark et al. 1996; Puce et al. 1996; Kanwisher et al. 1997; McCarthy et al. 1997; Tsao et al. 2003, 2006, 2008; Liu et al. 2010; Barraclough and Perrett 2011; Dzhelyova et al. 2011). Results from transcranial magnetic stimulation are consistent with these regions being functionally important for face recognition (Polk et al. 2007; Pitcher et al. 2008, 2009).

Prosopagnosia, first reported by the German neurologist Joachim Bodamer (1947), is the deficit of face recognition, not due to lower-level visual or higher-level semantic problems. So far, nothing is known at the molecular level about prosopagnosia or face recognition.

Congenital prosopagnosia (CP), also known as developmental prosopagnosia or hereditary prosopagnosia (OMIM 610382), was first reported in 1976 (McConachie 1976) and is a selective impairment of visual learning and recognition of faces, in the absence of any detectable neurological injuries (McConachie 1976; Damasio et al. 1990; Nunn et al. 2001; Kress and Daum 2003; Behrmann and Avidan 2005; Duchaine and Nakayama 2006b; Gruter et al. 2008; Susilo and Duchaine 2013). Both a questionnaire-based screening method (Kennerknecht et al. 2006, 2007; Kennerknecht, Ho et al. 2008; Kennerknecht 2021) and behavioral tests (Bowles et al. 2009) have estimated the prevalence of CP at 1.8–2.9% in the general population, providing a global estimate of tens of millions of CP individuals (CPs). Familial studies (McConachie 1976; De Haan 1999; Galaburda and Duchaine 2003; Dobel et al. 2007; Duchaine et al. 2007; Grueter et al. 2007; Kennerknecht et al. 2006, 2007; Kennerknecht, Pluempe et al. 2008; Schmalzl et al. 2008; Lee et al. 2010; Johnen et al. 2014) and twin studies (Polk et al. 2007; McKone and Palermo 2010; Wilmer et al. 2010; Zhu et al. 2010) suggest that CP and face recognition abilities are highly heritable. In pedigree analysis, a simple autosomal dominant mode of inheritance has been observed (De Haan 1999; Kennerknecht et al. 2006; Duchaine et al. 2007; Grueter et al. 2007; Schmalzl et al. 2008; Lee et al. 2010), indicating that mutations in a single gene can lead to face recognition defects.

Beginning with a large pedigree including 18 members with obvious difficulties in face recognition in daily life, we have discovered a CP susceptibility gene encoding the multiple C2 domains transmembrane 2 protein (*MCTP2*, GenBank: NM_018349). Additional rare mutations in *MCTP2* and correlations were detected in people with face recognition problems in daily life. fMRI results indicate that impaired recognition of individual faces by CPs with the *MCTP2* mutations is associated with abnormal responses to repeated faces of the same identities in the right fusiform face area (rFFA). Our discovery may stimulate further research using genetics and genomics to study higher cognition in humans.

Materials and methods

Subjects details

This study has been approved by the Committee for Protecting Human and Animal Subjects at Peking University. Written informed consent to participate in the research study and to have the results of this research work published was obtained from participants or their legal representatives prior to any tests. Genomic DNA was isolated from whole blood [BD Vacutainer 3.2% Sodium Citrate (1:9)] using the Gentra Puregene Blood Kit (QIAGEN) or saliva using the GeneFiX DNA Saliva Collector and Isolation Kit.

Family A

The proband V:11 in family A (Fig. 1a, Table 1) was ascertained by self-referring. Thirty-five available family individuals (18 CPs, including 9 males and 9 females, aged from 16 to 72; 17 non-CPs, including 9 males and 8 females, aged from 15 to 78) were assessed based on a standardized semi-structured interview (Kennerknecht et al. 2006; Carbon et al. 2007; Grueter et al. 2007; Kennerknecht 2021). Twenty-five family members younger than 60 years of age were tested with the Cambridge Face Memory Test-Chinese (CFMT-C) (Bowles et al. 2009; McKone et al. 2012), the matched Cambridge Car Memory Test (CCMT) (Dennett et al. 2012), and the Face Inversion Effect (FIE) Discrimination Test (Yovel and Kanwisher 2005). Thirty-four individuals (not including VI:9, who contacted us voluntarily after we had finished genotyping) were included in the linkage study. Nine individuals (V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19, and VI:8) were selected for whole-genome sequencing (WGS). This information is listed in Supplementary Table 1. None of the persons showed signs of an autism spectrum disorder or neurodegenerative disorders.

Additional CP individuals with mutations in MCTP2 *screened from the first cohort of 2,904 individuals*

To investigate more CP individuals and examine whether rare functional mutations in *MCTP2* are present in more CPs, the first cohort of 2,904 individuals (average age of 19.25 ± 1.30, 2,161 females, 743 males, Jiangxi province) from the Westlake BioBank for Chinese (WBBC) pilot project (Zhu, Liu et al. 2021; Cong, Bai et al. 2022; Cong, Khederzadeh et al. 2022), were screened with a questionnaire adapted from the 20-item self-report measure (see CP Questionnaire in Methods details) for quantifying CP traits. Seventy-eight individuals scored worse than the mean by 2 SDs (Fig. 2a). Seventy-five of them provided DNA samples. Forty-four individuals including seven individuals with *MCTP2* mutations agreed to an interview for CP diagnosis and family members were contacted for availability for further studies.

Gene-based association analysis in the second cohort of 1,928 individuals

The second cohort of 1,928 individuals (average age of 18.51 ± 0.93, 1,085 females, 843 males, Jiangxi province) used in the gene-based association of the rare functional alleles in *MCTP2* with face recognition ability were also from the WBBC project (Zhu, Liu et al. 2021; Cong, Bai et al. 2022; Cong, Khederzadeh et al. 2022). The coding sequences of the *MCTP2* gene for each person were analyzed by tagged-amplicon deep sequencing.

Individuals with the c.239delG (p.S80fs) mutation in MCTP2 *screened from a third cohort of 1,757 individuals*

A third cohort of 1,757 individuals (average age of 19.13 ± 1.07, 1,295 females, 462 males, Guangdong province) were sequenced for the presence of the c.239delG (p.S80fs) mutation in the exons of *MCTP2*. The coding sequences of the *MCTP2* gene for each person were analyzed by tagged-amplicon deep sequencing. For individuals carrying p.S80fs, their family members were further contacted to test for the S80fs mutation by direct Sanger sequencing and assessed by the standardized semi-structured interview. The differences in the behavior of daily face recognition between the 14 carriers and 19 noncarrying volunteers from the same cohort were analyzed by independent sample t-test.

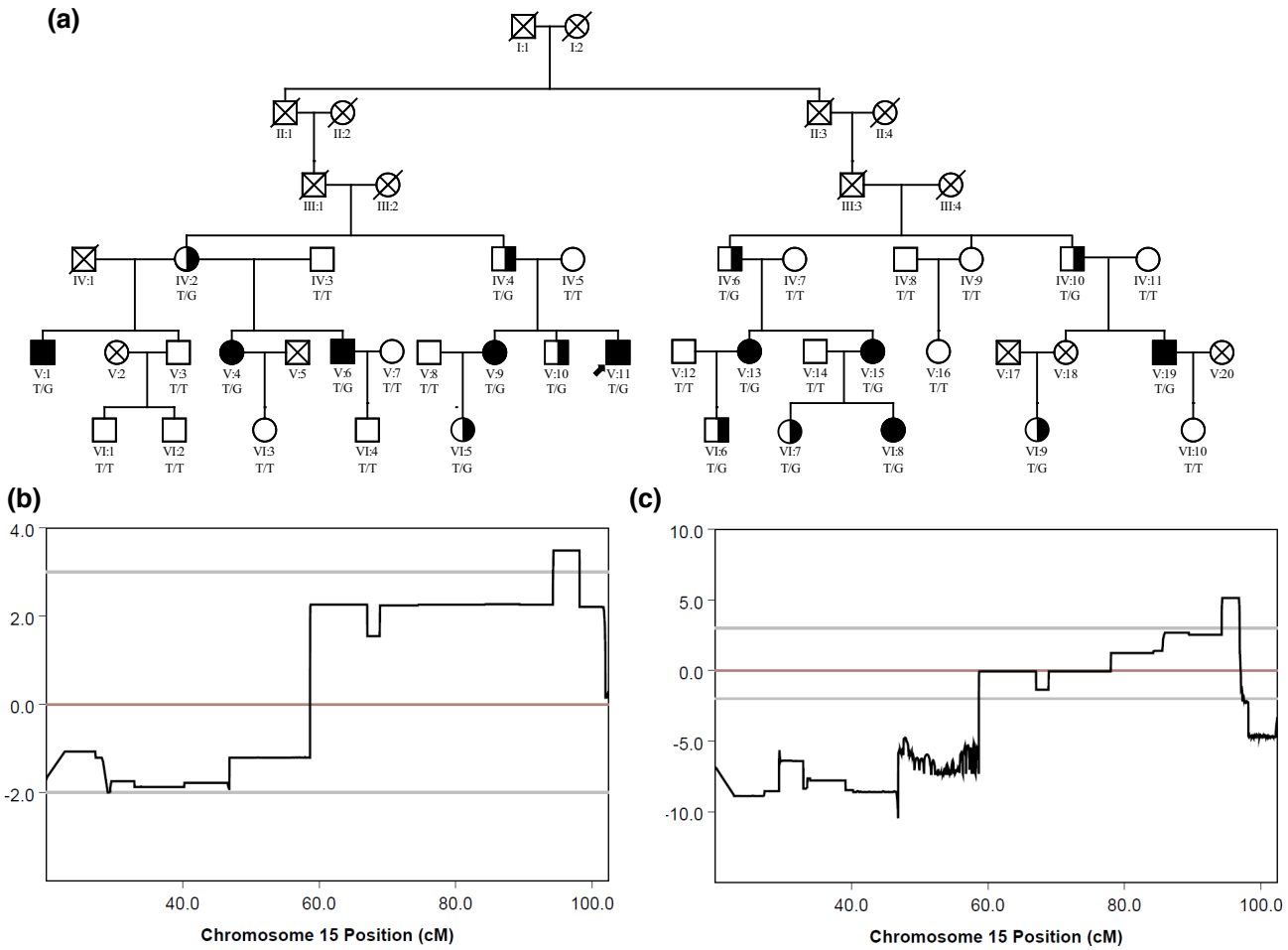

Fig. 1. Mapping of a novel autosomal dominant CP locus to the short arm of chromosome 15 (15q26). a) The pedigree plot of family A with genotypes for c.2147T > G (p.I716S), GenBank: NM_018349 and phenotypes. Crosses, DNA samples not available; diagonal slashes, dead members; filled symbols, family members poor on both interviews and the behavioral CFMT test; half-filled symbols, family members who had daily face recognition problems but appeared normal on CFMT or founders with daily face recognition problems; an arrow head, the index of family A. b) Graphical representation of parametric linkage results of linkage 1 on chr15 (LOD score = 3.49) in family A with diagnosis based only on interviews as well as the CFMT behavioral test, assuming a rare dominant model. c) Graphical representation of parametric linkage results of linkage 2 on chr15 (LOD score = 5.13) in family A with diagnosis based on interviews not behavioral tests, assuming a rare dominant model.

Control samples for behavioral tests

Three hundred and thirty-eight normal participants (average age of 42.68 ± 16.53, 164 females, 174 males, Beijing) were tested. These participants were unrelated. Participants were not selected for face recognition ability with no known history of major brain injury, or other major disorders likely to affect face recognition (e.g. Alzheimer's disease), representing a random sample of the community. They were tested on a battery of tests including the CFMT-C, the CCMT, the FIE Test, and the Cambridge Face Perception Test-Chinese (CFPT-C).

fMRI subjects

Age-related dedifferentiation and compensatory changes in the functional network underlying face processing have been found in studies (Le Grand *et al.* 2006; Goh *et al.* 2010; Germine *et al.* 2011; Lee *et al.* 2011; Park *et al.* 2012; Burianova *et al.* 2013; Zebrowitz *et al.* 2016). Therefore, in order to exclude age influence on fMRI results, we mainly studied family members younger than 30 years old. Family members who participated in the fMRI experiment were on a voluntary basis. In family A, three *MCTP2* mutant CP individuals (VI:5, VI:7, and VI:9) and three nonmutant and non-CP individuals (VI:1, VI:2, and VI:10) took part in fMRI; in family 3-2, III:4 (CP, with S80fs) and III:2 (non-CP, without S80fs) took part in fMRI.

Twenty-one non-CP students (average age = 23.63 ± 3.71, 6 females, 15 males) were recruited for fMRI analysis.

CP referred to those with obvious face recognition problems in daily life diagnosed by the structured interview.

All participants reported normal or corrected to normal vision, no history of neurological or psychiatric conditions and all were right-handed. Anatomical volumes (i.e. structural MRIs) had been routinely checked. One of the normal students was excluded from neuroimaging studies because the maximum head rotation was over 1.5 degree or the maximum translation was over 2 mm during localization.

We adopted the methods of studying single-cases that the severity of each individual could be reported by comparison with the control population (Hadjikhani and de Gelder 2002; Schiltz *et al.* 2006; Bentin *et al.* 2007; Dricot *et al.* 2008; Righart *et al.* 2010; Busigny and Rossion 2010; Rossion *et al.* 2011; Gao *et al.* 2019). In fMRI analysis, each family member was compared individually to a small sample of normal controls by a modified t-test (Crawford and Howell 1998; Crawford and Garthwaite 2002; Crawford *et al.* 2010).

Table 1. Diagnosis of CP in family A.

	Key Manifestations								Facultative symptoms		Memory		Discrimination	
Family Member	Lasting and irritating subjective uncertainty of face recognition	Face recognition deficit especially in crowded places or out-of-context encounters	False negative and false positive face recognition events	Face recognition time longer than socially accepted	Face learning time longer than socially accepted	Development of adaptive behavior	Use of explicit learning strategies for visual person recognition	First Time to Realize*	Affected first degree relatives	Images of close friends' faces	Gaze contact necessary in conversation	CFMT	CCMT	FIE	Upright
IV:2 F72	often mistaking people, cannot recognize her son with changed hairstyles			taking longer time to recognize people than others, as described by her children		depending on nonfacial clues		in childhood	yes	blur face	yes	-	-	-	-
IV:3 M78	no			no		no		-	yes	clear face	yes	-	-	-	-
IV:4 M67a	cannot recognize someone whom he is obviously expected to know, hard to recognize people in their uniforms, hard to recognize actress in a movie, making out his son on the photos by looking over and over again			Could not recognize the whole class after a semester when he was a student		depending on separated facial and nonfacial features		in childhood	yes	blur face	yes	-	-	-	-
IV:5 F62	no			no		no		-	yes	clear face	yes	-	-	-	-
IV:6 M67b	greeting to others only after getting responses or hints from others, needing the plots and the expressions on actors' faces to follow the movie, hard to recognize people with changed hairstyle, cannot recognize relatives in their uniforms			glimpsing others over and over again		depending on separated facial characters and voice		after contacted	yes	blur face	no	-	-	-	-
IV:7 F66	no			no		no		-	yes	clear face	yes	-	-	-	-
IV:8 M70	no			no		no		-	no	clear face	yes	-	-	-	-
IV:9 F65	no			no		no		-	yes	clear face	yes	-	-	-	-
IV:10 M61	"voices are more important for recognizing people compared to faces, since faces could be very similar while voices would never be"			hard to follow actors through a movie		combining with voice and gait		not realize by himself	yes	whole body and action	no	-	-	-	-
IV:11 F61	no			no		no		-	yes	clear face	yes	-	-	-	-
V:1 M51	cannot recognize people with changed age, following the characters in films by plots not by faces			needing several steps to recognize people, from top to bottom		After conformation, the face he referred to and depended on was the contour profile of a face or the shape of cheeks and a head. combining with voice, hairstyle, stature, gesture, recognizing waitresses by work cards		not realize by himself	yes	body and wearings	deliberately need	−2.06	−0.11	−1.33	−2.96

(continued)

Table 1. (continued)

	Key Manifestations								Facultative symptoms		Memory		Discrimination	
Family Member	Lasting and irritating subjective uncertainty of face recognition	Face recognition deficit especially in crowded places or out-of-context encounters	False negative and false positive face recognition events	Face recognition time longer than socially accepted	Face learning time longer than socially accepted	Development of adaptive behavior	Use of explicit learning strategies for visual person recognition	First Time to Realize*	Affected first degree relatives	Images of close friends' faces	Gaze contact necessary in conversation	CFMT	CCMT	FIE	Upright
V:3 M49	no			no		no		-	yes	clear face	yes	−0.98	0.67	−0.05	0.94
V:4 F40	cannot recognize people with changed hairstyle or out of context			should pay special attention to people to recognize them		depending on separated facial and nonfacial features		after contacted	yes	blur face	no	−1.60	0.56	−1.41	−0.94
V:6 M36	seldom using face, needing others' feedback before greeting to others			needing some time to make a decision		depending on contour, stature and talking		after contacted	yes	local face	no	−1.61	0.35	−1.62	0.11
V:7 F39	-			-		-		-	-	clear face	yes	−0.25	0.63	0.48	0.45
V:8 M41	no			no		no		-	yes	clear face	yes	−0.16	1.90	−0.35	1.33
V:9 F42a	hard to distinguish faces, do not know where to look to recognize people, cannot recognize someone whom she is obviously expected to know, cannot recognize people in their uniforms, having to remind people that she is bad with recognizing faces			taking longer time to recognize people than others by glimpsing at the person over and over again or keeping recalling things related to the person		depending on face shape, expression in one's eyes and status		in middle school	yes	only facial expression	yes	−2.67	−0.09	−1.62	−0.34
V:10 M40	following the characters in films by plots and bodies not by faces, cannot recognize relatives on old photos			taking longer time to recognize people than others		depending on face shape, head shape, contour, expression in one's eyes, and shape of organs on the face		at university	yes	contour	deliberately need	−0.06	0.40	2.90	1.31
V:11 M37	cannot recognize someone whom he is obviously expected to know, hard to recognize people in a static state, hard to recognize actress in a movie			taking longer time to recognize people than others		depending on status, manner, gait, clothes, hairstyle; greeting first to others no matter who is, classifying people by different features		in middle school	yes	blur face	deliberately need	−2.09	0.37	−2.56	−0.71
V:12 M43	no			no		no		-	yes	clear face	yes	−1.11	−0.91	0.06	0.25
V:13 F43	often cannot recognize people at that time, recalling them later by thinking slowly, hard to recognize people in their uniforms, sometimes mistaking relatives			difficult to learn and memorize new faces, recognizing others after greeted		body and face contour are important, asking others to confirm the identity of roles when seeing a film		not realize by herself	yes	whole body	no	−3.27	0.06	−0.51	−1.73
V:14 M44	-			-		-		-	yes	clear face	yes	1.13	0.46	−0.40	0.26
V:15 F42b	cannot recognize people in their uniforms, hard to follow actors through a movie			taking longer time to recognize people than others by staring at faces		depending on separated facial and nonfacial features		from the age of 30	yes	blur face	yes	−2.03	−0.74	−0.65	−1.55

(continued)

Table 1. (continued)

	Key Manifestations								Facultative symptoms		Memory		Discrimination	
Family Member	Lasting and irritating subjective uncertainty of face recognition	Face recognition deficit especially in crowded places or out-of-context encounters	False negative and false positive face recognition events	Face recognition time longer than socially accepted	Face learning time longer than socially accepted	Development of adaptive behavior	Use of explicit learning strategies for visual person recognition	First Time to Realize*	Affected first degree relatives	Images of close friends' faces	Gaze contact necessary in conversation	CFMT	CCMT	FIE	Upright
V:16 F38	no			no		no		-	no	clear face	yes	−0.52	−0.82	−0.27	−0.70
V:19 M39	having difficulties in recognizing his daughter in school uniforms, hard to recognize people in crowded places			taking face shapes as faces, so thinking normal in recognizing and learning faces		depending heavily on the face contours		not realize by himself	yes	blur face	yes	−2.79	−0.55	−1.15	−1.52
VI:1 M23	no			no		no		-	no	clear face	yes	−0.13	0.72	0.30	−0.14
VI:2 M22	no			no		no		-	no	clear face	yes	0.84	0.17	−0.58	1.25
VI:3 F19a	no			no		no		-	yes	clear face	yes	0.48	−0.66	1.16	0.35
VI:4 M15	-			-		-		-	yes	clear face	yes	0.71	−0.89	0.24	−0.01
VI:5 F19b	cannot recognize someone whom she is obviously expected to know, even her parents; never greeting to others first due to poor face recognition			taking longer time to recognize people than her classmates		depending on separated facial and nonfacial features		in middle school	yes	what she images is not the same as she sees, "a kind of feeling"	no	−1.37	−0.39	−1.81	−0.50
VI:6 M20	"hair has great impact on me." depending on the plots to recognize characters in a film, cannot recognize himself on old photos			taking longer time to recognize people than his classmates		depending on hairstyle, face shape		at university	yes	face contour	yes	−0.56	0.41	−0.36	−0.48
VI:7 F21a	cannot recognize people (not sure) with changed hairstyle, out of usual context			-		depending on expression in one's eyes		not realize by herself	yes	blur face	deliberately need	1.26	1.31	1.48	0.95
VI:8 F16	people often comment on failure to recognize them, hard to follow movies because of difficulties in recognizing characters, hard to remember new faces, easily forgetting new faces, mistake strangers as acquaintances			difficult to decide immediately whether she knows a face, take longer time to recognize or remember people than others		ask others to confirm the identity, staring at people for a while to recognize, depending on face shape, special features and clothing		after contacted	yes	no face	yes	−2.05	−0.05	0.05	−1.40
VI:9 F21b	cannot recognize someone whom she is obviously expected to know, cannot recognize people in their uniforms, the face in her brain is not the same as she is looking at			taking longer time to recognize people than her friends		to remember people by looking at their photos repeatedly, depending on features		in middle school	unknown	what she images is not the same as she sees, "a kind of feeling"	deliberately need	1.01	2.52	−0.71	0.67
VI:10 F18	-			-		-		-	yes	clear face	yes	−0.53	−0.86	0.07	0.89

F = female, M = male, numbers after F or M indicate age. Small letters indicate different members. Face processing Z scores for members younger than 60 years of age in Family A are coded as described in the method such that negative values indicate performances poorer than the mean.

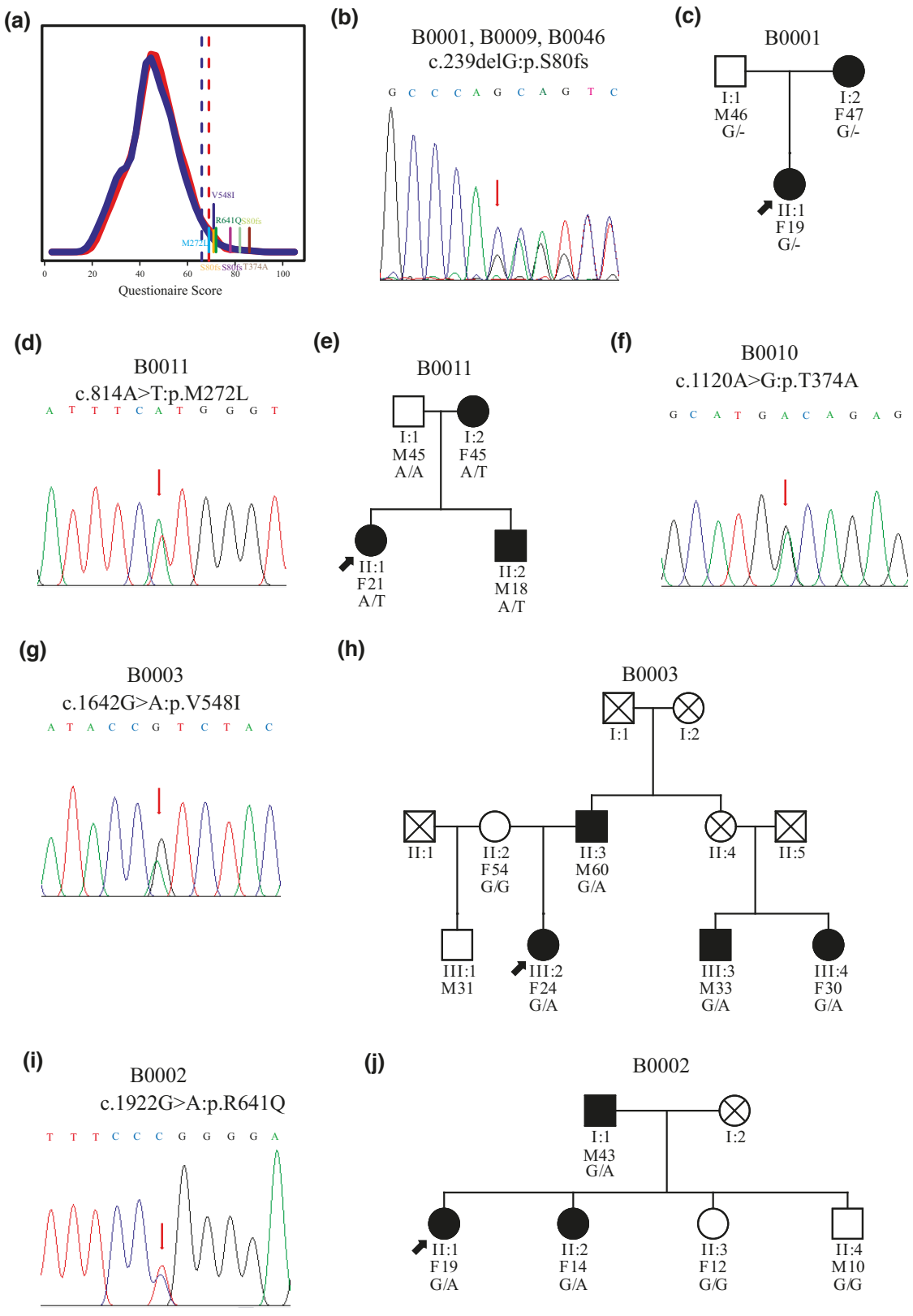

Fig. 2. Mutations detection in *MCTP2* and co-segregation in CP. a) The distribution of the 20-item questionnaire scores in 743 males (the blue approximate normal curve) and 2161 females (the red approximate normal curve). Dashed lines indicate the cut-off of 2 SDs poorer than the mean. Sticks with different colors indicate different individuals with different mutations. b) A mutation c.239delG, leading to p.S80fs in individuals B0001, B0009, B0046 with CP. All three of them were aware of difficulties with face recognition early in their life (Supplementary Table 2). c) Correlation of the (c.239delG, p.S80fs) genotype with the CP phenotype in the family of B0001, with three members tested. d) A mutation c.814A > T, leading to p. M272L in individual B0011. e) Correlation of the genotype (c.814A > T [p.M272L]) with the CP phenotype in the family of B0011. f) A mutation c.1120A > G, leading to p.T374A in individual B0010. g) A mutation c.1642G > A, leading to p.V548I in individual B0003. h) Correlation of the (c.1642G > A [p.V548I]) genotype with the CP phenotype in the family of B0003, with 6 members tested (Supplementary Table 2). i) A mutation c.1922G > A, leading to p.R641Q in individual B0002. j) Correlation of the (c.1922G > A [p.R641Q]) genotype with the CP phenotype in the family of B0002, with 5 members tested (Supplementary Table 2).

Methods details

Structured interview for CP diagnosis

The diagnosis of CP was based on a standardized semi-structured interview (Tables 1, Supplementary 2 and 3) (Kennerknecht *et al.* 2006; Grueter *et al.* 2007; Gruter *et al.* 2008), which documented a variety of impressive qualitative differences between CP and non-CP, and had been validated with objective face recognition tests in previous studies (Carbon *et al.* 2007; Grueter *et al.* 2007). These criteria were employed in recent literature on CP (Kennerknecht, Pluempe *et al.* 2008; von Kriegstein *et al.* 2008; Gruter *et al.* 2009; Carbon *et al.* 2010; Stollhoff *et al.* 2010, 2011; Dinkelacker *et al.* 2011; Bate *et al.* 2014, 2019; Verfaillie *et al.* 2014; Esins *et al.* 2015, 2016; Zhao *et al.* 2016, 2018).

The interviewer asked questions in a semi-structured interview format with three or four questions about each diagnostic item. Interviews were held to embed the questions into conversations and questions about the same diagnostic items not asked sequentially. Interviews included a medical history in order to exclude conditions which might cause or mimic prosopagnosia. Affected people present a lack of confidence with face recognition. Symptoms include lasting and irritating subjective uncertainties of face recognition, failure to recognize familiar people out of context or in crowded places, overlooking familiar people and confusing strangers with familiar people, face recognition/learning time longer than socially accepted, development of adaptive behavior of critical situations and strategies for visual recognition of people, and time of onset.

Consistent with the interview results, some individuals were aware of their CP before we contacted them. Some individuals who identify people via nonfacial features such as voice, gait and general appearance and manner, or were unaware of face recognition problems, but had developed obvious compensatory strategies to cope with difficulties were also diagnosed as CPs.

CP questionnaire

To effectively screen CP candidates from big samples, we adapted a Chinese 20-item version from the 20-item self-report measure for quantifying prosopagnosic traits (Shah *et al.* 2015), which asks about tangible experiences. This 20-item Questionnaire was included in a set of questionnaires for many research purposes and filled out by two cohorts of individuals online. Invalid questionnaires were dropped due to no distinction between forward and reverse questions. In total, 2,904 valid questionnaires for the first cohort and 1,928 valid questionnaires for the second cohort were collected. The internal reliability measured by Cronbach's α was 0.828 and 0.902, respectively. In the first cohort, 343 individuals finished the questionnaire for a second time several weeks later and the correlation for the first and second results across each individual was very high by Pearson correlation coefficient analysis, $r = 0.081$, $P < 0.001$. There was a significant difference of the score distribution between the female and male participants ($P < 0.001$, two-tailed t-test), so the candidate CPs were screened and the gene-based association study were carried with different genders respectively. An individual with a score above 2 SDs of the mean of the controls was defined as a CP candidate.

Stimuli and procedures of behavioral tests

All behavioral tests were adapted and integrated into a whole set using the Hyper Text Markup Language. All participants were tested individually. The tests were run on a desktop PC with screen resolution $1,024 \times 768$, refresh rate 85 Hz. Participants were seated at a viewing distance of approximately 50 cm from the screen. All participants were tested wearing their usual optical correction. Participants were asked to confirm that they could focus without seeing blur on the computer screen. No participant reported any difficulty with focus at these distances. Gray-scale adult Chinese faces were used.

Cambridge face memory test-Chinese. The Chinese face version of CFMT (McKone *et al.* 2012) was kindly provided by Professor Jia Liu of Beijing Normal University which we integrated with other behavioral tests into a whole set, and performed according to the standard procedure including the practice phase, the "Learn" phase with 18 trials, the "Novel Images" phase with 30 trials and the final "Novel Images with Noise" with 24 trials. All faces were Chinese male, shown without hair or facial blemishes and with neutral expressions. Participants were instructed to press the key corresponding to the number 1, 2, and 3 below faces. The test includes a total of 72 trials. Scores were reported as percent correct across the full test.

Cambridge car memory test. The CCMT is a test similar in the experimental design as CFMT, with stimuli replaced by whole cars (Dennett *et al.* 2012). We used the CCMT as a control of the CFMT to test for potential general object recognition deficits and to quantify the individual ability of performing such kind of tests. The original version of CCMT was kindly provided by Professor Bradley Duchaine of Dartmouth College, USA, which we integrated with other behavioral tests into a whole set, and performed according to the standard procedure (Dennett *et al.* 2012)

Cambridge face perception test-Chinese. We developed a version of CFPT using Chinese faces as stimuli (CFPT-C), according to the standard procedure (Duchaine *et al.* 2007) by morphing six different individuals with the target face, containing 88%, 76%, 64%, 52%, 40%, and 28% of the target face in turn. The Chinese faces were male, shown without hair or facial blemishes and with neutral expressions. All faces were photographs of Chinese students at Peking University, with written consent forms collected before photographing. Each individual was photographed in the same range of views and lighting conditions. Eight upright and eight inverted trials were intermixed, with the upright trial occurring first half the time. Participants had one minute to arrange six morphed faces according to their similarity to a target face by clicking on a face and indicating where that face should be moved by clicking in the area between two faces. Scores were computed according to the previous paper (Duchaine *et al.* 2007). The internal reliability measured by Cronbach's α in our sample of 170 individuals was 0.705 for upright faces, and 0.483 for inverted faces. However, after our pilot study, the CFPT-C was excluded from further study, because strategies such as just comparing partial facial features were used in normal people as in CPs and inconsistent results were reported by others (Anstey *et al.* 2005; Duchaine *et al.* 2007; Bowles *et al.* 2009).

Face inversion effect discrimination test. The stimuli consisted of 20 gray-scale individual face images, cropped using the same 4×4.5 cm oval window (4.6°×5.2° of visual angle) to remove cues from the hairline and face contour. All faces were photographs of Chinese students at Peking University, with written consent forms collected before photographing. Photographs were not repeatedly used in different tests. Pairs of face stimuli were presented sequentially either upright or inverted in a randomized order. The first face stimulus was presented in the upper-left quadrant of the screen for 0.5 s. After an interstimulus interval of 0.5 s, the second stimulus was presented in the lower-right

quadrant for 0.5 s. The next trial will not begin until a same or different response was made by pressing one of two keys to respond by the participant. Eighty trials were conducted in this test, half of them with upright faces and half with inverted faces. In each condition (upright or inverted), the chance with the two identical faces was 50%. A few practice trials were presented before the beginning of the experiment. Scores were reported as percent correct for each condition. For the measure of the FIE, the difference in performance level between upright and inverted faces, an FIE index was calculated by entering the correction of performance for upright and for inverted faces in the following formula: FIE = (upright – inverted)/(upright + inverted).

Data analysis for behavioral tests. Due to possible effects of ageing and sex difference on the scores of the CFMT-C, CCMT, upright faces and inverted faces in the FIE and the FIE index, we used multiple stepwise regression analyses to identify the covariates (sex, age) specific to each trait from 338 participants (aged 15–83 years, 164 females, 174 males). The results of the CFMT-C and the CCMT showed noticeable age-related decline and sex differences (Supplementary Fig. 1). The scores of upright faces and inverted faces in the FIE correlated with ageing but not sex (Supplementary Fig. 2), while the FIE index was not affected by age or sex among the control samples.

Examining function curves suggested that the behavior performance remained stable across early middle age, but began to decline noticeably at approximately 50 years of age. This is consistent with previous studies. In terms of the validity of the behavioral scores, only individuals with ages under 60 (average age = 36.51 ± 12.34, 130 females, 138 males) were included to calculate the best estimate of CP cut-offs.

We used the fit-and-residual procedure to calculate the standard residual of each participant (Z score) for CP family members as described previously (Bowles *et al.* 2009). The regression function describing the relationship between age, sex, and CFMT was: CFMT score = –0.212 age + 6.188 sex + 73.724. The standard deviation (SD) of the controls' residuals of CFMT score was 11.189. The regression function for CCMT was: CCMT score = –0.134 age – 2.968 sex + 69.444, and SD was 10.252. The regression function for upright faces was: Upright score = –0.170 age + 87.641, and SD was 8.862. Z score was calculated by dividing the participant's residual by the SD of the controls' residuals.

For the FIE index, there was no correlation with age or sex. Normalized Z score was calculated for each subject by subtracting the mean of the control sample and dividing by the control samples' SD.

Genetic analyses

Genome-wide genotyping for linkage analysis

DNA samples were genotyped using Infinium Human OmniZhongHua BeadChips (Illumina), and normalized bead intensity data obtained for each sample were converted into SNP genotypes using Genome Studio. SNPs were then selected according to the following parameters: genotyping rate >95%, minor allelic frequency >1% and no significant deviation from Hardy–Weinberg proportions ($P > 0.001$) by PLINK software (Purcell *et al.* 2007). Gender corresponding to each DNA sample was checked by analysis of X chromosome heterozygosity using PLINK. The initial Mendelian inheritance in family A was analyzed by PLINK and KING toolset (Manichaikul *et al.* 2010).

Data analysis for linkage study

For the preliminary linkage analysis in Family A (named linkage 1) (Supplementary Table 1), we diagnosed nine family members as CP cases (V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19, and VI:8) with the criteria of not only abnormality in face recognition exhibited through interviews, but also poor with the CFMT behavior test (under –1.5 SDs). 11 family members with normal daily face recognition by interview and Z scores of all the behavior tests over –1.5 SDs were taken as normal controls (V:3, V:7, V:8, V:12, V:14, V:16, VI:1, VI:2, VI:3, VI:4, and VI:10). The remaining subjects in the pedigree were set as unknown at this stage of analysis, including those over 60 and not suitable for behavioral tests.

We did a second linkage analysis (linkage 2) after adding four individuals who had daily face recognition problems but appeared normal on behavioral tests (V:10, VI:5, VI:6, and VI:7) and four founders with daily face recognition problems (IV:2, IV:4, IV:6, and IV:10) as CPs (Supplementary Table 1), and the remaining six founders without daily face recognition problems (IV:3, IV:5, IV:7, IV:8, IV:9, and IV:11) as controls. They were set as unclear in the linkage analysis analyzed above (linkage 1).

Parametric linkage analysis was performed with the Merlin programs (Abecasis *et al.* 2002), assuming autosomal dominant inheritance with 100% penetrance, disease allele frequency 0.001, and phenocopy rate 0.05. Because the presence of linkage disequilibrium (LD) might inflate linkage statistics, LD maps were constructed with the PLINK tool within family members with the LD thresholds ($r^2 < 0.5$). Following data QC, 177,126 ($r^2 < 0.5$) informative SNPs were selected for linkage analysis with Merlin (Abecasis *et al.* 2002). 1,000 simulation analyses were performed to exclude false positive results due to random chances under the null hypothesis of no linkage, with simulated data, while maintaining the pedigree structure, allele frequencies, and recombination fraction. For positive regions, haplotypes were constructed and subsequently checked manually on the basis of the minimal number of recombination.

Generation of copy number variations calls

Copy number variations (CNVs) were identified for each member. Genotyping and signal intensity data were exported from the GenomeStudio software 2011.1 (San Diego, CA, USA). The subsequent CNV calling analyses were performed using PennCNV (v.2011 Jun16) (Wang *et al.* 2007) according to the manual. No correlation was detected between the CNV genotypes and the phenotypes for each linkage analysis.

Whole-genome sequencing

WGS was performed by the Next-Generation Sequencing Center of Biomedical Pioneering Innovation Center, PKU. Sequencing libraries were built with NEBNext Ultra DNA Library Prep Kit for Illumina. 150 bp paired-end sequencing was done on Illumina HiSeq 4000.

Data analysis for WGS

FastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) was applied to perform quality checks on various aspects of sequencing quality. Low-quality bases were removed by Trimmomatic software (Bolger *et al.* 2014) with the parameters HEADCROP:5, LEADING:25, TRAILING:25, SLIDINGWINDOW:4:15 MINLEN:35. After that, clean sequences were aligned to human genome build hg19 and SNPs, INDELs or structural variants were called by SPEEDSEQ (Chiang *et al.* 2015). BAM files locally realigned around INDELs were used to determine the average coverage, using

GATK DepthOfCoverage package and default settings (McKenna et al. 2010). After the alignment and variant calling, the mean depth of all samples was 34, and 96% of the mapped bases were covered at more than 10-fold on average (Supplementary Table 4). In the linkage region, 100% coding bases were covered at more than 20-fold in at least one of the four individuals. All variants were annotated to RefSeq hg19 and ANNOVAR (Wang et al. 2010) were used to add alternative allele frequencies, variant effect predictions and functional annotations. We excluded variants with minor allele frequency (MAF) > 0.05 in multiple databases, including the dbSNP (v150) (Sherry et al. 2001), the 1,000 Genomes Project (1,000g2015aug) (Genomes Project Consortium et al. 2010; 2012; 2015), the Exome Aggregation Consortium (ExAC03) (Lek et al. 2016) and the Genome Aggregation (gnomAD, v2.1.1, http://gnomad.broadinstitute.org) databases.

Tagged-amplicon deep sequencing

Target-specific primers for the coding sequences and the exon–intron boundaries of the *MCTP2* gene (GenBank: NM_018349) were designed with universal primer sequences (termed CS1 and CS2) appended at the 5′-end and sequencing was performed as described previously (Forshew et al. 2012).

Data analysis for tagged-amplicon deep sequencing

The raw paired 150 bp-long reads were mapped to the human reference genome (build hg19) using BWA. GATK (McKenna et al. 2010) was then used to perform local realignment and recalibrate base quality scores, producing a BAM file for each individual. All variants were annotated to RefSeq hg19 and ten algorithms (Sift, Polyphen2_HDIV and HVAR, LRT, MutationTaster, MutationAssessor, FATHMM, PROVEAN, MutPred, and VEST) integrated by ANNOVAR (Wang et al. 2010) were used to add alternative allele frequencies, variant effect predictions and functional annotations. Among these 10 algorithms, if a site was predicted as deleterious by Sift, LRT, FATHMM, or ROVEAN, as probably or possible damaging by Polyphen2HDIV or HVAR, as disease_causing_automatic or disease_causing by Mutation Taster, as high or medium by Mutation Assessor, and with scores greater than 0.5 by MutPred or VEST, it could be considered harmful for the specific algorithm. 91% of targeted bases were covered at ≥100-fold per individual (Supplementary Table 4). We manually inspected each mutation using the Integrative Genomics Viewer (Robinson et al. 2011; Thorvaldsdottir et al. 2013) to rule out false positive findings. If the coverage for each exon was under 100-fold depth in each individual, we performed direct Sanger sequencing to verify these regions.

The single gene-based burden analysis of *MCTP2* in the second cohort of 1928

We resequenced all 22 exons, 5′UTR, 3′UTR, and the exon–intron boundaries of *MCTP2* by the tagged-amplicon deep sequencing and did a single gene-based burden test for overall, female and male cohorts using the unified optimal sequence kernel association test (SKAT-O) (Lee et al. 2012). A total of 54 rare coding, four splice variants and 19 synonymous variants in NM_018349.4 with MAF ≤ 0.005 in EAS of 1000G, ExAC, and gnomAD were identified and verified by Sanger sequencing (Supplementary Table 5). Primary analyses tested 1) all variants: disruptive variants (nonsense, essential splice site and frameshifts) plus all missense variants (154 individuals carrying); 2) more likely to be harmful: disruptive variantsplus missense variants predicted to be harmful by at least five algorithms (79 individuals carrying); and 3) synonymous variants (35 individuals, an individual with both a synonymous mutation and a mutation from 1) considered as a 1) carrier).

Sequence validation

Mutations were amplified by PCR and validated by direct Sanger DNA sequencing. All reactions were 100% successfully validated. Primer sequences for PCR amplification are included in Supplementary Table 6.

Founder origin testing

We genotyped nine multiallelic microsatellite markers (CHLC.ATA22D04, AFMB077YD5, GATA128A02, AFM072YB11, AFM357TD9/D15S1038, CHLC.GATA73F01, GATA161C02, AFM217ZG1, AFM309VG9) around the c.239delG (p.S80fs) mutation of *MCTP2* from 94255659 to 96210769 bp on chromosome 15 in families B0001, C2149, C2666, C3030, C3049, and C3164. The inferred haplotypes were estimated by comparison to these microsatellites data collected on mother–father–offspring trios to test the possibility of the same founder origin.

Neuroimaging

Stimuli

In the localizer experiment, images of faces, nonface objects (e.g. chairs, food, and tools), and texture patterns (scrambled faces) were presented at the center of the screen, subtended 6.2°×6.2°. In the adaptation paradigm, the stimuli were gray-scale images of young Chinese men (hair cropped with neutral expressions). The stimuli were presented by a MRI compatible projector system (SA-9900, The Shenzhen Sinorad Medical Electronics Co., Ltd, China, http://www.sinorad.com), with a spatial resolution of 1,024 × 768 and a refresh rate of 60 Hz.

Experimental design and procedures

Each participant completed the same single scan session consisting of one functional localizer run and five runs for the adaptation paradigm. During the experiment, participants lay on their back in the scanner, using earplugs to reduce noise and sponges to hold their heads in place to reduce head movement. Participants viewed the stimuli presented on a translucent screen visible via a mirror mounted to the head coil at a distance of 60 cm. In the localizer run which lasted 360 seconds (s), with a 12 s dummy at the beginning of the run, images appeared at a rate of 2 Hz in blocks of 12 s, interleaved with 12 s blank blocks. There were five blocks for each type of images in the run. Each image was presented for 300 milliseconds (ms), followed by a 200 ms blank interval. Subjects performed a one-back task during scanning to ensure maintenance of attention to the stimuli. In the adaptation paradigm, pairs of face or house stimuli were presented sequentially either in the upright or the inverted manner in a randomized order that was optimized for the extraction of the hemodynamic response in an event-related fast presentation design. Each trial lasted 2000 ms. The first and second stimuli were presented for 250 ms, with an interval of 500 ms and followed by 1 s fixation. Blank screen with white cross fixation point was set between trials, with a presentation time of a random even number in the range of 0–10 s to optimize the efficiency of the event-related fMRI design by optseq2 (http://surfer.nmr.mgh.harvard.edu/optseq). Each run lasted 332 s, containing eight conditions (upright same face, upright different face, inverted same face, inverted different face, upright same house, upright different house, inverted same house, and inverted different house). Five runs were included, each containing

12 trials for each condition. Subjects made a same/different response on each trial. Here we focus only on the face stimuli.

fMRI scanning

The fMRI data were collected in a 3T GE MR 750 scanner, with an 8-channel phase-array head coil (GE Healthcare, Waukesha, WI) at Peking University Center for MRI Research.

The gradient-echo echo planar imaging (EPI) sequence was employed for the blood oxygenation level-dependent (BOLD) signal images acquisition, and the imaging parameters were as below: repetition time (TR) = 2,000 ms, echo time (TE) = 30 ms, field of view (FOV) = 224 mm × 224 mm, matrix = 64 × 64, flip angle = 90°, slice thickness = 3.5 mm with 0.7 mm spacing, voxel size = 3.5 × 3.5 × (3.5 + 0.7) mm, 33 oblique slices covering the whole brain.

The structure images were acquired by a 3D inversion recovery-prepped T1-weighted sequence (fSPGR, sagittal acquisition, TR = 6.65 ms, TE = 2.92 ms, TI = 450 ms, flip angle = 12°, FOV = 256 mm × 256 mm, matrix = 256 × 256, 192 continue slices with 1 mm slice thickness, voxel size = 1 mm × 1 mm × 1 mm).

Data analysis for neuroimaging studies

Preprocessing and data analysis were performed with SPM12 (Wellcome Trust Centre for Neuroimaging, London; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Functional images were sequentially processed in accordance with the standard SPM approach as follows: interpolated to correct for slice timing, realigned to the middle volume, co-registered to structural scans using the mean functional image, spatially normalized to a standard echo-planar image (EPI) template based on the Montreal Neurological Institute reference brain template (MNI152, Asia brain), and spatially smoothed with an isotropic 8 mm full width at half-maximum Gaussian kernel. For anatomical reference, the statistical maps computed were overlaid to the 3D T1-weighted scans. First, face-selective regions were localized in each subject by BOLD signals. By comparing the "faces" condition with the "nonface" condition in the localizer experiment at the first-level analysis, we assessed the face-selective region of interest (ROI) for every participant by building a 5-mm radius sphere surrounding the coordinate of the maximum activation in rFFA at a threshold $P < 0.05$, the family-wise error (FWE) correcting for multiple testing, with MARSBAR followed by visual confirmation of their anatomical location. For participants who lacked a face-selective area with this criterion, we explored liberal uncorrected significance thresholds (as liberal as $P < 0.05$), to avoid missing effects that might be apparent at less stringent uncorrected thresholds. Because faces are processed more dominantly in the right hemisphere and because the ROIs in this study were localized more consistently in the right hemisphere, we chose to restrict our ROI-based analyses to regions in the right hemisphere (unless noted otherwise). Second, the above-defined ROI were tested for the adaptation to facial identity using the contrast (up different faces > up identical faces) by BOLD signals at the first-level analysis. Third, the time course of percent signal change from baseline fixation was extracted from the ROI for each condition in each individual with MARSBAR, and was plotted for each condition in controls (±SD) and family members by an in-house Matlab program. Fourth, in order to directly compare each family member with the control subjects, the percent signal change in the ROI was computed for each condition. Three data points around the peak of the hemodynamic response defined individually were averaged to estimate the percent signal change. Fifth, the percent signal change was used to compute the adaptation scores (upright different face—upright identical face) for each subject, allowing a comparison between each family member with the control group by means of Z scores and the modified t-test score (Crawford and Howell 1998; Crawford and Garthwaite 2002; Crawford *et al.* 2010).

Results were visualized using xjView toolbox (http://www.alivelearn.net/xjview) in addition to built-in visualization in SPM12.

Quantification and statistical analysis

Where applicable, statistical parameters including sample size, precision measures (standard error or SD) and statistical significance are reported in the figures and corresponding legends. *P*-values of less than 0.05 are significant.

Results

A three-generation pedigree with CP

Thirty-five members from a three-generation pedigree (family A) (Table 1, Supplementary Table 1, Fig. 1a), were interviewed. 18 family members showed obvious difficulties in face recognition in daily life: nine individuals (IV:2, IV:4, V:9, V:10, V:11, V15, VI:5, VI:6, and VI:9) had been aware of this deficit in their early life before we contacted them; four individuals (IV:6, V:4, V:6, and VI:8) had difficulties in recognizing people for a long time without knowing the reason; and five individuals (IV:10, V:1, V:13, V:19, and VI:7) who ignored this problem in their daily life, adopted strategies relying on cues other than the face (Table 1). There was a significantly negative correlation between the spontaneous need of gaze contact and the experience of face recognition difficulty or the use of compensatory strategies ($P < 0.001$, $r = -0.658$, $n = 35$).

Consistent with previous studies (Schmalzl *et al.* 2008; Johnen *et al.* 2014), there was intra-familial heterogeneity in the CFMT-C, CCMT, and the FIE Discrimination test. For the 14 family members, who had substantial real-world face recognition difficulties, 10 individuals were found to be impaired on at least one of the face behavioral tests. V:1, V:9, V:11, V:13, V:15, V:19, and VI:8 had a score more than two SDs below the normal level on the CFMT-C, and V:4 ($z = -1.60$) and V:6 ($z = -1.61$), performed noticeably poorly (under −1.5 SDs). In the FIE discrimination test for holistic processing, the face-inversion effect of V:6 ($z = -1.62$), V:9 ($z = -1.62$), V:11 ($z = -2.56$), and VI:5 ($z = -1.81$) was impaired. V:1 ($z = -2.96$), V:13 ($z = -1.73$), V:15 ($z = -1.55$), and V:19 ($z = -1.52$) also performed poorly on the ability of discriminating upright faces. There were four individuals (V:10, VI:6, VI:7, and VI:9) who reported everyday difficulties but performed at normal levels on the tests of face recognition. All of them performed well in the CCMT test, indicating that their recognition of other physical stimuli was normal and independent of their abilities to recognize faces. Z scores for each member were listed in Table 1.

A specific region on chromosome 15q containing a candidate CP susceptibility gene

To err on the side of caution, for the preliminary linkage analysis in Family A (named linkage 1, see Methods details) (Supplementary Table 1), we diagnosed nine family members as CP cases (V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19, and VI:8) with the criteria of not only abnormality in face recognition exhibited through interviews, but also poor with the CFMT behavior test. With the highest LOD (logarithm of odds) score 3.49, which suggested a possible CP-linked gene, a major candidate region (MCR) of 3.9 megabases (Mb) spanned from rs12148885 (chr15:94251330, 15q26.1) to rs288435 (chr15: 98160439, 15q26.2)

corresponding to the 1-LOD drop-down region on chromosome 15, based on the hg19 assembly (Fig. 1b). Results of the genome-wide screen are shown in Supplementary Fig. 3a. Computer simulations with 1,000 replicates led to an empirical *P* value of 0.023, suggesting that this result was significant at the genome-wide level. Another region 9q21.13 had LOD scores exceeding 1.0 (Supplementary Fig. 3a), but did not reach genome-wide significance by computer simulations. Shared haplotypes within the MCR are shown in Supplementary Fig. 4a.

It is possible that some affected persons completed face recognition tasks with coping strategies for individual recognition without face recognition, leading to ambiguities in classifications (Dalrymple and Palermo 2016; Duchaine and Weidenfeld 2003; Grueter *et al.* 2007). Thus, we did a second linkage analysis (linkage 2, see Methods details) after adding four individuals who had daily face recognition problems but appeared normal on behavioral tests (V:10, VI:5, VI:6, and VI:7) and four founders with daily face recognition problems (IV:2, IV:4, IV:6, and IV:10) as CPs (Supplementary Table 1), Linkage 2 analysis extended results of Linkage 1 in further supporting the region between rs6497114 (chr15:94245722) and rs11045 (chr15: 96883321) with LOD scores over 3 (maximum LOD score = 5.13), spanning 2.64 Mb on chromosome 15q26.1-26.2 (Figure 1c, Supplementary Fig. 3b). Another region 10q24.2 had LOD scores over 1. A significant $P < 0.008$ for the maximum LOD score on chr15 existed after simulations. Shared haplotypes within the MCR are shown in Supplementary Fig. 4b.

Candidate genes annotated by the newest NCBI database (https://www.ncbi.nlm.nih.gov/genome/gdv/) in the MCR are listed in Supplementary Table 7.

A mutation in *MCTP2* revealed by WGS

To find causative mutations on chromosome 15q26.1-26.2 linked to CP in family A, we employed the WGS approach with nine affected individuals (V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19, and VI:8, Supplementary Table 1) in linkage 1. In the MCR, only one variant (NM_018349.4:c.2147T > G, NP_060819.3:(p.I716S)) in *MCTP2* at chr15:94983466, was heterozygous in all the nine CPs. This missense mutation (c.2147T > G) was private to family A, not present in the dbSNP (v150), 1000, ExAC03 and genomAD(v2.1.1) databases, albeit at this location another multiallelic SNP rs200314451 had been reported with an MAF of 0.000 for NM_018349.4:c.2147T > C, NP_060819.3:p.I716T and 0.0001088 for NM_018349.4:c.2147T > A, NP_060819.3:p.I716N in East Asian in gnomAD v2.1.1. In our expanded cohorts of 3,600 Chinese samples, we did not find the same mutation.

To investigate whether this variant is a strong candidate of CP predisposition, we performed direct Sanger sequencing and co-segregation analysis in the pedigree. In addition to the nine cases in Linkage Analysis 1, the mutation c.2147T > G in *MCTP2* also exists in four founders with poor face recognition, who were not suitable for behavioral tests because of age, and five family members who performed normally in the CFMT-C test but showed poor face recognition in daily life (Fig. 1a, half-filled symbols).

Thus, the *MCTP2* mutation encoding NP_060819.3:p.I716S seems to be the only functional variant shared in the MCR by all patients with daily face recognition problems in this large CP family. I716S is predicted to be disease-causing by SIFT (Ng and Henikoff 2001). The full length of the *MCTP2* gene spans 180 kilobases (kb) of genomic DNA, with 22 coding exons, encoding a protein with 878 amino acid residues separated into three C2 domains and two transmembrane regions (TMRs) (Supplementary Fig. 5a). NP_060819.3:I716, located in the first TMR, is highly conserved with primate species (Supplementary Figs. 5, a and 5b) well developed in face processing (Tsao *et al.* 2003, 2006, 2008; Moeller *et al.* 2008; Hung *et al.* 2015; Freiwald *et al.* 2016).

Additional *MCTP2* mutations in CPs and CP families identified by expanded screening

On the basis of theoretical and experimental considerations, it has been suggested that rare functional alleles are important contributors to the genetics of phenotypes (Pritchard 2001; Cirulli and Goldstein 2010; Jordan *et al.* 2010; Heinzen *et al.* 2015). The results from the study of a typical CP family A indicate that rare and even private, functional mutations in *MCTP2* could be related to a CP phenotype.

In the first cohort of 2,904 individuals screened with a questionnaire (see Methods details), we identified 75 individuals whose scores deviated at least 2 SDs from the average and sequenced their *MCTP2* exons. Five rare heterozygous functional variants including one frameshift and four missense mutations were found in seven individuals (Figs. 2a and Supplementary 5a, Supplementary Table 8).

The frameshift mutation (NM_018349.4:c.239delG, NP_060819.3:p.S80fs) in exon 1 of *MCTP2* was found in three of those 75 who reported poor performance in face recognition (individuals B0001, B0009, and B0046) (Fig. 2b). Further interviews revealed that all three individuals carrying p.S80fs reported lasting and irritating subjective uncertainties of face recognition, and realized this condition in their early life (Supplementary Table 2). One relative of individual B0001 carries p.S80fs and had adopted a strategy to observe other features, which took her more time to recognize a person (Fig. 2c, Supplementary Table 2).

In the family of individual B0011, those who carry the NP_060819.3:p.M272L mutation in exon 5, reported their own strategies to recognize others, but still coped poorly with their difficulties (Figs. 2d and 2e, Supplementary Table 2). The NP_060819.3:p.T374A mutation in exon 8 was detected in individual B0010 who was aware of having a severe deficit in face recognition (Fig. 2f, Supplementary Table 2). In the family of individual B0003, the mutation NP_060819.3:p.V548I in exon 12 was correlated well with the phenotypes (Figs. 2g and 2h, Supplementary Table 2). In the family of individual B0002, the mutation NP_060819.3:p.R641Q was found to segregate in all affected children of the family (Figs. 2i and 2j). These mutations are also evolutionarily conserved in animals (Supplementary Fig. 5b).

A link between rare alleles in *MCTP2* and face recognition revealed by a gene-based association analysis

In the next step, we further aimed to evaluate the association of the alleles in *MCTP2* that harbor rare coding variants of moderate or large effects on protein coding with face recognition abilities in the second cohort of 1,928 individuals who took the same questionnaire as the first cohort of 2,904 mentioned above.

Significant association was detected with the disruptive variants plus all missense variants (all variants, $p_{burden} = 0.0009$, $p_{optical} = 0.0021$) and the more likely to be harmful variants ($p_{burden} = 0.0032$, $p_{optical} = 0.0063$) in the male cohort based on burden testing, even after multiple corrections. No association was observed in the female cohort and for the synonymous variants. Details of the variants contributing to these significant test results are shown in Table 2. Our results suggest a high proportion of causal variants in *MCTP2* exert effects in the same direction and indicate the association between a variant burden and face recognition in the male cohort, at least in part, by the effects of *MCTP2*.

Table 2. Gene-based association analysis for rare variants in *MCTP2*.

		All	Male	Female
All variants	Burden	0.0155	**0.0009**	0.7415
	SKAT-O	0.0295	**0.0021**	0.9221
More likely to be Harmful	Burden	0.0590	**0.0032**	0.9729
	SKAT-O	0.1103	0.0063	1.0000
Synonymous Variants	Burden	0.2903	0.1410	0.8786
	SKAT-O	0.4688	0.2408	1.0000

The positive results after multiple corrections are bolded.

A frameshift mutation in CP individuals

Results of pedigree and population studies support correlation of rare alleles in *MCTP2* changing protein coding with the ability of face recognition, implicating *MCTP2* in face recognition. As mentioned above, 3 of 75 individuals with poor face recognition screened from 2,904 individuals carry the frameshift deletion c.239delG (p.S80fs) in the first exon of *MCTP2* which would eliminate most of the MCTP2 protein. These frequencies lie within the reported range of CP prevalence and are high enough to allow identification of additional carriers consenting to analysis of face recognition through a reverse-phenotyping approach.

We further screened this frameshift mutation in a third independent cohort of 1,757 individuals. We detected 16 individuals carrying this mutation in a heterozygous condition with an MAF of 0.0046. Among them, 14 individuals agreed to be further examined (Supplementary Table 3). Our interviews documented qualitative differences in the behavior of daily face recognition between the 14 carriers and 19 noncarrying volunteers from the same cohort (Table 3).

Four individuals C2180, C2666, C3164, and C3282 recognized their difficulties in face recognition before we contacted them. Examination of all available family members of C2666 and C3164 showed that this mutation segregated with face recognition deficits in both families (Figs. 3, a and b, Supplementary Table 3).

Individual C3049 did not report difficulties in recognizing people/faces, but he did feel different from others in the way of recognizing people/faces (Supplementary Table 3). In the family of C3049 (Fig. 3c, Supplementary Table 3), the mutation was also identified in two relatives (II:2 and III:1), who reported daily difficulties in face recognition.

For the remaining nine individuals during the interview, they thought they were the same as others or even better than others in face recognition (Supplementary Table 3). However, eight individuals (C2149, C2259, C3030, C3234, C3358, C3420, C3649, and C3731) developed adaptive behaviors and depended on explicit learning strategies for recognition, which made it not hard to recognize acquaintances (the whole person, not just the face) in their daily life. When they encountered strangers with few features, or actors especially actresses on the screen, or familiar people out-of-context, the strategies would not always work properly, but they could make adjustments and update the information quickly. The relatives of individual C2149 who carry this mutation complained difficulties in recognition (Fig. 3d, Supplementary Table 3). For individual C3030, the strategy to recognize people should be inherited from both parents (Fig. 3e, Supplementary Table 3). The relative of individual C3649 did not show prosopagnosia and do not carry the mutation (Fig. 3f, Supplementary Table 3). One individual, C2147 did not show obvious abnormal face recognition ability during the whole interview.

The inferred haplotypes around the c.239delG (p.S80fs) mutation were estimated by comparison to microsatellites data collected on mother–father–offspring trios (Supplementary Fig. 6) and excluded the possibility of the same founder origin.

Table 3. Differences in daily face recognition between target group and controls regarding the p.S80fs mutation.

Manifestations of poor face recognition	Target group N = 14 with the p.S80fs mutation (6 males/8 females)	Controls N = 19 without the p.S80fs mutation (5 males/14 females)	Fisher's exact test, *P* value, two-tailed
Lasting and irritating subjective uncertainty of face recognition	9/14	1/19	<0.001
Face recognition deficit especially in crowded places or out-of-context encounters	12/14	4/19	<0.001
False negative and false positive face recognition events	10/14	4/19	0.006
Face recognition time longer than socially accepted	11/14	3/19	<0.001
Face learning time longer than socially accepted	11/14	3/19	<0.001
Development of adaptive behavior	12/14	5/19	0.01
Use of explicit learning strategies for visual person recognition	13/14	4/19	<0.001
Self-evaluation of impaired visual recognition of faces	5/14	1/19	0.062

Neuroimaging studies of family CPs with the *MCTP2* mutation

With six young family members from the Family A, we found that abnormal responses to individual faces in the FFA were associated with the *MCTP2* mutation of I716S.

The rFFA is consistently involved in detecting the presence of a face and in discriminating individual faces (Puce *et al.* 1996; Kanwisher *et al.* 1997; Haxby *et al.* 2000; Grill-Spector *et al.* 2004; Yovel and Kanwisher 2004; Rotshtein *et al.* 2005; Zhang *et al.* 2012; Rangarajan *et al.* 2014). As in the rFFAs of normal participants (Supplementary Fig. 7a), there were significant activities in the rFFAs of family members both with I716S (A-VI:5, Supplementary Fig. 7b, A-VI:7, Supplementary Fig. 7c, and A-VI:9, Supplementary Fig. 7d) and without I716S (A-VI:1, Supplementary Fig. 7e, A-VI:2, Supplementary Fig. 7f, and AVI:10, Supplementary Fig. 7g). These suggest that the rFFA of the members in family A could respond specifically to faces independent of the mutation.

To test whether the rFFA of family members could process facial identities, we conducted experiments using an fMRI adaptation paradigm in an event-related design (Yovel and Kanwisher 2005) (Fig. 4a). In the group of normal subjects, the expected repetition suppression from fMRI adaptation to facial identity was highly significant in the rFFA (paired t-test $P < 0.0001$, Fig. 4b). In addition, in every single control subject there was a higher activation level in response to pairs of up different faces (UDF) than to

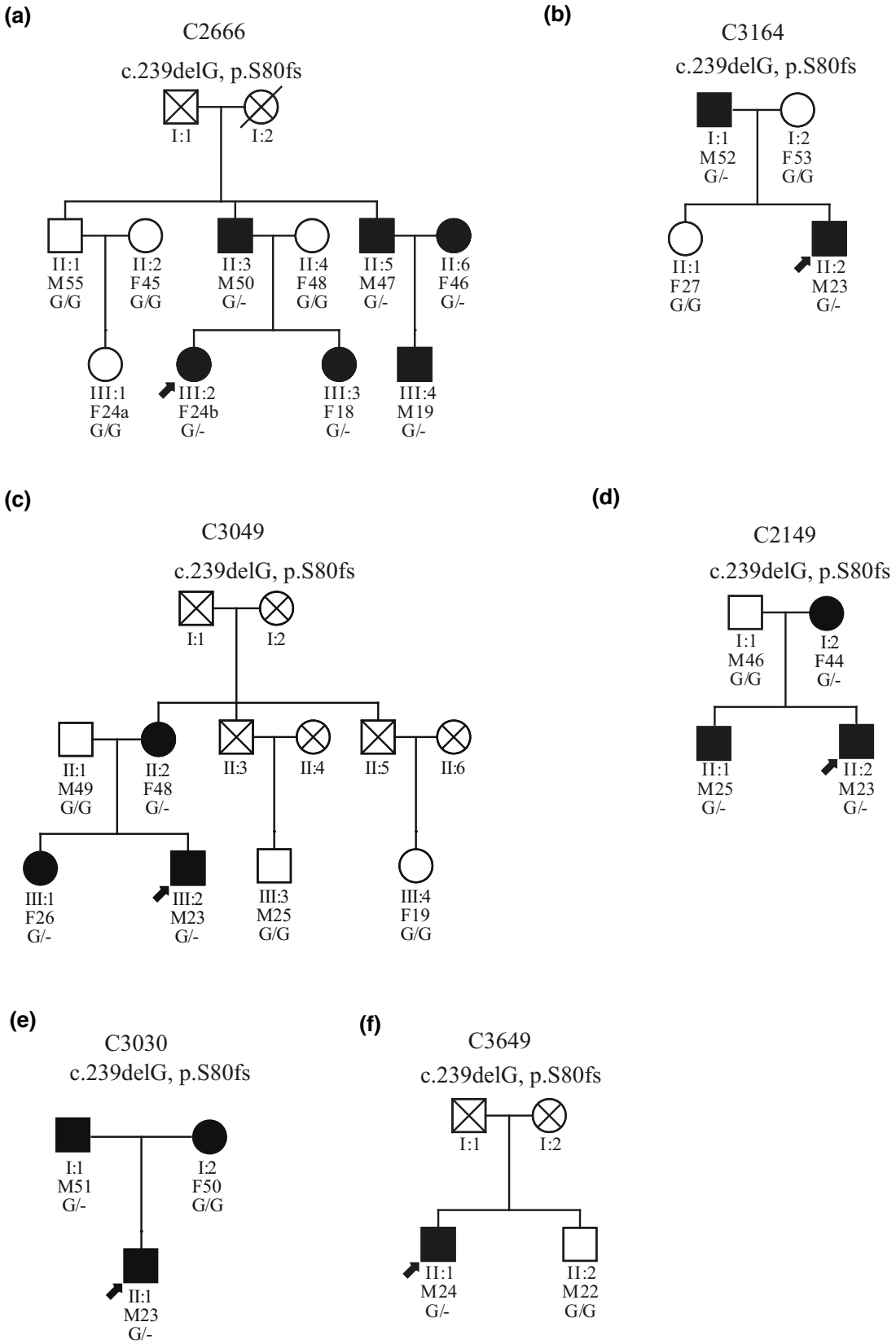

Fig. 3. Co-segregation of c.239delG (p.S80fs) in *MCTP2* in CP. 16 individuals with the frameshift deletion mutation (c.239delG [p.S80fs]) were detected in a cohort of 1,757 students. Fourteen of them were available for further analysis. More members from six families were available (Supplementary Table 3). a) Correlation of the (c.239delG [p.S80fs]) genotype with the CP phenotype in the family of C2666, with 10 family members tested. b) Correlation of the (c.239delG [p.S80fs]) genotype with the CP phenotype in the family of C3164, with 4 family members tested. c) Correlation of the (c.239delG [p.S80fs]) genotype with the CP phenotype in the family of C3049 with 6 family members tested. d) Correlation of the (c.239delG [p.S80fs]) genotype with the CP phenotype in the family of C2149 with four family members tested. e) Correlation of the (c.239delG [p.S80fs]) genotype with the CP phenotype in the family of C3030, with three members tested. f) The pedigree plot of family C3649 with genotype and phenotype.

pairs of up identical faces (UIF): the contrast "UDF > UIF" was significant at $P < 0.05$ in 18/20 normal subjects and showed a nonsignificant trend in the predicted direction in the remaining subjects ($P < 0.057$, $P < 0.25$). In each family member without I716S (A-VI:1, Fig. 4c, A-VI:2, Fig. 4, d and a-VI:10, Fig. 4e), there was a higher activation level in response to pairs of UDF than to pairs of UIF. The contrast "UDF > UIF" was significant at $P < 0.05$ in each family member without the *MCTP2* mutation. In contrast, the fMRI signals in the rFFA of the members with I716S did not show larger response to different faces than identical faces (A-VI:5, Fig. 4f, A-VI:7, Fig. 4g, and A-VI:9, Fig. 4h). The adaptation score (percent signal change under the upright different condition vs the upright identical condition within the ROI) was lower for members with I716S than for every individual control subject (Fig. 5), and there was a nonsignificant trend in the same direction for members with I716S compared to normal controls (A-VI:5, $P = 0.05407$, A-VI:7, $P = 0.12832$, and A-VI:9, $P = 0.06548$). The attenuation of neuronal activity in rFFA due to repetition of identical faces appeared to be reduced in individuals with I716S, while different faces yielded similar responses in the rFFA in CPs, non-CPs and normal controls. These results suggest that rFFA responses to identical faces are impaired in members with the *MCTP2* mutation, which may imply a mechanism underlying the difficulty in identifying seen-before faces.

In the C2666 family with the frameshift mutation c.239delG (p.S80fs) in *MCTP2*, we observed normal responses to faces in rFFA at the categorical level both in III:4 with p.S80fs (Supplementary Fig. 7h) and III:2 without p.S80fs (Supplementary Fig. 7i), but a failure of repetition from fMRI adaptation to facial identity also occurred in the rFFA of III:4 (Fig. 4j) with difficulties in face recognition in his daily life.

Discussion

Molecular genetic studies of face recognition

CPs represent a model for genetic analysis of human cognition: face recognition. Several extended CP pedigrees have been reported (Duchaine *et al.* 2007; Johnen *et al.* 2014; Schmalzl *et al.* 2008), but the underlying genes remain unclear. Our study represents the first molecular genetic study of human cognition in general and face recognition in particular with extended families.

Our findings indicate that mutations in the *MCTP2* gene contribute to CP in humans. This conclusion is supported by the following: 1) a CP locus at 15q26.1-q26.2 containing *MCTP2* was identified by linkage analysis in Family A with autosomal dominant CP (Fig. 1, Supplementary Fig. 3); 2) a private mutation c.2147T > G (p.I716S) in *MCTP2* was the only mutation altering the protein sequence identified by WGS in the MCR that fully co-segregated with CP in the entire family A (Fig. 1); 3) 5 rare functional mutations in *MCTP2* were found in 7 CP individuals from a group of 75 with poor face recognition out of a cohort of 2,904 individuals (Fig. 2); 4) of those seven CPs, family members from four CPs were available for analysis and showed phenotype-genotype correlations (Figs. 2, c and e, 2h and 2j); 5) 16 individuals from another cohort of 1,757 subjects contained the same frameshift deletion mutation c.239delG (p.S80fs) as three CP individuals in 4), with 14 available for further analysis. Differences in the behavior of daily face recognition were detected between the 14 carriers and 19 noncarrying volunteers from the same cohort (Table 3); 6) four of 14 had unambiguous CP with two families available for analysis and all supported the correlation between c.239delG (p.S80fs) and CP (Figs. 3a and 3b), with further support from additional families (Figs. 3, c and d, 3e and 3f) who have developed explicit strategies to recognize people with nonfacial clues to overcome their difficulties in face recognition; 7) correlation between the rare alleles in *MCTP2* and face recognition ability was detected in males by a gene-based association analysis in a cohort of 1,928 individuals; 8) impaired face recognition in family members with the *MCTP2* mutations was associated with abnormal responses to individual faces in the rFFA by neuroimaging studies.

Diagnosis of CP

Investigations of CP on different cognitive tasks show heterogeneities (Kress and Daum 2003; Behrmann and Avidan 2005; Le Grand *et al.* 2006; White and Burton 2022). While specific tests have proven useful (Duchaine and Nakayama 2006a), no single test is of sufficient discriminatory power for the entire spectrum of CP (Duchaine and Weidenfeld 2003; Duchaine and Nakayama 2004, 2006a; Grueter *et al.* 2007; Shah *et al.* 2015).

Regardless of the specific task used, it should be treated with caution that the exact severity of the individual CP cases by behavioral tests is affected by many factors such as behavioral adaption, other cognitive skills, experience with faces or testing forms, even within a single family of similar genetic and environmental background (Schmalzl *et al.* 2008; Lee *et al.* 2010; Johnen *et al.* 2014). In some CP cases, they had trouble recognizing people, but they could still do a good job in behavioral tests. Poor performance on tasks of face processing could predict the impairment in face recognition, but the reverse is not the same.

In addition to using behavioral tests to diagnose face recognition, individual self-reports are also commonly relied upon. But the Dunning–Kruger (DK) effect, a metacognitive phenomenon of illusory superiority in which individuals who perform poorly on a task believe they performed better than others, yet individuals who performed very well believe they under-performed compared to others, needs to be taken into account (Kruger and Dunning 1999; Dunning *et al.* 2003). DK Effects was also found in self-reports of face recognition (self-estimates) and estimates of other people (peer estimates) (Zhou and Jenkins 2020). Cautions should be taken when interpreting self-report measures of face recognition: it is likely that CP cases may be unaware of their face recognition impairments. But through detailed interviews, they could be found to have strategies and everyday habits. At the same time, in the DK effect, although good performers will underestimate their ability, they only tend to judge themselves as average, so this will not have a significant impact on the subsequent determination of phenotypes, at least they will still be considered as normal. Therefore, in our study, we conducted detailed interviews with the family members as the primary diagnostic basis.

Roles of MCTP2

The *MCTP2* gene encodes a protein with three C2 domains and two transmembrane regions with resemblance to proteins involved in synaptic transmission (Shin *et al.* 2005). Its C2 domains can bind Ca^{2+} (Shin *et al.* 2005). Many proteins that bear the Ca^{2+}-binding C2 domain are involved in membrane and vesicle trafficking, playing a central role in neural transmission (Cho and Stahelin 2006; Shupliakov and Brodin 2010).

The C2 domains and transmembrane regions of MCTPs are evolutionarily conserved from invertebrates such as *Caenorhabditis elegans* and *Drosophila melanogaster*, which only have one *MCTP* gene, to mammals which have two genes (*MCTP1* and *MCTP2*). MCTP1 is expressed in the central nervous system and has been implicated in regulating endocytic recycling of specific CNS neurons and synapses (Qiu *et al.* 2015). In Drosophila, MCTP is involved in stabilizing synaptic transmission and homeostatic plasticity (Genc *et al.*

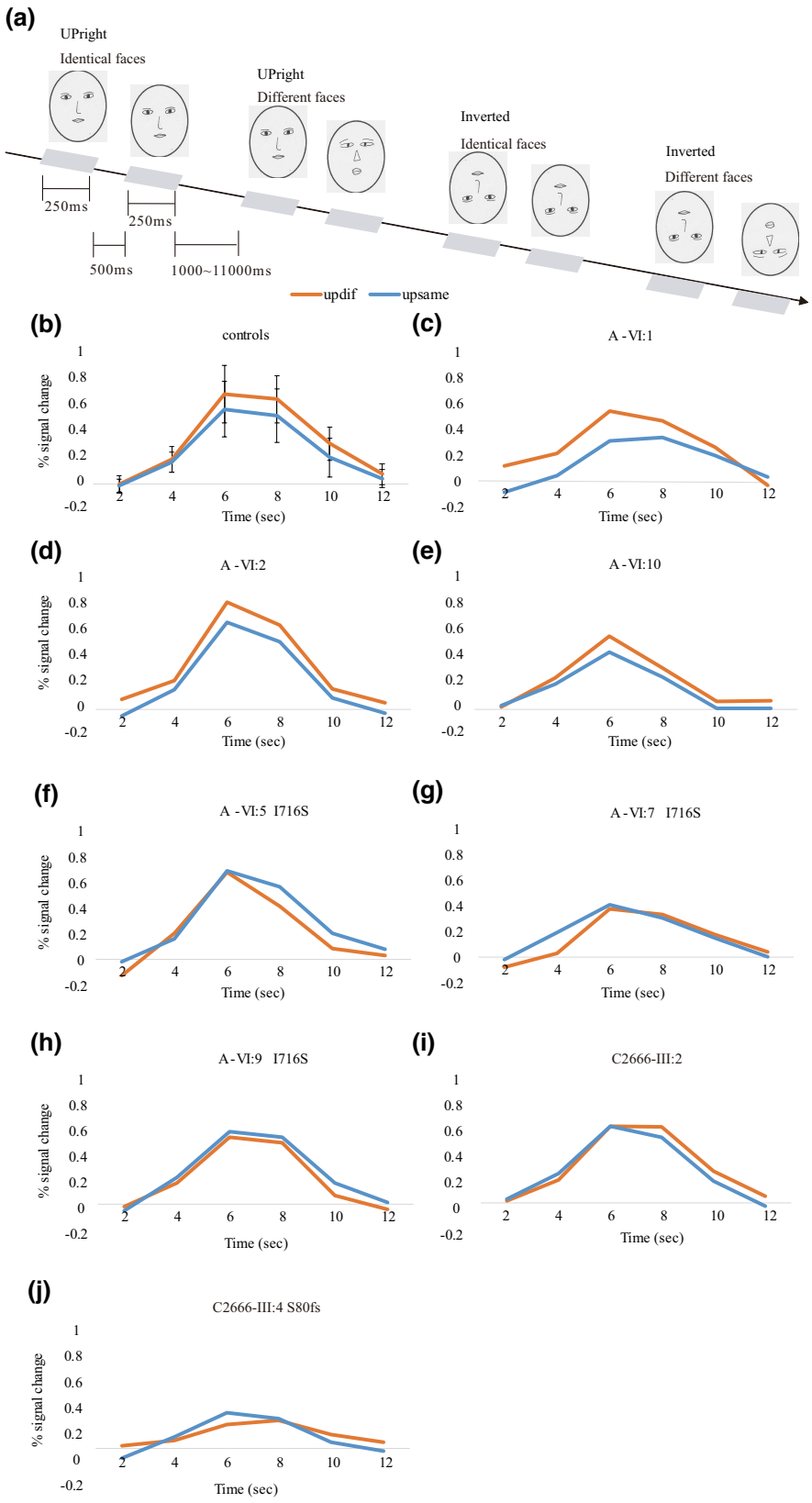

Fig. 4. rFFA activation in face discrimination. Experimental paradigm as Fig. 4a. The average percent signal change (±SD for controls) from baseline fixation is plotted for the different and identical upright face conditions. Bold response to pairs of upright different faces or identical faces in the rFFA of controls ($n = 20$) b); non-CP members A-VI:1 c), A-VI:2 d), A-VI:10 e) and CP members A-VI:5 f), A-VI:7 g), and A-VI:9 h) from family A with the I716S mutation in *MCTP2*; non-CP C2666-III:2 i) and CP C2666-III:4 j) from family C2666 with the S80fs mutation in *MCTP2*.

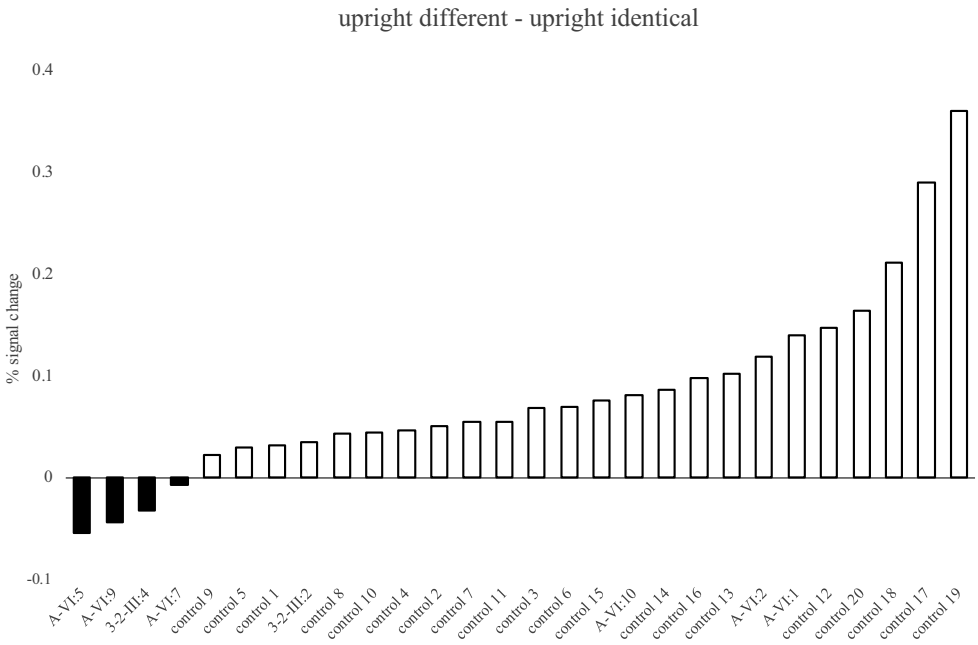

Fig. 5. Comparison between CP and control individuals in the adaptation experiment. The adaptation score (difference in percent signal change between responses to upright different faces and upright identical faces) is plotted for CP individuals (black bars) and each individual control subject (white bars) in an increasing order.

2017). The four zebrafish *MCTP* genes are expressed mainly in the nervous and muscular systems. Knocking down *MCTP2b* impaired embryonic development (Espino-Saldaña *et al.* 2020).

Gene expression microarray data from thousands of samples of different tissues showed that MCTP2 was expressed in the human brain, including the temporal lobe (McCall et al. 2011). FFA, the core brain region most consistently and robustly activated by the face selectively, is a small region in the fusiform gyrus of the temporal lobe. The human protein atlas also gives an overview of MCTP2 protein expression and distribution in the human brain including the fusiform gyrus (Sjostedt *et al.* 2020).

Both *MCTP2* and *MCTP1* had been associated with attention-deficit/hyperactivity disorder (ADHD), a highly heritable neuropsychiatric disorder (Mick *et al.* 2010; Kweon *et al.* 2018). The gene ontology "calcium ion binding" was significantly enriched in the 14 ADHD-associated genes (Poelmans *et al.* 2011). Genome-wide analyses have identified *MCTP1* single nucleotide polymorphism (SNP) in bipolar diseases (Scott *et al.* 2009). There was also a report of *MCTP2* SNP in schizophrenia (Djurovic *et al.* 2009).

Among the 1,757 people in the third cohort mentioned above, a total of 64 coding and splice-site rare variants with MAF < 0.005 were identified and verified by Sanger sequencing (data in house). Interviews were conducted with the consent on a voluntary basis. Sixteen individuals carry the frameshift deletion c.239delG (p.S80fs) with a MAF of 0.0046 and 14 of them accepted the interview. The association is maintained in unrelated carriers of the S80fs variant with the ability of face recognition. We also harvested a S80fs family (C2666) containing 10 family members with the correlation of face blindness. Interestingly, II:6, the wife of II:5 who has a foreign allele of S80fs also showed face recognition problems. We further interviewed individuals with other lower frequency mutations in *MCTP2*. Additional individuals and their family members with frameshift mutations and splicing sites also showed abnormal facial recognition.

fMRI as a diagnostic means for endophenotype and for mechanistic link between genotype and brain activity

fMRI reveals areas of neuronal activation for specific tasks/behaviors or conditions. Endophenotypes such as fMRI are believed to better represent underlying pathophysiology than clinical diagnostic categories in complex neurobehavioral disorders (Rasetti and Weinberger 2011). Neuroimaging-genetic readouts allow more stratified delineation of the effects of particular risk alleles on brain activities rather than on simply diagnosed phenotypes.

In this study, we included the imaging-genetic study to show genetic influences in affected family members with I716S or S80fs in the adaptation paradigm (Grill-Spector and Malach 2001; Henson and Rugg 2003; Grill-Spector *et al.* 2006). Whereas the time course of percent signal changes in normal controls and family members without mutations in *MCTP2* showed an attenuation of neural activity across repetitions of pairs of the same faces in the rFFA, this was not obvious in family members with *MCTP2* mutations.

In future research, fMRI can be considered as an important endophenotype of face recognition.

Genes involved in face recognition

Our genetic results provide evidence that *MCTP2* gene mutations underlie CP and our fMRI results suggest that *MCTP2* is involved in neural circuits required for distinguishing faces.

But higher cognition involves many cells and molecules. *MCTP2* is not the only gene involved in CP. Only 7 of the 75 CPs from the 2,904 cohort carried *MCTP2* mutations. Rare alleles in *MCTP2* were not correlated with face recognition ability in females from the cohort of 1928. More linkage studies would be helpful.

We have found more families with unknown genetic basis which require more analysis. Hypothesis-free genomic analysis should be reconsidered with the next-generation sequencing method covering both common and rare genetic variants through larger sample sizes, exceeding a million human participants, to

find more genetic clues and replicate our *MCTP2* results in human face recognition in the future.

Data availability

The raw sequence data reported in this paper have been deposited in the Genome Sequence Archive (Tingting Chen *et al.* 2021) in National Genomics Data Center (Nucleic Acids Res 2024), China National Center for Bioinformation/Beijing Institute of Genomics, Chinese Academy of Sciences (GSA-Human: HRA005784) that are publicly accessible at https://ngdc.cncb.ac.cn/gsa-human. Supplemental data include seven figures and eight tables.

Supplemental material available at GENETICS online.

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Conflicts of interest

The author(s) declare no conflict of interest.

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