11A　　脸识别

虽然人类认知非常有趣，对人类认知的分子研究却罕见。通常，先在动物研究某些基因，然后在人类研究它们。这种途径限制了研究在动物必需有的表型，而且常常是低等动物，因为在非人灵长类动物很难通过功能研究发现基因。因此，对于只在人类存在的认知、或在低等动物不存在的认知进行分子研究，远远落后于对于简单行为的分子研究。同种动物之间相互识别脸既是很高级的视觉认知，也是社会认知。对此，科学发掘了很多现象，也有一些机理研究，但理解有限。

脸识别能力

人识别脸的能力强于黑猩猩和猴（Rosenfeld and van Hoesen，1979；Parr，2011）。黑猩猩、猴、绵羊、鸟类（鸡和鸽）、狗等动物也有脸识别细胞（Kendrick and Baldwin，1987；Ryan and Lea，1994；Kendrick *et al.*,1996；Pascalis and Kelly，2009）。绵羊不仅有识别绵羊脸的细胞，还有识别人脸、狗脸的细胞（Kendrick and Baldwin，1987）。羊羔一到两个月认识母亲的脸（Kendrick *et al.*，1998）。雌绵羊还对雄绵羊的脸有偏好（Kendrick *et al.*, 1995）。低等动物一般依赖嗅觉，但有两种蜂（wasps，*Polistes fuscatus* 和 *Polistes metricus*），*P fuscatu* 是群居的、*P metricus* 是独居的，前者有识别个体脸的能力，后者没有（Sheehan and Tibbets, 2011）。

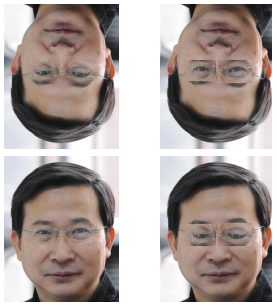

图 11-19　倒置效应

脸识别能力有倒置效应，对正立的脸敏感性远远大于倒置的脸（Yin，1969；Thompson，1980）。

用行为检测显示人对脸的关注在出生很早期就可能出现：9 分钟左右就对脸的反应大于其他（Goren，Sarty and Wu，1975），5 周就注视脸（Haith, Bergman and Moore, 1977），对脸是否好看也有不同的反应（Slater，1998，2000）。在 4 天区分不带围巾的母亲与其他人的脸、35 天区分带围巾的母亲和其他人的脸（Bushnell，Sai and Mullin，1989；Walton，Bower and Bower，1992；Pascalis *et al.*, 1995；Bruce *et al.*, 2000；Bartrip，Morton and De Schonen，2001）。3 个月识别熟悉的脸（De Haan *et al.*，2001）。用 fMRI 检测观察到，两个月的婴儿的对脸反应脑区被脸激活情况类似成人，但脸还激活婴儿的语言区域（Tzourio-Mazoyer *et al.*，2002）。脸激活与成人一样在 9 岁儿童（Gathers *et al.*，2004）、或 12 岁（Golarai *et al.*，2007）。黑猩猩在 4 周左右识别母亲的脸（Myowa-Yamakoshia，2005）。

对脸特异反应的神经细胞

1980 年代的一系列电生理实验证明猴的神经元对脸有特异反应（Bruce，Desimone and Gross,1981;Perret, Rolls and Caan,1982; Desimone *et al*., 1984; Perrett *et al*., 1984, 1985a, 1985, 1988b; Rolls, Baylis and Leonard, 1985; Saito *et al*., 1986; Perret, Mistlin and Chitty, 1987）。

初级视皮层 V1 继续投射到更高的区域，分为识别 where（物体空间位置）的背侧通路和识别 what（物体本征）的腹侧通路。

腹侧通路从 V1 到 V2、V4、及更远的区域，其可分辨的图像特征越来越复杂（Kobatake and Tanaka，1994）。颞下皮层（inferotemporal cortex，IT）可以识别更复杂的图形，如：圆、方块、多刺圆、手等（Gross, Bender and Rocha-Miranda，1969；Gross, Rocha-Miranda and Bender，1972）。

普林斯顿大学心理系科学家在猴的 IT（Gross, Rocha-Miranda and Bender，1972；Perret *et al.*, 1982；Desimone *et al.*, 1984）和颞上回（superior temporal sulcus，STS）（Bruce *et al.*, 1981）发现了识别脸的细胞，其中 IT 的脸识别细胞几乎都对脸特异反应，而对其他物体没有反应（Desimone *et al.*, 1984）。

STS 多感觉区域有只对脸反应的细胞（Bruce *et al.*, 1981）。例如，记录 497 个 STS 细胞，48 个只对脸反应，被脸持续激活，28 个细胞在脸有转向、或颜色、大小、距离变化后反应不变（Perret, Rolls and Caan，1982）。早期在 IT 一次记录中，41 个没有反应，110 个有反应的细胞中，66 个有选择性反应，其中 20 对形状反应、2 个对手反应、3 个对脸有选择性反应（Desimone *et al.*, 1984）。可以比较对脸和物体、脸和身体的反应，找到对这三种分别有选择性反应的细胞（Pinsk et al., 2005）。通过 fMRI 辅助确定电生理电极插入位置，可以找到特定区域内 97%的细胞都对脸有选择性反应（Tsao *et al*., 2006; Friewald, Tsao and Livingston, 2007），说明有脸特异区块（patch）。用脑表面光学成像观察，可以看到对脸呈现有选择性反应的脑区紧密相连（Wang, Tanaka and Tanifuji, 1996, 1998）。从而提出可能有脸朝向的功能柱（Tanaka，2003）。功能核磁共振实验也支持具有相似朝向选择性的面孔细胞在皮层上聚集（Dubois *et al*., 2015）。

脸识别细胞对于脸的要求是一个圆加两点一杠（大体相当于脸、眼和嘴）（Kobatake and

Tanaka，1994）。对脸有全面的识别和部件的敏感（Freiwald，Tsao and Livingston，2009）。在猴的脸识别细胞研究中，提出抑制性神经元可能对于脸识别很重要，去除 GABA 的抑制性作用后，原对脸（和其他物体）有特异反应的细胞失去反应特异性（Wang，Fujita and Murayama，2000）。用微电流刺激猴的面孔加工脑区 50-200 毫秒，可以增加其对脸的反应以及对个人面孔的识别（Afraz, Kiani and Esteky, 2006；Moelle *et al*., 2017）。

猕猴面孔脑区中较低级区域的神经元对面孔朝向非常敏感，而高级区域的神经元则可区分不同个体的面孔，且反应不依赖于面孔朝向，说明高级区域表征面孔个体这一抽象概念 (Freiwald and Tsao, 2010)。进一步的研究对面孔个体的具体编码方式进行了探索，用计算模型生成上千张参数化的面孔，给动物呈现面孔图片的同时记录猕猴的面孔脑区，发现面孔细胞的反应和面孔模型中的抽象特征呈简单的线性关系，从~200 个细胞的反应可相当准确地重构呈现给动物的原始面孔 （Chang and Tsao, 2017）。

人对脸反应的脑区类似于猴（Tsao *et al*., 2003; Tsao, Moellet and Freiwald, 2008；Pinsk *et al*., 2009；Srihasam *et al*., 2012）。在开颅手术的病人经过允许能用颅内记录事件相关电位改变（Allison *et al*., 1999; McCarthy *et al*., 1999, Puce, Allison and McCarthy, 1999），记录到脸特异反应。也直接记录到神经细胞对脸反应（Kreiman, Koch and Fried，2000）。更多的是用正电子扫描（PET）（Sergent，Ohta and MacDonald，1992；Haxby *et al*., 1994）和 fMRI（Malach *et al*., 1995；Puce *et al*., 1996; Clark *et al*., 1996; Kanwisher, McDermott and Chun，1997；McCarthy *et al*., 1997）。可以分别观察几个脑区（FFA、OFA 和 fSTS）对脸的部件和构型的敏感性（Liu, Harris and Kanwisher，2010）。跨颅磁刺激（TMS）是一种研究脑功能的方法（Walsh and Cowey，2000）。用 TMS 作用于特定脑区，可以观察到脸反应的变化（Pitcher *et al*., 2007, 2008, 2009）。FFA 对脸的部件和构型都敏感，OFA 和 fSTS 只对真的脸部件反应、对其构型不反应（Dzhelyova, Ellison and Atkinson, 2010）。

先天脸盲的遗传性

人类有不能识别脸的个体，诊断为脸盲（prosopagnosia，faceblind）（Bodamer，1947），分为先天型（发育型）和获得型。脸盲者可以识别其他物体，而不能识别脸（Farah, Levinson and Klein, 1995； Farah, 1996; Henke *et al*., 1998; Nunn, Postma and Pearson, 2001; Duchaine and Nakayama, 2005; Duchaine *et al*., 2006; Li and Song, 2007; Riddoch *et al*., 2008）。也有患者可以识别脸但不能识别其他物体（Feinberg *et al*., 1994; Moscovitch, Winocur and Behrmann，1997；McMullen，Fisk and Phillips，2000；Germine *et al*., 2011）。对于脸盲的机理，有多种解释，有些脸盲可能确实是脸识别能力的特异变化（Duchaine，2006）。

后天获得的脸识别异常，可以是病变或外伤（Yin, 1970; Meadow *et al*., 1974; Landis *et al*., 1986; Barton *et al*., 2002；Bouvier and Engel，2006；Schiltz *et al*., 2006； Steeves *et al*., 2006）。右脑单侧外伤就可以导致脸盲。如果可以在脑成像观察到病变部位，有助于了解参与脸识别的脑区（Riddoch *et al*.,2008）。这些可以与在正常人脑进行的核磁共振成像、外科手术人脑电生理记录相辅相成（Kanwisher, McDermott and Chun，1997；Tsao *et al*., 2003；Barraclouth and Perret，2011）。

双生子研究显示脸识别能力有高度遗传性（Polk *et al*., 2007；Wilmer *et al*.，2010；Zhu *et al*., 2010）。先天脸盲(congenital prosopagnosia, CP)，也称为发育性或遗传性脸盲(OMIM 610382)，最初在1976年被报道(McConachie, 1976) 是对脸的视觉学习和识别的选择性损害，缺乏任何可以检测到的神经损伤(Behrmann and Avidan, 2005; Damasio et al., 1990; Duchaine and Nakayama, 2006b; Gruter et al., 2008; Kress and Daum, 2003; McConachie, 1976; Nunn et al., 2001; Susilo and Duchaine, 2013)。问卷式的筛选方法(Kennerknecht, 2021; Kennerknecht et al., 2006; Kennerknecht et al., 2008a; Kennerknecht et al., 2007)与行为测试(Bowles et al., 2009) 都估计一般人群CP发病率在1.8 to 2.9%, 全球估计数千万CP个体。家系研究(De Haan, 1999; Dobel et al., 2007; Duchaine et al., 2007; Galaburda and Duchaine, 2003; Grueter et al., 2007; Johnen et al., 2014; Kennerknecht et al., 2006; Kennerknecht et al., 2008b; Kennerknecht et al., 2007; Lee et al., 2010; McConachie, 1976; Schmalzl et al., 2008) 和双生子研究 (McKone and Palermo, 2010; Polk et al., 2007; Wilmer et al., 2010; Zhu et al., 2010) 提示CP与脸识别能力具有高度遗传性。家谱分析观察到简单的常染色体显性遗传模式(De Haan, 1999; Duchaine et al., 2007; Grueter et al., 2007; Kennerknecht et al., 2006; Lee et al., 2010; Schmalzl et al., 2008)，显示单个基因的突变可以导致脸识别缺陷。这些表明经典遗传学和基因组学可以用于研究脸识别。

对人类疾病的遗传研究非常成功(Gusella et al., 1983; Schrott et al., 1972; Tsui et al., 1985)。对于用遗传学研究的可行性来说，没有必要假定人类认知与疾病有根本的差别。遗传学提供了可以研究人类认知的无创途径。近十年来，我们实验室进行了几次人类认知的全基因组相关研究

(GWAS)，从记忆、社会从众性、到视觉认知的感知切换和下行控制(Chen et al., 2018a; Chen et al., 2018b; Zhu et al., 2019; Zhu et al., 2016; Zhu et al., 2018; Zhu et al., 2020)。虽然我们发现了相关的标记，但我们不知道涵盖标记的基因、或标记附近的基因与所研究的认知有没有因果关系。遗传学上，大家系的连锁分析成功地找到人类疾病的基因突变。因此，我们决定进行人类遗传分析，寻找影响脸盲的基因。

我们从一个含 18 位日常生活中识别脸困难的大家系出发，发现了一个 CP 罹患基因，编码“多重 C2 区域跨膜 2”蛋白质 (*MCTP2,* GenBank: NM_018349)。在日常生活脸识别困难的人中找到更多的 *MCTP2* 罕见突变和相关性。fMRI 结果显示 *MCTP2* 突变 CP 患者对个体脸识别缺陷相关于右侧纺锤体脸区域(rFFA)对同样脸的重复呈现反应异常。我们的发现可以刺激用遗传学和基因组学研究人类高级认知。

三代含 CP 患者的家系

我们面试了一个三代家庭(家庭 A)的 35 位成员(表 1，附表 S1，图 1a)。18 家庭成员明显在日常生活中有脸识别困难: 9 位 (IV:2, IV:4, V:9, V:10, V:11, V15, VI:5, VI:6 and VI:9)在我们联系之前就知道他们早期生活就有这一问题；4 位 (IV:6, V:4, V:6 and VI:8)很长时间认人有可能但不知道原因; 5 位 (IV:10, V:1, V:13, V:19 and VI:7) 无视其日常生活中这一问题，而采取措施依赖脸之外线索的策略(表 1)。自动注视接触需求与脸识别困难或用代偿策略之间有显著的负相关($p < 0.001$, r = -0.658, n = 35)。

与以前研究(Johnen et al., 2014; Schmalzl et al., 2008)一致，家庭内就有异质性，无论是剑桥脸记忆检测-中文(Cambridge Face Memory Test-Chinese， CFMT-C) (Bowles et al., 2009; McKone et al., 2012)，配对剑桥车记忆检测(the matched Cambridge Car Memory Test，CCMT) (Dennett et al., 2012)还是脸倒置效应 (the Face Inversion Effect，FIE) 区别检测 (Yovel and Kanwisher, 2005)。14 位在真实世界有脸识别困难的家庭成员中 10 位在至少一种行为测试中有缺陷。V:1, V:9, V:11, V:13, V:15, V:19 和 VI:8 在 CFMT-C 得分中有一个分数低于正常水平的两个标准差(SDs)，而 V:4 (z = -1.60) 和 V:6 (z = -1.61)行为也明显差 (低于-1.5 SDs)。在检测整体加工的 FIE 区分试验, V:6 (z = -1.62), V:9 (z = -1.62), V:11 (z = -2.56)和 VI:5 (z = -1.81) 的导致效应缺陷。V:1 (z = -2.96), V:13 (z = -1.73), V:15 (z = -1.55)和 V:19 (z = -1.52) 区别正置脸的能力也很差。有四位(V:10, VI:6, VI:7 和 VI:9)日常有困难，但在脸识别的检测中表现无异。他们都在 CCMT 检测很好，显示他们识别其他物理刺激的能力正常，与其识别脸无关。每位成员的 Z 分见表 1。

染色体 15q 上特异区域含候选 CP 罹患基因

为了错在过分小心，家庭 A 的初步连锁分析(称为连锁 1，见方法)(附表 S1)，我们诊断 9 个家庭成员为 CP 患者(V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19 and VI:8)，诊断标准不仅是面谈显示脸孔识别异常，而且还在 CFMT 行为检测表现差。最高 LOD (logarithm of odds)分数为 3.49，提示可能有一个 CP 连锁基因，一个 3.9 兆碱基对 (Mb)的主要候选区域 (major candidate region，MCR)从 rs12148885 (chr15:94251330, 15q26.1)跨到 rs288435 (chr15: 98160439, 15q26.2)，对应于 15 号染色体上 1-LOD 下降区，依据于 hg19 组装 (图 1b)。基因组筛选结果显示于附图 S3a。一千次重复的计算机模拟显示经验 p 为 0.023，提示这一结果在基因组水平有显著性。另一区域 9q21.13 的 LOD 分数超过 1.0 (附图 S3a)，但计算机模拟没有达到基因组显著性。MCR 内同享的单倍型见附图 S4a。

有可能有些患者用应对策略完成了个体识别、而不是脸识别，导致分类的模糊(Dalrymple and Palermo, 2016; Duchaine and Weidenfeld, 2003; Grueter et al., 2007)。因此，我们进行了第二次连锁分析(连锁2，见方法)。较连锁1在患者中增加了4位日常有脸识别问题而在行为检测表现正常的(V:10, VI:5, VI:6 and VI:7)和4位日常脸识别问题的先证者(IV:2, IV:4, IV:6 and IV:10) (表S1)。连锁2分析延伸了连锁1，继续支持rs6497114 (chr15:94245722)和rs11045 (chr15: 96883321) 之间的区域LOD分数高于3 (最高LOD分数= 5.13)，跨染色体15q26.1至26.2之间的2.64 Mb (图1c，附图S3b)。另一区域10q24.2的LOD 分数高于1。模拟后，15号染色体上最高LOD分数有统计显著性($p < 0.008$)。MCR内同享的单倍型见附图S4b。

MCR 内用最新 NCBI 资料库(https://www.ncbi.nlm.nih.gov/genome/gdv/)注释的候选基因列在附表 S7。

全基因组测序揭示 *MCTP2* 基因的一个突变

为了找到 A 家庭连锁 CP 的染色体 15q26.1-26.2 区域的影响脸识别的因果关系突变，我们对连锁 1 的 9 位受影响个体(V:1, V:4, V:6, V:9, V:11, V:13, V:15, V:19 和 VI:8，表 S1)做了全基因组

测序(WGS)。MCR 内，染色体 chr15:94983466 上 *MCTP2* 只有一个变异(NM_018349.4:c.2147T>G, NP_060819.3:(p.I716S))在全部 9 位 CP 都是杂合体。这个异义突变 (c.2147T>G) 为 A 家庭特有，不存在于 dbSNP (v150), ExAC03 和 genomAD(v2.1.1)几个资料库，虽然这一位置还报道过另外多等位单碱基多样性(SNP)位点 rs200314451 ：在东亚 gnomAD v2.1.1 库, NM_018349.4:c.2147T>C, NP_060819.3:p.I716T 以最小等位基因频率(MAF) 0.000 存在， NM_018349.4:c.2147T>A, NP_060819.3:p.I716N 以 MAF 0.0001088 存在。在我们扩大的 3600 中国人队列中，我们没有检测到同一突变。

为了研究这一变异是否罹患 CP 的强候选者，我们在家系直接家系 Sanger 测序，并进行共分离分析。除了连锁分析 1 的 9 位, *MCTP2* 的 c.2147T>G [p.I716S]也存在于 4 位脸识别能力弱、但因为年龄不合适用行为检测的前辈，也存在于 CFMT-C 检测正常但日常生活中识别脸能力弱的 5 位家庭成员 (图 1a, 半实符号)。

所以, *MCTP2* 编码 NP_060819.3:p.I716S 的突变看来是这一大 CP 家系所有有日常脸识别问题的病人在 MCR 唯一共享的功能变异。SIFT (Ng and Henikoff, 2001)预计 I716S 致病。*MCTP2* 基因全长占基因组 DNA 的 180 千碱基对，有 22 个编码的外显子，编码的蛋白质有 878 个氨基酸残基，分成三个 C2 区域和两个跨膜区 (TMRs) (图 S5a)。第一个 TMR 的 NP_060819.3:I716 在发展出很好脸加工的灵长类高度保守 (附图 S5a 与 S5b) (Freiwald et al., 2016; Hung et al., 2015; Moeller et al., 2008; Tsao et al., 2003; Tsao et al., 2006; Tsao et al., 2008)。

扩大筛选找到更多 CP 和 CP 家系含更多 *MCTP2* 突变

在理论和实验考虑的基础上，罕见的功能等位基因被认为是表型遗传的主要贡献者(Cirulli and Goldstein, 2010; Heinzen et al., 2015; Jordan et al., 2010; Pritchard, 2001)。从典型的 A 家庭获得的结果显示罕见、甚至特有的 *MCTP2* 基因功能突变可能与 CP 表型有关。

在问卷筛选的第一个队列的 2904 人(见方法)中，我们找到 75 位分数与平均至少差 2 SDs 并测了其 *MCTP2* 外显子的序列。7 位中发现了 5 个罕见杂合子功能变异体，包括一个移码突变和 4 给异义突变 (图 2a 和附图 S5a, 附表 S8)。

MCTP2 基因外显子 1 的移码突变(NM_018349.4:c.239delG, NP_060819.3:p.S80fs)见于报告脸识别困难的 75 位中的 3 位(个体 B0001, B0009 和 B0046) (图 2b)。进一步面试揭示所有 3 位携带 p.S80fs 的报告长期且恼人的脸识别主观不确定性，在其早年意识到这一问题 (附表 S2。B0001 的一位亲戚携带 p.S80fs，采取了观察其他特征的策略，这样她需要更长时间识别人(图 2c, 附表 S2)。

在个体 B0011 的家庭，含外显子 5 的 NP_060819.3:p.M272L 突变的那些人报告他们自己认人的策略，但还是难于应对其困难(图 2d 与 2e, 表 S2)。外显子 8 的 NP_060819.3:p.T374A 突变见于 B0010 个体，自己认识到有严重的脸识别缺陷 (图 2f, 附表 S2)。 B0003 的家庭，外显子 12 的 NP_060819.3:p.V548I 突变与表型相关性很好(图 2g 与 2h, 附表 S2)。B0002 的家庭，NP_060819.3:p.R641Q 突变与家庭所有有表型儿童共分离(图 2i 与 2j)。这些突变位点在动物进化中保守(图 S5b)。

依据基因的相关分析揭示 *MCTP2* 罕见等位基因与脸识别的关联

下一步，我们在第二个有 1928 人的队列中也用问卷检查，得到脸识别能力，评估其与 *MCTP2* 等位基因对蛋白质编码有中度或重度影响的罕见变异的相关性。

基于负荷测验，在男性队列中，即使多次校正，检测到破坏性变异加全部异义突变有显著相关(所有变异 $p_{\text{burden}} = 0.0009$, $p_{\text{optical}} = 0.0021$，更可能有害的突变 $p_{\text{burden}} = 0.0032$, $p_{\text{optical}} = 0.0063$)。女性队列和同意变异中没有观察到相关性。表 2 显示贡献于这些显著性检测的变异的细节。我们的结果提示 *MCTP2* 基因高比例的因果变异往同一方向其作用，显示男性队列变异负荷与脸识别的相关性至少部分是因为的 *MCTP2* 作用。

CP 个体中移码突变

家系和群体研究结果支持改变蛋白质编码的 *MCTP2* 罕见等位基因与脸识别能力相关，意指 *MCTP2* 参与脸识别。如上所述，2904 位个体筛选到 75 位脸识别弱者中 3 位携带 *MCTP2* 基因第

一个外显子的移码突变 c.239delG (p.S80fs)，这去除 MCTP2 蛋白质的大部分。这样的频率在已报到的 CP 发生率范围中，足够高到可以通过反向表型途径在同意分析脸识别的人中找更多的携带者。

我们进一步在第三个含 1757 人的独立队列找这一移码突变。我们检测到 16 位杂合子携带者 MAF 为 0.0046。其中 14 人同意进一步检查(附表 S3)。我们的面试记录了 14 位携带者与 19 位来自同一队列的非携带志愿者之间人才脸识别行为的定量差别(表 3)。

四位(C2180、C2666、C3164 和 C3282)在我们联系之前就意识到其脸识别困难。检测 C2666 和 C3164 的全部能够检测的家庭成员显示这一突变在其两个家庭都与脸识别缺陷共分离 (图 3a 和 3b, 附表 S3)。

C3049 没有报告自己认人、认脸有可能，而是感到自己与其他人认人、认脸不同(附表 S3)。C3049 的家庭 (图 3c, 附表 S3)内，突变还见于两个亲戚(II:2 and III:1)，都有日常认脸困难。

其余 9 位在面试中认为自己与其他人一样、甚至更能认脸(附表 S3)。但是，其中 8 位(C2149、C2259、C3030、C3234、C3358、C3420、C3649 和 C3731)发展了适应的行为，依赖明确的学习策略认脸，这样日常识别熟人(全人，不局限脸)不难。当他们遇到没有特征的生人，屏幕上的演员(特别是女演员)，或者熟人但脱离场景，策略就不会都很好地工作，但他们再调节、并很快更新信息。C2149 的携带这一突变的亲戚抱怨识别困难(图 3d, 附表 S3)。C3030 的认人的策略遗传自父母(图 3e, 附表 S3)。C3649 的亲戚没有脸盲、也不携带这一突变(图 3f, 附表 S3)。C2147 在整个面试中没有显示明显的异常脸识别。

通过收集母-父-后代三人的微卫星资料(附图 S6)，排除共同祖先来源的可能性，估计出 c.239delG (p.S80fs)突变旁推测的单倍型。

MCTP2 突变 CP 家族神经成像研究

用 A 家族的 6 位成员，我们发现 FFA 区域对脸的异常反应与 *MCTP2* 基因的 I716S 突变相关。

多多年的研究一直观察到 rFFA 参与检测脸的存在和区分不同的脸(Grill-Spector et al., 2004; Haxby et al., 2000; Kanwisher et al., 1997; Puce et al., 1996; Rangarajan et al., 2014; Rotshtein et al., 2005; Yovel and Kanwisher, 2004; Zhang et al., 2012)。正如在正常参试者的 rFFAs (附图 S7a), 有 I716S 突变(A-VI:5, 附图 S7b, A-VI:7, 附图 S7c 与 A-VI:9, 附图 S7d)和没有 I716S 突变(A-VI:1, 附图 S7e, A-VI:2, 附图 S7f 与 AVI:10, 附图 S7g)的家庭成员都有显著的 rFFAs 活动。这些提示，独立于突变，A 家庭成员的 rFFA 都特异地对脸有反应。

为了检测家庭成员的rFFA能否加工脸的个体差异，我们用事件相关设计fMRI适应模式进行实验(Yovel and Kanwisher, 2005) (图4a)。在正常组，fMRI对脸个体特征适应的可预计的重复压制在rFFA高度显著(配对 t-建议 $p < 0.0001$, 图4b)。而且，每单个受试者对一对正置的不同的脸(UDF) 的引起的活动水平都高于一对正置的相同的脸(UIF): 'UDF>UIF' 的差别在20位正常人的18人中呈$p < 0.05$的显著，并在其余受试者中在预计的方向有非显著的趋势($p < 0.057, p < 0.25$)。在每一位没有I716S突变的家庭成员 (A-VI:1, 图4c, A-VI:2, 图4d 与A-VI:10, 图4e), UDF对引起的活动高于UIF对。'UDF>UIF'差别在每一位没有*MCTP2*突变的家庭成员呈$p < 0.05$的显著性。相反，有I716S突变的家庭成员(A-VI:5, 图4f, A-VI:7, 图4g and A-VI:9,图4h)之rFFA区域fMRI信号对不同脸的反应并不高于相同脸。有I716S突变的家庭成员的适应分(在感兴趣区域ROI，正置不同条件对正置相同条件百分比的变化) 低于每一位正常对照受试者(图5)，有I716S突变的家庭成员对比正常对照有相同方向缺乏显著的趋势(A-VI:5, $p = 0.05407$, A-VI:7, $p = 0.12832$ 与A-VI:9, $p = 0.06548$)。因为重复同样脸而导致rFFA神经活动降低看起来也在有I716S突变的个体减少，而不同脸在CP、非CP家庭成员和正常对照引起类似的rFFA活动。这些结果提示*MCTP2*基因突变的家庭成员rFFA对相同脸的反应受损，这样可以有机制解释为什么识别已经见过的脸有困难。

C2666 家有 *MCTP2* 基因的 c.239delG (p.S80fs) 突变，我们观察到 p.S80fs 的 III:4 (附图 S7h) 和无 p.S80fs 的 III:2 (附图 S7i)的 rFFA 都对脸有正常反应，但在日常脸识别困难的个体 III:4 (图 4j)的 rFFA 之 fMRI 对同样脸的重复也缺乏适应。

脸识别的分子遗传学研究

这是对人类高级认知的第一个分子遗传学研究，具体来说是用延伸家庭对脸识别的第一项分子遗传学研究。

我们的发现 *MCTP2* 基因的突变对人类 CP 有贡献。这一结论依据于：1) 连锁分析常染色体显性 CP 家庭 A 发现位于 15q26.1-q26.2 的 CP 位点(图 1, 附图 S3); 2) 一个 *MCTP2* 基因的特有突变 c.2147T>G (p.I716S)是 A 家系中在 MCR 全基因组测序找到的唯一完全与 CP 共分离的可以

改变蛋白质序列的突变(图 1); 3) 从 2904 人组成的队列中找到的 75 位脸识别困难的个体中 7 位脸盲者中发现 *MCTP2* 基因 5 个罕见突变 (Figure 2); 4) 这 7 位脸盲者中，4 位的家族成员愿被分析，皆显示基因型与表型的相关性 (图 2c, 2e, 2h 与 2j); 5) 1757 受试者的另一队列有 16 位携带与第 4 点里面 3 位脸盲个体相同移码缺失突变 c.239delG (p.S80fs), 其中 14 愿被进一步分析。14 位携带者日常脸识别行为不同于来自同一队列的 19 位非携带者 (图 3); 6) 14 位的 4 位有无疑的脸盲，其中两个家系愿被分析，结果都支持 c.239delG (p.S80fs) 与脸盲相关(图 3a 与 3b), 进一步的支持来自更多家系(图 3c、3d、3e 与 3f)，他们发展了明确的策略用非脸的线索克服其脸识别困难; 7) 在1928位组成的队列基因相关分析也检测到了 *MCTP2* 基因罕见等位基因与脸识别能力的相关性； 8) 在神经成像研究中，*MCTP2* 基因突变的家族成员脸识别缺陷与 rFFA 对个体脸反应异常相关联。

CP 的诊断

不同的认知任务研究 CP 显示异质性(Behrmann and Avidan, 2005; Kress and Daum, 2003; Le Grand et al., 2006; White and Burton, 2022)。虽然特异检测被证明有用(Duchaine and Nakayama, 2006a)，没有一个单独的检测有足够区分全部 CP 的能力(Duchaine and Nakayama, 2006a; Duchaine and Nakayama, 2004; Duchaine and Weidenfeld, 2003; Grueter et al., 2007; Shah et al., 2015)。

无论用哪个特定的任务，即使在同一个家庭类似的遗传和环境背景中(Johnen et al., 2014; Lee et al., 2010; Schmalzl et al., 2008)，都需要谨慎行为检测个体 CP 的严重性受很多因素影响，例如行为代偿，其他认知技能，脸或检测范式的经历。在有些 CP 病例，他们识别人有困难，但他们在行为检测中却还能表现相当好。脸加工任务表现差可以预计脸识别缺陷，而相反不成立。

除了用行为检测诊断脸识别，也常常需要依赖个体自我报告。但是需要考虑 Dunning-Kruger (DK)效应，一种元认知现象，在某个任务表现差的人错误地自认为比其他人更好，而表现很好的人自认为不如其他人(Dunning et al., 2003; Kruger and Dunning, 1999)。DK 效应见于脸识别自我报告 (自我估计)和他人估计 (同行估计) (Zhou and Jenkins, 2020)。理解脸识别自我报告检测时需要谨慎：很可能病例不知道其脸识别缺陷。但是通过仔细面试，可以发现他们有策略和日常习惯。同时，在 DK 效应中，虽然好的受试者低估其能量，他们只估计自己相当于平均，因此这不会显著影响其后表型判断，至少他们还被考虑为正常。因此，在我们的研究中，我们通过仔细面试家系成员作为首要的诊断基础。

MCTP2 的作用

MCTP2 基因编码的蛋白质有 3 个 C2 区域和两个跨膜区，类似参与突触传递的蛋白质(Shin et al., 2005)。其 C2 区域结合 Ca^{2+} (Shin et al., 2005)。很多有 Ca^{2+}结合 C2 区域的蛋白质参与膜和囊泡转运，在神经传递其关键作用(Cho and Stahelin, 2006; Shupliakov and Brodin, 2010)。

MCTP 类蛋白质的 C2 和跨膜区在非脊椎动物就保守，如线虫和果蝇只有一个 *MCTP* 基因，到哺乳类有两个基因 (*MCTP1* 与 *MCTP2*)。MCTP1 表达于纸上神经系统，被意指参与中枢神经系统神经元和突触的内吞循环(Qiu et al., 2015)。在果蝇， MCTP 参与稳定突触传递和自稳态可塑性(Genc et al., 2017)。斑马鱼的 4 个 *MCTP* 基因表达在神经和肌肉系统。 敲低 *MCTP2b* i 影响胚胎发育(Espino-Saldaña et al., 2020)。

人的 *MCTP2* 与 *MCTP1* 基因都与高度遗传的神经精神疾病注意缺乏/多动症(ADHD)有关联(Kweon et al., 2018; Mick et al., 2010)。“钙离子结合”的基因类别在 14 中 ADHD 相关基因中富集(Poelmans et al., 2011)。基因组分析在双极病找到 *MCTP1* 单碱基多样性 (SNP) (Scott et al., 2009)。也有一篇报道精神分裂症的 *MCTP2* SNP (Djurovic et al., 2009)。

在上面提到的 1757 人的第三个队列中，共找到并用 Sanger 测序验证了 MAF < 0.005 的 64 位编码或剪接位点罕见变异。在志愿同意的基础上进行了面试。16 位个体携带 移码确实突变 c.239delG (p.S80fs) (MAF of 0.0046) ，14 位接受了面试。在无关的 S80fs 变异携带者与脸识别能力直接维持了相关性。我们找到一个携带 S80fs 家庭 (C2666)有 10 位成员，突变与脸盲也有相关性。有趣的是，不仅携带 S80fs 的 II:5 有脸盲，其妻子 II:6 也有同样突变并有脸识别困难。我们进一步面试了 *MCTP2* 基因其他低频突变的个体。还有更多的个体及其家庭含移码突变和剪接位点突变也显示脸识别异常。

从成千样本得到的基因表达微队列资料显示 *MCTP2* 基因表达于人脑，包括颞叶(McCall et al., 2011)。被脸选择性一致可靠地激活的脑区 FFA，是颞叶皮层纺锤回的一个小区。人脑蛋白图谱显示了 MTCP2 蛋白质表达和分布概括，包括在纺锤回(Sjostedt et al., 2020)。

fMRI 作为诊断内表型的方法并提供表型与脑活动之间的机理联系

fMRI 显示特定任务/行为或条件下神经元激活区域。在复杂的神经行为异常疾病，内表型例如如 fMRI 被认为可以较临床检测类别更好地代表病理生理学(Rasetti and Weinberger, 2011)。神经成像-遗传读出允许更分层地区分特定危险等位基因对脑活动的影响，而不仅是简单诊断表型。

在本研究，我们在适应范式(Grill-Spector et al., 2006; Grill-Spector and Malach, 2001; Henson and Rugg, 2003)加入了成像-基因研究来显示家庭中脸识别困难成员受 I716S 或 S80fs 突变的影响。在正常对照者、以及家庭中没有 *MCTP2* 突变的成员中，在重复呈现同样的脸的时候，rFFA 区域的神经信号显示降低，而在携带 *MCTP2* 突变的家庭成员中没有这种适应。未来研究中， fMRI 可以考虑为脸识别的重要内表型。

参与脸识别的基因

我们的遗传结果提供证据表明 *MCTP2* 基因突变导致先天脸盲，我们 fMRI 结果提示 *MCTP2* 基因参与区分脸所需要的神经环路。

当然，高级认知需要很多细胞和分子。*MCTP2* 不会是唯一参与 CP 的基因。从 2904 人队列找到的 75 位 CP 患者中只有 7 位携带 *MCTP2* 基因突变。从 1928 人队列中女性脸识别能力与 *MCTP2* 罕见等位基因没有相关性。更多的连锁研究将有帮助。

我们发现更多家庭没有遗传基础，这需要更多分析。无假设的基因组分析可以考虑用下代基因组分析，包括常见和罕见遗传变异，需要大样本，超过百万人，找到更多遗传线索，也验证我们有关人脸识别的 *MCTP2* 结果。

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