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Ⅲ．研究成果の刊行物・別刷

2010(平成22)年，肝炎対策推進のため，肝炎対策基本法が施行された。

(小松正子)

G 精神疾患

厚生労働省の2008(平成20)年の調査では，精神疾患の患者は323万人にのぼり，237万人の糖尿病，152万人のがんなど他の4大疾病を大幅に上回った。少子高齢化の影響でアルツハイマー型認知症が増加する一方で統合失調症や気分障害は減少傾向にあるが，2011(平成23)年調査でも患者数は320万人を超えている。このような現状を受け同省は2013(平成25)年4月から精神疾患をがん，脳卒中，急性心筋梗塞，糖尿病と並ぶ「5大疾患」と位置づけ，「5疾患5事業」をスタートさせた。この事業は精神疾患の早期発見と共に地域での精神医療(病院・診療所・訪問看護ステーションの連携強化など)の向上を図ることで精神疾患患者の増加を抑制する事を目標としている。

a 気分障害(双極性障害，うつ病性障害)

気分障害は統合失調症と並ぶ内因性(現在時点でははっきりした原因がわからないが，脳の機能的障害に基づくだろうと推測されている)精神病の一つとされていた。しかし，最近はできるだけ症状に基づいた分類を行うという方針から内因性等の区別なく診断されるようになった。そのため，従来は「神経症」に分類されていた心因に基づくうつ状態も気分障害に分類されるようになった。近年のうつ病増加の原因の一つに診断基準の変化もあると考えられている。**DSM-IV-TR**(アメリカ精神医学会，精神科疾患の診断・統計マニュアル第4版TR)では気分障害を双極性障害とうつ病性障害(以下うつ病と略)に大別している。双極性障害は躁病(気分の高揚と活力および活動性の増加)とうつ病(気分の低下と活力および活動性の減少)のエピソードが反復するものである。生涯有病率は日本では双極性障害0.4～1%，うつ病(非双極性)は双極性障害よりも多く1.3～17.8%と推定されている。うつ病は2：1の割合で女性に多く，年齢的には思春期・青年期に多い。具体的な症状としては，抑うつ気分，気力の低下，興味・関心の喪失，注意・思考力の低下，易疲労感，不眠，食欲・性欲の減退を訴えることが多い。治療は患者に強い希死念慮(具体的な自殺方法を考えている)がある場合を除いて外来で行われることが多い。薬物療法と精神療法の一つである認知行動療法が効果的で，ほとんどの患者は完全寛解し，予後は一般に良好である。うつ病で問題となっていることに①地域社会にいるうつ病者のうち医師を訪れるのはわずかで，その中でも専門の精神科医を訪れる患者は更に少ないこと(氷山現象)，②子供にはうつ病はないとの思い込みから小・中学生のうつ病が見逃されていることである。最近の報告によると，100人のうち小学生は1～2人が，中学生は4～5人が「うつ病」の可能性があるという(傳田，2002)。③従来では適応障害と診断されていたと思われる自ら「うつ病」と訴えるうつ病(未熟型うつ病，回避型うつ病，逃避型うつ病；広瀬哲也，新型うつ病など)が増加している。抗うつ薬は余り効果がなく，精神療法に導くことも困難なケースが多い。

うつ病は出現頻度が高く，経過も長いので，これが人類の健康に及ぼす影響の大きさが注目されている。世界保健機関は疾病や傷害が世界人類の健康に及ぼす負担(the global burden of disease: GBD)を計算し，2020年にはうつ病性障害が虚血性心疾患に次いで負担になるだろうと予測している。日本では中高年の自殺が増加し，自殺の背景としても注目されている。

b　統合失調症

以前 schizophrenia は「精神分裂病」と和訳されていた。この診断名はまるで「精神が分裂している病で，何をするかわからない恐ろしい病気」といった暗いイメージを一般の人に与えていたため，実際は回復可能な病気にも関わらず，患者や家族は偏見に基づく苦痛を強いられていた。また，病名に悪いイメージがあるために精神科医も病名告知をためらいがちとなっていた。そのため患者は自分の病名を知らずに治療を継続する困難さを感じ，利用可能な福祉サービスにも無頓着となっていた。そこで，2002(平成14)年に，日本精神神経学会において，本疾患の日本語の呼称を「**統合失調症**」と変更することが決定された。現在では，厚生労働省の諸手続きもこの病名の使用が定着している。

わが国における一般人口中における出現頻度(発生率または罹患危険率)は0.7%前後と高く，**精神病院入院患者**の60～70%を占めている。この出現頻度は洋の東西を問わずほぼ一致している。発生率には性差が無く，10代後半～30歳代に発症することが多い。成因は不明であるが，病的素因または中枢神経系の脆弱性があり，これが環境因(心因)を誘因として症状を形成する(**脆弱性・ストレスモデル**)との考え方が有力である。症状は**陽性症状**，**陰性症状**，**認知障害**の3つに大別されている。陽性症状は被害妄想や幻視・幻聴といった症状で，一般の人には基本的には体験できない。陰性症状は意欲の減退や喜怒哀楽の感情が乏しくなるなど，一般の人が本来もっている基本的な精神活動が減退するものである。認知の障害としては注意障害・記憶の障害・概念形成障害などが認められる。

現在では，特に薬物療法の進歩により，入院期間が短縮し，60%以上の患者が寛解・不完全寛解に至っている。しかしながら，服薬継続下の寛解であるため，服薬を中止すると社会的ストレスなどの為に容易に再発する。このように退院と再発後の再入院を繰り返す現象は回転ドア現象と呼ばれ，薬物療法の効果への過信を戒めるとともに，精神福祉の重要性を強調するものである。

c　神経症性障害，ストレス関連障害，および身体表現性障害

以前は神経症(neurosis)とよばれ，精神的要因(心因)によって精神的あるいは身体的症状が出現する状態をさす。現在は後に述べるように，この障害に心因以外の要素も関連する可能性も示唆され概念が揺らいでいる。そのため，ICD-10(国際疾病分類10改訂版)では表題のように「神経症」という名称は便宜上使用されているものの，DSM-IV-TR では「神経症」という名称はもはやない。この障害の精神症状は不安(不安障害)，強迫症状(無意味であるとわかっていても，同じ考えや確認行為を繰り返す；強迫性障害)，各種の解離性精神症状(意識障害や痙攣など；解離性(転換精)障害)などがあり，身体症状は身体的原因のない身体不調(身体表現性障害)がある。最近，特に注目されている障害は**心的外傷後ストレス障害**(post-traumatic stress disorder: PTSD)とパニック障害である。

PTSD は自然災害，大事故，テロ等の例外的に著しく脅威的あるいは破壊的な性質をもったストレスが心的外傷(トラウマ)となり，遅延または遷延した反応として現れる。日本では，阪神・淡路大震災でその存在を注目されてから，一般的となった。典型的な症状は無感覚と感情鈍化，外傷を重い出させる状況を避けているのに，ストレスとなった場面が無意識に思い出される**フラッシュバック**，夢の中で繰り返される外傷の再体験である。時に強い恐怖感，パニック，攻撃性が急激に生じることがある。強い驚愕反応，不眠，不安，抑うつを伴い自殺念慮を伴うこともある。

パニック障害は突然起こる反復性の重篤な不安発作(パニック発作)を主症状とし，発作時には窒息

感・動悸・めまい感・胸痛が出現して「死」の恐怖感を伴うことが少なくない。窒息感や動悸などの身体症状が呼吸促迫を起こして二次的に過呼吸症候群を生じ，四肢のしびれ感，冷感，苦悶感も加わることがある。不安発作は概ね数分間で治まるが，また同じような発作が起こるのではないかという不安(予期不安)に苛まれ，日常生活に支障をきたすこともある。乳酸ナトリウムの注射が患者のパニック発作を誘発することから心因だけでない生物学的な要因も関与すると考えられている。

d　薬物依存

精神作用物質使用による精神障害および行動の障害には，アルコール，アヘン類，マリファナのような大麻類，鎮痛剤や催眠剤，コカインや他の覚せい剤，タバコや揮発性溶剤などの使用により起こる障害が含まれる。その状態は，中毒，有害な使用，依存症や精神病性障害を含んでいる。有害な使用とは，身体あるいは精神面の健康に害を及ぼすときに使用される。依存は「薬物の使用による快楽を得るため，あるいは離脱(薬物の使用を中止すること)による不快を避けるために，有害であることを知りながらその薬物を続けて使用せずにはいられなくなった状態」を指し，薬物の反復摂取は報酬系を中心とした脳の機能変化を引き起こすと考えられている。

世界的に最も広く使用されている**精神作用薬物**はたばこと**アルコール**であるが，これらについては他項(喫煙・飲酒)を参照されたい。わが国では，**覚せい剤**と**有機溶剤**の乱用が多く，特に覚せい剤は1995年から第3次乱用期に入ったが，2005年頃からピーク時の3割程度に減少し，その後は横ばいの状況となっている。これは，一部外国人による密売の増加，乱用の低年齢化，インターネットなど新しい通信技術の悪用などの特徴を持ち，対策が困難となっている。また，覚せい剤は単に依存を形成するだけでなく，統合失調症に酷似した症状をもつ**覚せい剤精神病**を引き起こす危険性があるので，特に注意が必要である。精神作用薬物は覚せい剤取締法などの法律によって厳しい規制が行われているが，最近は“合法あるいは脱法(法の規制を受けていない薬物；ある種の「ハーブ」など)”が簡単に入手でき，若者を中心に乱用が増加し，社会問題となりつつある。中には使用で死亡する事もあり，精神のみならず生命にも危険を及ぼす。

e　児童期にみられる精神・行動の障害

広汎性発達障害：当初はカナー(L. Kanner)が「聡明な容貌・常同行動・高い記憶力・機械操作の愛好」などを特徴とする一群の幼児に対し，「自閉症」(オーティズム)と名づけられた。その後，親の育て方で自閉症になるなどの間違った認識もあったが，現在は先天性の脳障害であることがわかり，広汎性発達障害の小児自閉症(自閉症)に分類されている。この障害には自閉症状と知的障害の2つの障害がいろいろな割合で存在し，多くは3歳までに気づかれる。知的障害がないものはアスペルガー症候群として自閉症とは区別されている。

自閉症状で問題となるのはコミュニケーションの障害や興味や関心が限局していることで，具体的には「視線を合わせない」，「おうむ返しの返答」，「友達と遊ばない」，「変化を嫌い，儀式などに固執する」，「思い通りにならないとひどい癇癪(かんしゃく)を起こしたり，手首を噛むなどの自傷行為を行う」ことである。今のところ治療法はなく，療育が中心となり，補助的に薬物治療を行うこともある。

注意欠陥多動性障害(ADHD)：極端に落ち着きがなく注意散漫で衝動的な行動をとる障害である。生後5か月ごろに発症し，女子より男子に多い。衝動的で，事故を起こしやすく，不注意から軽率な規則違反を起こし，親の躾(しつけ)の問題と誤解されることがある。しかし，これは脳の機能障害が原因と考えられ，親の躾が原因ではない。知的障害を伴わなければ，知能は普通である。不注意や衝動性などから学業の成績によい時と悪い時の波があることが多い。

薬物療法としては行動を鎮静するために覚醒剤の一種であるメチルフェニデートなどが効果を示す場合がある。いずれにせよ薬物療法は補助的であり，学校と家庭が連携して療育を行うことが肝要と思われる。むやみに叱ったり，教師と親の対応が全く異なるなど学校と家庭の療育の連携が悪いと，反抗挑戦性障害や行為障害，最悪の場合犯罪に発展する場合もあると考えられている(DBD マーチ，DBD：disruptive behavior disorder，破壊的行動障害)。児童・思春期の精神疾患はいずれも学校や家庭の連携ある対応が重要であるが，ADHD においてはその重要性はさらに高いと思われる。

H　自殺，不慮の事故，虐待，暴力

a　自　殺

自殺は世界的には15～34歳の年齢群で死亡原因の上位3位にあり，世界公衆衛生上の重大な問題となっている。自殺率は10万人につき15.1人とされ，老年期を除き圧倒的に男性に多い(男：女3.5：1)。警察庁生活安全局の報告によると日本では，中高年の自殺の増加に伴い，2003(平成15)年の自殺既遂者は34,000人を越えてピークとなり，以後約3万人で推移していたが，2012(平成24)年の速報では3万人を下回り，減少傾向を示している。自殺未遂者は自殺既遂者の20倍以上になるといわれ，日本でも大きな社会問題となっている。同局の報告によると2011年度の自殺の原因・動機としては，「健康問題」が最も多く，「経済・生活問題」，「家庭問題」がこれに続いている。精神障害による自殺のなかでは，うつ病が最も多く(Pokorny, 1964, 2011年生活安全局統計)，その自殺は繰り返される傾向がある。統合失調症，薬物依存などの精神疾患も原因となっている。

自殺予防の1つとして，自殺の危険性が高い精神疾患であるうつ病の有無を明らかにして，治療に結びつけることが挙げられる。うつ病は治る病気であることから，家族や職場でうつ病に関する教育を行い，うつ病の場合には早急に治療を受けさせるようにすることが重要である。「仕事の失敗から」，「借金を苦にして」，「人間関係に疲れて」などによるとされる自殺のかなりの部分は，適切な医療を受ければ治癒し得るうつ病によるものと考えられている。また，中高年男性の自殺には飲酒が少なからず関連する事が分かっており，アルコールの有害作用に関する対策(啓発や依存症自助団体支援・関連機関の連携強化)も行っている。老年期の自殺予防には孤独感や疎外感をもたせないこと，何らかの役割をもたせる事が有効とされている。また，一度自殺企図を行った人は，繰り返す傾向があるので充分な注意が必要である(一度自殺を図って助かった人は二度と自殺しないというのは間違いである)。

b　不慮の事故

不慮の事故とは言葉通り「思いがけずに」遭遇する事故を指し，具体的には交通事故・窒息・転倒

転落・溺死・火災・中毒に分類されている。厚生労働省の平成21年度「不慮の事故死亡統計」によると，1969～1972(昭和44-47)年の42,000～43,000人をピークに急激に減少し，1988(昭和63)年の28,000人で減少のピークを迎えて再び増加し，1995(平成7)年の阪神・淡路大震災で一時45,000人に急増したが，1996(平成8)年以降2008(平成20)年までは37,000～40,000人台で推移している。大震災が起こるとピンポイント的に増加するので東日本大震災のあった2011(平成23)年の統計数は一過性に急増すると予想される。

さて，現時点で最新である2012年の不慮の事故で最も多かったのは，窒息10,338，溺死及び溺水7,963，転倒・転落7,761，次いで交通事故6,414が続いている。窒息は乳幼児と65歳以上の高齢者に多く，乳幼児では吐物や異物が高齢者では餅などの食物が原因になることが多い。交通事故は年々減少しているが，10～20歳と高齢者に多く，両者共に交通安全の徹底が重要と考えられている。高齢者は聴力・反応速度の低下など加齢による身体能力の低下が原因になる事が多い。転倒転落や溺死も高齢者に多く，少子高齢化に伴い高齢者の不慮の事故は増加する傾向がある。

c　虐待，暴力

暴力は哲学的・心理学的・社会学的・政治的にも盛んに議論されており，厳密な定義は難しいが，「個人(または集団)の力を他者の意思に反して強制的に加える事」という認識は共通している。戦争・テロリズムなど事象は多岐にわたり，後に述べる虐待も暴力の一つである。

虐待とは自分の保護下にある者(ヒト，動物など)に対して，長期間にわたり暴力を加えたり，日常的に嫌がらせや無視をするなどの行為を行うことをいう。虐待の内容により殴るけるなどの身体的暴力を加える身体的虐待，バカ・ブスなど心理的な暴力を加える心理的虐待，性的暴力を加える性的虐待，無視や責任を放棄するネグレクト，金銭を与えないなどの経済的虐待に分類される。虐待の対象による分類である児童・配偶者・高齢者虐待という言葉は残念ながら日常でもよく聞かれる。厚生労働省によると2011(平成23)年度の児童虐待相談件数は統計を取り始めた1990(平成2)年の1,101件から急激に増加し，59,919件に達して，深刻な社会問題となっているが，虐待による死亡者は2009年度の142人をピークにここ数年は100人を下回っている。

虐待は世代間連鎖されることが少なくなく，自らの被虐待経験を綴った「"It"(それ)とよばれた子」(デイブ・ペルザー著)のなかでも自分を虐待する母もまた祖母に虐待されていた事実を知り，虐待の連鎖を断ち切る苦悩を述べている。一方，幼少期に虐待を受けると成長して境界性人格障害や多重人格に発展する危険性がある。

(吉田寿美子)

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ORIGINAL ARTICLE

Genome-wide association study identifies a potent locus associated with human opioid sensitivity

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Opioids, such as morphine and fentanyl, are widely used as effective analgesics for the treatment of acute and chronic pain. In addition, the opioid system has a key role in the rewarding effects of morphine, ethanol, cocaine and various other drugs. Although opioid sensitivity is well known to vary widely among individual subjects, several candidate genetic polymorphisms reported so far are not sufficient for fully understanding the wide range of interindividual differences in human opioid sensitivity. By conducting a multistage genome-wide association study (GWAS) in healthy subjects, we found that genetic polymorphisms within a linkage disequilibrium block that spans 2q33.3–2q34 were strongly associated with the requirements for postoperative opioid analgesics after painful cosmetic surgery. The C allele of the best candidate single-nucleotide polymorphism (SNP), rs2952768, was associated with more analgesic requirements, and consistent results were obtained in patients who underwent abdominal surgery. In addition, carriers of the C allele in this SNP exhibited less vulnerability to severe drug dependence in patients with methamphetamine dependence, alcohol dependence, and eating disorders and a lower 'Reward Dependence' score on a personality questionnaire in healthy subjects. Furthermore, the C/C genotype of this SNP was significantly associated with the elevated expression of a neighboring gene, *CREB1*. These results show that SNPs in this locus are the most potent genetic factors associated with human opioid sensitivity known to date, affecting both the efficacy of opioid analgesics and liability to severe substance dependence. Our findings provide valuable information for the personalized treatment of pain and drug dependence.

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Keywords: analgesia; dependence; opioids; pharmacogenetics

INTRODUCTION

The opioid system has important roles in both antinociception and reward.[1,2] Therefore, opioids, such as morphine and fentanyl, are widely used not only as effective analgesics for the treatment of acute and chronic pain but also as abused drugs. The opioid system is also involved in the rewarding effects of morphine,[3] ethanol,[4] cocaine,[5] and various other drugs[6–8] or behaviors. However, opioid sensitivity is well known to vary widely among individual subjects,[9] resulting in differences in the effectiveness of opioid analgesics and vulnerability to dependence on opioids and other drugs or behaviors. Individual differences may be attributable to both genetic and environmental factors,[10] although the relative influence of each of these factors can be diverse. To date, several candidate genetic polymorphisms have been reported to be associated with opioid sensitivity in human studies.[10–14] However, such polymorphisms have not sufficiently explained the wide range of interindividual variance observed in the sensitivity to opioid analgesics. A genome-wide approach has not yet been adopted to explore the best candidates, although this approach has been applied to other pharmacogenomics-related traits. Several genetic polymorphisms have been found to be associated with the sensitivity to pharmacotherapies.[15–17] In this study, we sought to comprehensively identify genetic polymorphisms in the human genome that could greatly contribute to individual differences in opioid sensitivity by conducting a genome-wide association study (GWAS) of healthy subjects and further analyses.

MATERIALS AND METHODS

Subjects

Enrolled in this multistage GWAS were 355 healthy patients who were scheduled to undergo cosmetic orthognathic surgery for mandibular prognathism at Tokyo Dental College Suidoubashi Hospital. The surgical

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protocol and subsequent postoperative pain management were fundamentally the same as a previous study[12] and are detailed in the Supplementary Information.

The subjects recruited in the additional analysis to confirm the association between the rs2952768 single-nucleotide polymorphism (SNP) and postoperative opioid analgesic requirements were 112 patients who underwent major open abdominal surgery at several related hospitals. The surgical protocol and subsequent postoperative pain management were fundamentally the same as a previous study[11,18] and are detailed in the Supplementary Information. Enrolled in the study to investigate the contribution of the rs2952768 SNP to the symptoms of drug dependence or related personality traits were 203 patients with methamphetamine (METH) dependence with clinical data that included their multisubstance abuse status, 438 patients with alcohol dependence with clinical data that included the number of drugs used, 228 patients with eating disorders with clinical data including the presence or absence of other psychiatric disorders such as substance dependence and 500 healthy volunteer subjects with personality profile data from the temperament and character inventory (TCI).[19–21] To examine the mRNA expression levels of the *METTL21A* (*FAM119A*) and *CREB1* genes, 100 post-mortem human brain specimens, from which DNA and RNA were extracted for experimental use, were obtained from the Stanley Medical Research Institute (SMRI; Bethesda, MD, USA) as samples independent of those in the association study with opioid sensitivity (SMRI samples).

All of the individuals included in the study originated from Japan, with the exception of those from whom the SMRI samples were obtained, whose racial background was mostly European American (see Supplementary Information).

The study protocol was approved by the Institutional Review Boards at the related hospitals, Tokyo Institute of Psychiatry (currently Tokyo Metropolitan Institute of Medical Science) and the ethics committee of each participating institute of the Japanese Genetics Initiative for Drug Abuse.[22,23] All of the subjects provided informed, written consent for the genetic studies. The detailed demographic and clinical data of the subjects are provided in Supplementary Tables 1, 5–8 and 10.

Genotyping

After total genomic DNA was extracted from whole-blood samples using standard procedures, whole-genome genotyping was performed using the Infinium assay II with an iScan system (Illumina, San Diego, CA, USA) according to the manufacturer's instructions. The data for the whole-genome genotyped samples were analyzed using BeadStudio or GenomeStudio with the Genotyping module v3.3.7 (Illumina) to evaluate the quality of the results. In the data-cleaning process, the samples with a genotype call rate of <0.95 were excluded from further analyses. As a result, one sample was excluded from further analyses. Markers with a genotype call frequency of <0.95 or 'Cluster sep' (that is, an index of genotype cluster separation) of <0.1 were excluded from the subsequent association study. A total of 295 036 SNP markers survived the filtration process and were used for the GWAS (Supplementary Figure S1).

For additional genotyping of the rs2952768 and rs2254137 SNPs, the TaqMan allelic discrimination assay (Life Technologies, Carlsbad, CA, USA) was mostly conducted after total genomic DNA was extracted from whole-blood or oral mucosa samples using standard procedures. For samples that were not appropriately genotyped by this assay, direct sequencing was alternatively adopted to genotype the rs2952768 SNP. A total of 112, 203, 438, 228, 500 and 105 DNA samples from patients who underwent major abdominal surgery, patients with METH dependence/psychosis, patients with alcohol dependence, patients with eating disorders, healthy volunteer subjects and SMRI, respectively, were used to genotype the rs2952768 SNP. In addition, a total of 105 DNA samples from the post-mortem specimens for the expression analysis were used to genotype the rs2254137 SNP, although genotyping this SNP for other samples was not conducted because of the strength of the linkage disequilibrium (LD) with the rs2952768 SNP. The genotype distribution of the rs2952768 SNP in patients with METH dependence/psychosis, patients with alcohol dependence and patients with eating disorders is provided in Supplementary Table 9.

Quantitative PCR procedure

The SMRI RNA samples were treated with DNase I using the RNase-Free DNase Set (Qiagen, Hilden, Germany), and clean-up was then performed using the RNeasy MinElute Cleanup Kit (Qiagen). First-strand complementary DNA for use in the real-time quantitative PCR was synthesized with the SuperScriptIII First-Strand synthesis system for quantitative reverse transcriptase-PCR (Life Technologies) with 100 ng purified total RNA according to the manufacturer's protocol and diluted properly with diethylpyrocarbonate-treated H_2O before the experiments.

To perform real-time quantitative PCR with a LightCycler 480 (Roche Diagnostics, Basel, Switzerland), TaqMan Gene Expression Assays (Life Technologies) were used as a probe/primer set specified for the *FAM119A* (*METTL21A*) gene and *CREB1* gene and a probe/primer set for the *ACTB* gene, a house-keeping gene that encodes β-actin. The expression level of the *FAM119A* (*METTL21A*) gene or *CREB1* gene was normalized to the expression level of the *ACTB* gene for each sample, and relative mRNA expression levels were compared between the genotype subgroups for each gene. The experiments were performed in triplicate (separate experiments) for each sample, and average values were calculated for normalized expression levels.

Statistical analysis

A three-stage GWAS was conducted for the patients who underwent painful cosmetic surgery to investigate the association between opioid sensitivity and the 295 036 SNPs that passed the quality control criteria in a total of 353 subjects (118, 117 and 118 subjects for the first-, second- and final-stage analyses, respectively). As an index of opioid sensitivity, postoperative patient-controlled analgesia fentanyl use during the first 24-h postoperative period was used because analgesic requirements likely reflect the efficacy of fentanyl in each individual. To explore the association between the SNPs and phenotype, linear regression analyses were conducted in each stage of the analysis, in which postoperative fentanyl use ($\mu g\,kg^{-1}$; log transformed) and the genotype data of each SNP were incorporated as dependent and independent variables, respectively. Additive, dominant and recessive genetic models were used for the analyses because of the previously insufficient knowledge about the genetic factors associated with opioid sensitivity. The GWAS procedure is summarized in Supplementary Figure S1. In the first-stage analysis of 118 subjects, the SNPs that showed statistical *P*-values of <0.05 were selected as the candidate SNPs for the second-stage analysis among the 295 036 SNPs. For these SNPs, the second-stage analysis was conducted; again, the SNPs that showed $P<0.05$ were considered potent candidates and selected for further final-stage analysis. In the final stage of the three stages, the *Q*-values of the false discovery rate were calculated to correct for multiple testing in addition to the *P*-values based on previous reports.[24,25] The SNPs that showed $Q<0.05$ in the analysis were considered genome-wide significant.

Additional analyses were conducted using the samples of the patients who underwent major abdominal surgery, patients with METH dependence/psychosis, patients with alcohol dependence, patients with eating disorders, healthy volunteers with personality profile data and post-mortem specimens for the expression analysis. For all of the genotype data used in these analyses, the distributions were checked using the χ^2 test, and the absence of significant deviation from the theoretical distribution expected from Hardy–Weinberg equilibrium was confirmed (Supplementary Table 13).

In the analysis of the patients who underwent major abdominal surgery, the calculated total dose of rescue analgesics administered during the first 24-h postoperative period was used as an index of opioid sensitivity. To explore the association between the SNPs and phenotype, Student's *t*-test or analysis of variance was performed, in which Bonferroni correction for multiple comparisons was used for the *post hoc* tests. For these analyses, postoperative analgesic use ($\mu g\,kg^{-1}$; log transformed) and the genotype data of each SNP were incorporated as dependent and independent variables, respectively. χ^2 Tests were performed to investigate the contribution of the SNPs to the vulnerability to the presence of serious symptoms of substance dependence. For the analyses in which the number of subjects in a cell in 2×2 contingency tables was <5, Fisher's exact tests were conducted instead of χ^2 tests. In the analysis of healthy volunteers with personality profile data, raw TCI scores were properly processed (see Supplementary Information). To explore the association between the SNPs and phenotype, linear regression analyses were conducted, in which the endpoint TCI score (log transformed) and genotype data of each SNP were incorporated as dependent and independent variables, respectively. The correction of multiple tests for the analyses of the seven phenotypes was not performed in the present exploratory study. In the analysis of the post-mortem specimens for the expression analysis, the calculated expression level of the *FAM119A* (*METTL21A*) gene or *CREB1* gene normalized to the *ACTB* gene for each

sample was used. To explore the association between the SNPs and phenotype, Student's *t*-test or analysis of variance was performed, in which Bonferroni correction for multiple comparisons was used as the *post hoc* test. For these analyses, the relative expression level and genotype data of each SNP were incorporated as dependent and independent variables, respectively.

For all of the statistical analyses described above, SPSS 18.0J for Windows (International Business Machines Corporation, Armonk, NY, USA), gPLINK v. 2.050, PLINK v. 1.07 (http://pngu.mgh.harvard.edu/purcell/plink/; accessed 1 March 2012),[26] and Haploview v. 4.1[27] were used. The criterion for significance was set at $P<0.05$, with the exception of the GWAS. Statistical corrections for multiple tests, such as Bonferroni adjustments on the multiple parameters analyzed, were not performed in the present exploratory study after the GWAS because it would be too conservative for genetic association studies,[28] meaning that the likelihood of type II errors is increased by Bonferroni adjustments, and truly important differences would be deemed nonsignificant.[29]

Additional *in silico* analysis

Additional *in silico* analyses and the Internet links for the websites of the databases referenced are provided in the Supplementary Information.

RESULTS

Identification of a potent locus associated with human opioid sensitivity by GWAS in subjects who underwent painful cosmetic surgery

We first explored the association between genetic variations and opioid sensitivity in a total of 353 healthy subjects who were scheduled to undergo cosmetic orthognathic surgery (mandibular sagittal split ramus osteotomy) for mandibular prognathism that involved the administration of opioid analgesics (Supplementary Table S1), in which the surgical procedure was uniform and thus the invasiveness and resultant pain would be regarded as homogeneous among the subjects. A GWAS was conducted as a consecutive three-stage analysis to identify potent SNPs associated with the requirements for an opioid analgesic, fentanyl ($\mu g\,kg^{-1}$), during the 24-h postoperative period (Supplementary Figure S1). Consequently, 9, 12 and 10 SNPs were selected as the top candidates for additive, dominant and recessive models for each minor allele, respectively, after the final stage (Supplementary Tables S2–4). Among these, several SNPs mapped to 2q33.3–2q34 showed significant associations after the final stage with 24-h postoperative fentanyl requirements in the additive and recessive models (additive model: combined $\beta=0.293$, nominal $P=8.044\times10^{-7}$; recessive model: combined $\beta=0.553$, nominal $P=9.382\times10^{-7}$; Supplementary Tables S2–4). The observed *P*-values of these SNPs, calculated as $-\log10$ (*P*-value), obviously deviated from the expected values from the null hypothesis of uniform distribution in the quantile–quantile plot for the entire sample (Supplementary Figure S2). The genes located in this region were found to include *METTL21A* (*FAM119A*) and *CREB1*, encoding methyltransferase like 21A and cyclic adenosine 3′,5′-monophosphate (cAMP) responsive element-binding protein 1 (CREB1), respectively.

For further fine mapping of this region, we used the remainder of the genotyped data and imputed the genotype data from the SNPs that spanned 300 kbp, including both the *METTL21A* and *CREB1* genes (Figure 1a), and analyzed the association. We then identified several other SNPs around the best candidate SNP, rs2952768, with nominal *P*-values from 1×10^{-6} to 1×10^{-4} (Figure 1b). After the LD analysis, all of these SNPs were found to be included in an LD block that spanned approximately 134 kbp and were in strong LD ($D'=1$, $r^2>0.8$) with rs2952768 (Figure 1c). Total fentanyl use during the 24-h postoperative period was 1.080 ± 0.053, 1.146 ± 0.049 and $1.666\pm0.083\,\mu g\,kg^{-1}$ (log transformed; mean ± s.e.m.) in subjects with the T/T, T/C and C/C genotypes, respectively (Figure 2a).

Association of rs2952768 SNP with sensitivity to opioid analgesics in patients who underwent major open abdominal surgery

To examine whether the SNPs identified in our GWAS generally affect individual differences in opioid sensitivity, we attempted to confirm the association between the rs2952768 SNP and postoperative opioid requirements in another cohort that underwent a different surgical procedure. The subjects recruited in this study were 112 patients who underwent major open abdominal surgery under combined general and epidural anesthesia (Supplementary Table S5),[18] mostly gastrectomy for gastric cancer and colectomy for colorectal cancer, which involves different modes of invasion from the orthognathic surgery and might cause different pain modalities. Appropriate doses of analgesics, mainly opioids such as morphine, buprenorphine, pentazocine and pethidine, were administered as rescue analgesics at the discretion of the surgeons whenever the patients complained of significant postoperative pain during the postoperative period, and the total dose administered was estimated for the association analysis. As a result, a significant difference in postoperative analgesic requirements was found between the subjects with the combined T/T and T/C genotype and subjects with the C/C genotype in the rs2952768 SNP. Interestingly, the subjects with the C/C genotype required significantly more analgesics than the subjects with the combined T/T and T/C genotype in the rs2952768 SNP ($t_{110}=-2.340$, $P=0.021$), a pattern similar to the one observed in the subjects who underwent cosmetic orthognathic surgery. Total analgesic use, equipotent with systemic fentanyl, during the 24-h postoperative period was 0.359 ± 0.073, 0.397 ± 0.068 and $0.741\pm0.169\,\mu g\,kg^{-1}$ (log transformed; mean ± s.e.m.) in the subjects with the T/T, T/C and C/C genotypes, respectively (Figure 2b).

Association of rs2952768 SNP with severity of drug dependence in patients in several cohorts

The results suggested that the subjects with the C/C genotype in the rs2952768 SNP required more analgesics than the subjects with the other genotypes, attributable to the decreased effectiveness of opioid analgesics in both cohorts. Given the fact that the opioid system is involved in both rewarding and analgesic effects, one could assume that decreased opioid sensitivity may reflect the decreased rewarding effects of various drugs or behaviors and less liability to serious dependence. To test this hypothesis, we investigated the contribution of the rs2952768 SNP to the vulnerability to substance dependence in additional subjects with METH dependence, alcohol dependence and eating disorders (Supplementary Tables S6–8). In the initial case–control analyses, no associations in the genotypic and allelic distribution of this SNP were found between the subjects with psychiatric disorders and corresponding control subjects (Supplementary Table S9). However, a significant difference in the genotypic distribution was found between the absent and present subgroups of polydrug use among the patients with METH dependence ($\chi^2=3.979$, $P=0.046$). Indeed, fewer polydrug abusers carried the C/C genotype compared with monodrug users (Table 1). A similar result was found in the patients with alcohol dependence. A significant difference in the genotypic distribution was found between the absent and present subgroups of drug use among patients with alcohol dependence ($\chi^2=3.860$, $P=0.049$, and $\chi^2=3.039$, $P=0.097$, in the additive and recessive models, respectively), and a lower proportion of drug abusers carried the C allele or C/C genotype compared with the alcoholics without drug abuse (Table 1). Furthermore, a significant difference in allelic distribution was found between the absent and present subgroups of comorbid dependence among the patients with eating disorders ($\chi^2=3.985$, $P=0.046$, and $\chi^2=4.488$, $P=0.034$, in the additive and dominant models, respectively), and a lower proportion of patients with drug dependence carried the C allele

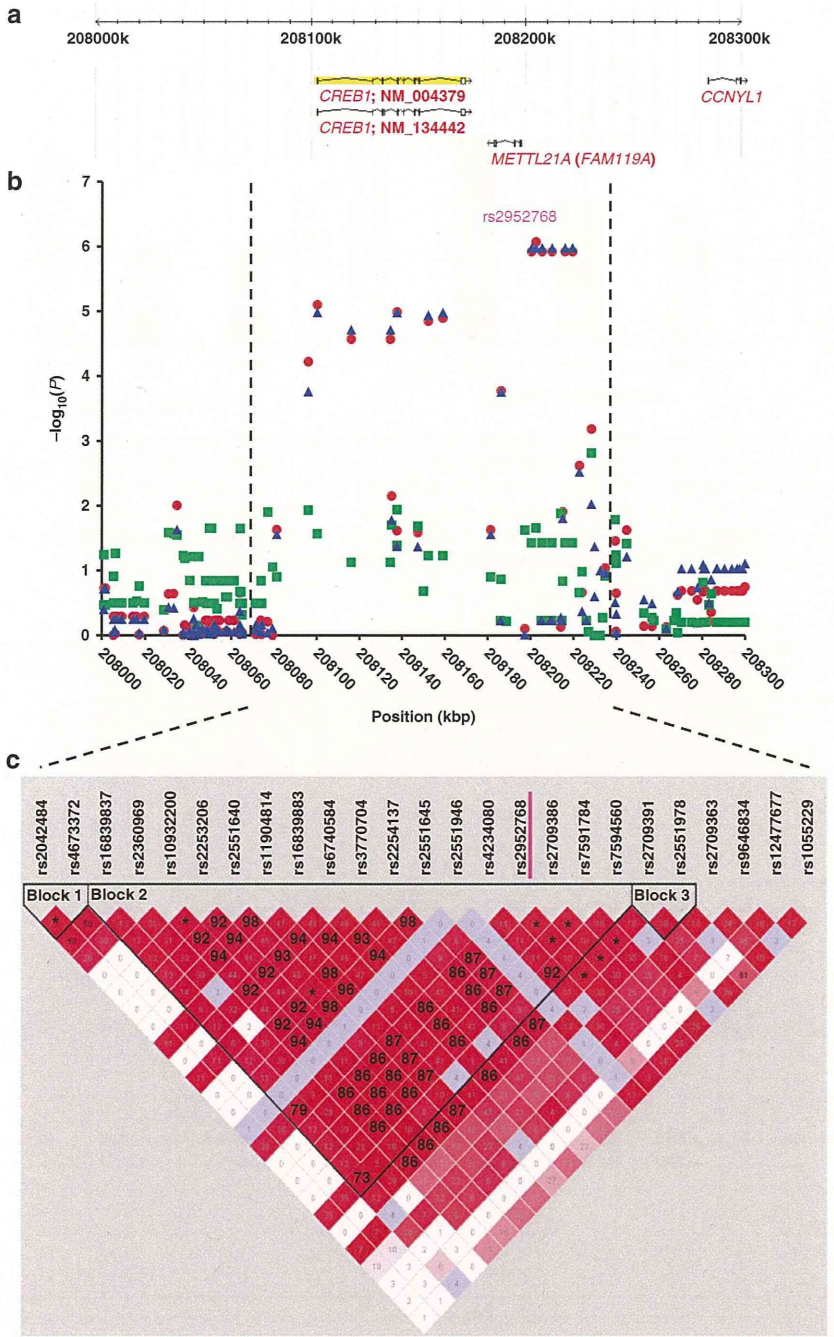

Figure 1. Candidate locus possibly associated with human opioid sensitivity. (**a**) Illustration of the genes in the genomic region from position 208 000 000 to 208 300 000 on chromosome 2 in the HapMap database (http://hapmap.ncbi.nlm.nih.gov/index.html.ja; accessed 1 March 2012). (**b**) Fine mapping of the candidate region after the imputation-based association analysis. The circle, square and triangle plots represent the results from the additive, dominant and recessive models, respectively. The area between the dotted vertical lines represents the genomic position from 208 070 000 to 208 240 000 on chromosome 2. (**c**) State of linkage disequilibrium (LD) between the SNPs in the genomic position from 208 070 000 to 208 240 000 on chromosome 2, based on the genotype data of the subjects who are derived from the Japanese population and underwent cosmetic orthognathic surgery. Numbers in squares in which two SNPs face represent the percentage of the r^2 values calculated from the genotype data of the SNPs. Squares with asterisks represent $r^2 = 1$. Only the values >0.70 are highlighted.

compared with the patients without drug dependence (Table 1). Although nonsignificant, likely because of the small sample size, a marginal difference was observed in allelic distribution between the absent ($\chi^2 = 3.780$, $P = 0.052$) and present subgroups with a comorbid alcoholic state among the patients with eating disorders, and a lower proportion of patients with an alcoholic state carried the C allele compared with the patients without an alcoholic state (Table 1). Altogether, these results showed that carriers of the C allele among the patients with psychiatric disorders, especially the C/C genotype, tended not to abuse polydrugs and not have comorbid alcohol or drug dependence. Although the association was nonsignificant in the recessive

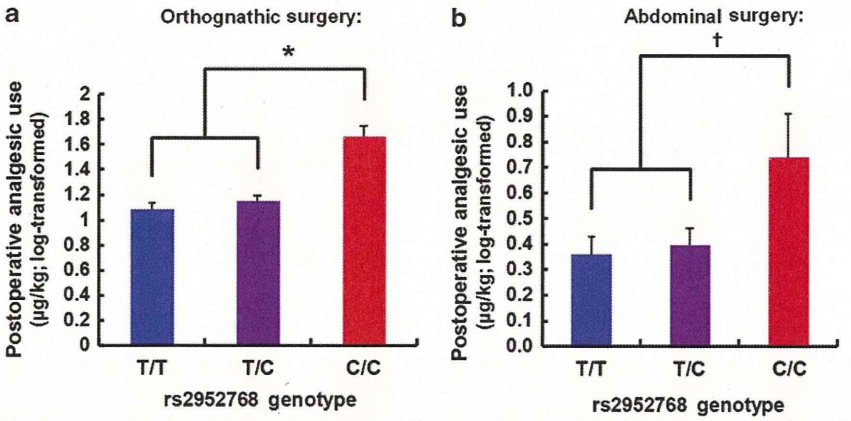

Figure 2. Association analysis between opioid analgesic requirements and the rs2952768 SNP. (**a**) Total dose of analgesics administered per body weight (μg kg^{-1}; log transformed) during the 24-h postoperative period after cosmetic orthognathic surgery (mandibular sagittal split ramus osteotomy). (**b**) Total dose of analgesics administered per body weight (μg kg^{-1}; log transformed) during the 24-h postoperative period after major open abdominal surgery. *$Q<0.05$, greater dose of analgesic administered in the C/C genotype compared with the T/C and T/T genotypes with genome-wide significance; †$P<0.05$, greater dose of analgesic administered in the C/C genotype compared with the T/C and T/T genotypes with nominal significance. The data are expressed as mean ± s.e.m.

Table 1. Distribution of genotypes of the rs2952768 polymorphism and odds ratio between the patient subgroups based on clinical status

	n	*Genotype*			*Allele frequency*		χ^2				*OR (95% CI)*		
		T/T	*T/C*	*C/C*	*T*	*C*	*P*				*C allele (vs T)*	*C/C + T/C genotype (vs T/T)*	*C/C genotype (vs T/T + T/C)*
							Genotype	*Allele*	*Dominant*	*Recessive*			
Polydrug use													
In METH dependence/psychosis patients													
Absence	53	19	22	12	0.556	0.444	3.979	2.262	0.450	3.979	0.71	0.80	0.44
Presence	141	58	67	16	0.644	0.356	0.137	0.133	0.503	0.046*	(0.45–1.11)	(0.42 – 1.54)	(0.19–1.00)
Drug use													
In alcohol dependence patients													
Absence	391	172	166	53	0.652	0.348	3.908	3.860	2.180	3.039	0.61	0.63	0.30
Presence	45	25	18	2	0.756	0.244	0.142	0.049*	0.140	0.097§†	(0.37–1.00)	(0.34–1.17)	(0.07–1.26)
Drug dependence													
In eating disorder patients													
Absence	200	85	93	22	0.658	0.343	4.552	3.985	4.488	0.793	0.45	0.37	0.40
Presence	21	14	6	1	0.810	0.190	0.103	0.046*	0.034*	0.705§	(0.20–1.00)	(0.14–0.96)	(0.05–3.16)
Alcoholic state													
In eating disorder patients													
Absence	151	61	72	18	0.642	0.358	3.995	3.780	3.731	1.171	0.65	0.57	0.57
Presence	70	38	27	5	0.736	0.264	0.136	0.052†	0.053†	0.279	(0.41–1.01)	(0.32–1.01)	(0.20–1.60)

Abbreviations: METH, methamphetamine; *n*, the number of samples; OR, odds ratio; 95% CI, 95% confidence interval. *$P<0.05$, †$0.05 \leqslant P<0.1$, §*P*-value from Fisher's exact test was presented instead of that from χ^2 test.

model for the C allele in all of the analyses, possibly because of a lack of statistical power caused by the limited sample size, the present results suggest that carriers of the C allele in this SNP have less inclination to abuse drugs, consistent with our assumption that various drugs of abuse have decreased rewarding effects in subjects with decreased opioid sensitivity, making these subjects less liable to the expression of symptoms of serious dependence.

Association of rs2952768 SNP with 'reward dependence' score on a personality questionnaire in healthy subjects

Another interest is whether this SNP also affects personality traits related to the reward system in healthy people. To address this issue, we investigated the association between this SNP and data from the TCI, a personality profiling questionnaire, in healthy volunteers (Supplementary Table S10). Intriguingly, among the seven dimensions of the TCI, a significant association was found only for reward dependence (RD) (novelty seeking: $\beta = -0.009055$, $P=0.2995$; harm avoidance: $\beta=0.004317$, $P=0.6819$; RD: $\beta = -0.0175$, $P=0.03265$; persistence: $\beta = -0.007554$, $P=0.6295$; self-directedness: $\beta = -0.01274$, $P=0.1709$; cooperativeness: $\beta = -0.004122$, $P=0.5302$; self-transcendence: $\beta=2.68E-06$, $P=0.9998$; Supplementary Figure S3). The RD value decreased as the copy number of the carried C allele increased among the subjects. The RD value on the TCI was previously shown to be positively correlated with activity of the caudate head,[30] which has

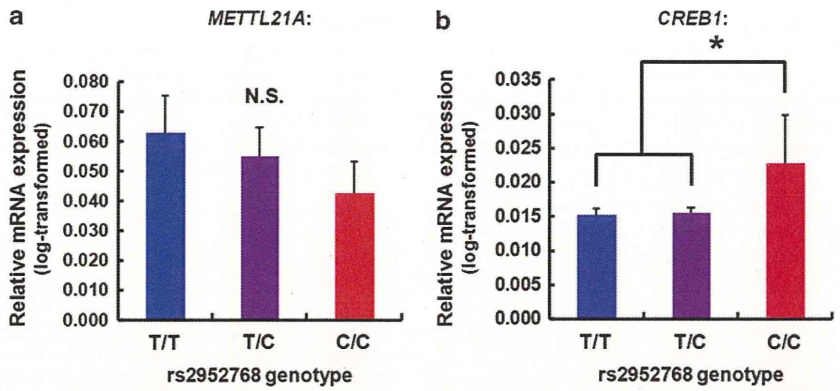

Figure 3. Relative mRNA expression level of the candidate genes between each genotype subgroup of the rs2952768 SNP in post-mortem brains. (**a**) Results for the *METTL21A* gene. (**b**) Results for the *CREB1* gene. NS, no significant association between relative mRNA expression and genotype subgroup ($P \geqslant 0.05$); $^*P < 0.05$, greater level of mRNA expression in the C/C genotype compared with the T/C and T/T genotypes with nominal significance. The data are expressed as mean ± s.e.m.

been shown to be associated with reward processing.[31] Although a future confirmatory study is needed, the present data suggest the possibility that this SNP is one of the predisposing factors that partially contribute to the developmental differentiation of personality traits related to RD.

Association of rs2952768 SNP with mRNA expression level of the *CREB1* gene

Considering the fact that the rs2952768 and all of the neighboring SNPs that showed similarly strong associations with opioid sensitivity were included in the LD block that comprised the *METTL21A* (*FAM119A*) and *CREB1* genes, a subsequent issue is the impact of these SNPs on the function of these genes. Our database search estimated that several of the SNPs could putatively cause functional alterations (Supplementary Table S11). To pursue this issue, we examined the mRNA expression levels of these genes using real-time quantitative PCR with RNA samples extracted from post-mortem subject specimens and compared the mRNA expression levels between the genotype subgroups for the rs2952768 SNP, which were determined by genotyping the DNA samples extracted from the corresponding subjects. Although no significant association was found in the relative mRNA expression level of the *METTL21A* (*FAM119A*) gene between the genotype subgroups ($F_{2,97} = 0.372$, $P = 0.690$), a significant association was found in the relative mRNA expression level of the *CREB1* gene between the combined T/T and T/C genotype subgroup and C/C subgroup (Figures 3a and b). These results showed that the C/C genotype of this SNP was significantly associated with elevated *CREB1* mRNA expression ($t_{98} = -2.561$, $P = 0.012$).

DISCUSSION

By conducting a multistage GWAS for the first time in healthy subjects who were treated with opioid analgesics, we identified a potent locus for opioid sensitivity that encompasses an LD block that includes the most significant SNP, rs2952768. The C allele of this SNP, especially homozygotes of the C allele, was associated with more analgesic requirements, suggesting the possibility to classify the patients into groups of high responders and low responders or non-responders to the given opioid, which would presumably correspond to the T/T or T/C and C/C genotype groups, respectively. Surprisingly, this SNP was also found to be significantly associated with postoperative analgesic requirements in subjects who also received opioids but underwent different surgical procedures. Moreover, the C allele with likely less opioid sensitivity in this SNP was associated with a lower risk for serious symptoms of substance dependence and a lower RD score on the TCI in healthy subjects. These results show that SNPs in this locus are the most potent genetic factors associated with human opioid sensitivity known to date, affecting both the efficacy of opioid analgesics and liability to severe substance dependence.

Opioids exert their effects by binding to opioid receptors (that is, G-protein-coupled receptors) and triggering signaling transmission to several downstream effectors, including inhibition of adenylyl cyclase, activation of G-protein-activated inwardly rectifying potassium channels, and inhibition of voltage-gated Ca^{2+} channels.[32–34] Inhibition of adenylyl cyclase inhibits the production of cAMP, thus decreasing the active form of protein kinase A, phosphorylating CREB, and decreasing gene expression in the nucleus related to the action of analgesia and reward.[35,36] Indeed, the administration of cAMP intracerebrally or intravenously antagonized morphine analgesia in nontolerant and tolerant mice.[37] Moreover, all of the major behavioral effects of morphine, including analgesia, tolerance, reward, and physical dependence and withdrawal symptoms, were attenuated in mice that lacked adenylyl cyclase 5.[38] Meanwhile, increased CREB function in the nucleus accumbens decreased the sensitivity to the rewarding effects of morphine and cocaine in animals, whereas decreased CREB function had the opposite effect.[35,36,39] Although no change in opioid-binding sites or morphine-induced analgesia was observed in CREBαδ-deficient mice,[40] alterations in dose-dependent morphine-induced reward were also reported in CREBαδ-deficient mice.[41] Altogether, these reports indicate the involvement of CREB and the cAMP pathway in the analgesic and rewarding effects of opioids. Higher mRNA expression levels of the *CREB1* gene in subjects with the C/C genotype in the rs2952768 SNP identified in our GWAS may indicate elevated CREB function and decreased sensitivity to the rewarding effects of opioids, resulting in greater postoperative opioid analgesic requirements and less vulnerability to dependence on other drugs.

The best candidate SNP, rs2952768, is located closer to the *METTL21A* (*FAM119A*) gene than to the *CREB1* gene on chromosome 2 (Figures 1a and b). However, no significant association was found between rs2952768 and *METTL21A* mRNA expression, precluding the attribution of phenotypic alterations related to this SNP to the expression levels of the *METTL21A* gene. Although the precise functions of METTL21A are poorly understood to date, a representative METTL, METTL11A, reportedly exhibited catalytic activity as a histone methyltransferase[42] and chronic morphine treatment exhibited the acetylation and trimethylation of histones.[43] Although future studies are imperative, the action of opioids might be partially modulated by histone methylation via METTL functions.