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感覚情報処理（3）

音に対する感覚フィルタリング機構

Sensory filtering system to auditory stimuli

平野　羊嗣　　鬼塚　俊明　　神庭　重信*
HIRANO Yoji　*ONITSUKA Toshiaki*　*KANBA Shigenobu*

聴覚フィルタリング機構とその障害に関して，主に統合失調症での所見を中心に，脳波および脳磁図の知見を概括した．聴覚P50抑制障害は統合失調症の重要な生物学的マーカーとして期待されており，さらに近年では，脳磁図での計測が可能となり，聴覚フィルタリング障害と症状および脳の形態異常との関連も報告されている．また，P50抑制に関与する神経伝達物質や薬物に加え，遺伝性や特定の遺伝子への関連性も解明されつつあり，より詳細な解析が可能となっている．今後はさらなる研究により，病態の解明から，評価，治療といった臨床的な応用が期待されている．

KEY WORDS　感覚フィルタリング，統合失調症，脳波，脳磁図，生物学的マーカー

はじめに

近年の脳機能画像や神経生理学的検査法の発達に伴い，ヒトの脳機能を観察できるようになったのはここ数十年の出来事であり，その革新的な発達により，多くの謎に包まれていた脳の機能や活動が明らかになりつつある．そのなかでも，脳波を用いた誘発電位や事象関連電位，脳磁図を用いた誘発磁場は，感覚刺激やある課題に対して脳内で起こる電気活動や電気活動の結果生じる磁場をミリ秒単位で測定できるため，より詳細な脳内の情報処理過程を調べることが可能である．感覚刺激のなかでも音による聴覚刺激はわれわれの生活上きわめて重要な情報であり，あらゆる音が氾濫するなか，必要とする音のみを入力し脳内で処理する必要がある．たとえば，同じ感覚刺激に連続して曝露された場合には，不要と思われる後者の刺激に対する前注意的な慣れの反応処理過程が存在する．これは感覚フィルタリングと呼ばれ，統合失調症をはじめとした精神疾患ではこの感覚フィルタリングが障害されているために，不要な感覚刺激に曝露されることとなり，その結果種々の精神症状が生じるとされている[1][2]．その感覚フィルタリングの指標とされるのが，連発クリック音を使った，P50（刺激後潜時50ミリ秒付近の聴覚誘発陽性電位）の振幅抑制度であり，健常者では第一刺激に対して第二刺激のP50の振幅が有意に抑制されるが，統合失調症者ではその抑制度が少ないと報告されている[2]．

本稿では，この指標をもとに，聴覚刺激に対する感覚フィルタリング機構について概観した後に，

九州大学大学院医学研究院精神病態医学　*教授
Address/HIRANO Y：Dept. of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, FUKUOKA 812-8582

0485-1447/07/¥50/ 頁 /JCLS

主に統合失調症者の感覚フィルタリング障害について，脳波および脳磁図による知見を中心にレビューする．

感覚フィルタリング

感覚フィルタリングとは，同じ感覚刺激に連続して曝露された場合に生じる，前注意的な慣れに対する反応のことを示す．この連続した刺激に対する反応の抑制機構は，不要もしくは無意味な刺激や重複した刺激を遮断することで，周囲の環境からの莫大な感覚情報と折り合いをつける処理能力であるといえる．

Venables[1]は，統合失調症者には感覚情報に対するフィルタリング機構の障害があり，それが種々の症状の原因と成り得ると提唱した．つまり統合失調症者は，感覚フィルタリング機構の障害のため，感覚情報の洪水に曝されることとなり，その結果として，急性期には幻聴または妄想などの陽性症状が生じ，慢性的には，感覚フィルタリング機構障害の代償としての注意の狭小化，周囲の環境に対しての興味の喪失や引きこもりといった陰性症状が出現すると論じた．またHemsley[3]は，統合失調症者の障害の基盤は，“過去に入力された情報の規則性に対する記憶を，現在の情報に照らし合わせ認知するという能力の低下である”と結論づけた．つまり統合失調症者は，無制限に知覚される騒音の洪水から必要とする情報を認知するための処理である“不要もしくは重複する知覚に対する記憶に基づいた照合”に破綻をきたしているといえる．

一方Adler[2]らは，連続クリック音を使用したパラダイムを，感覚フィルタリングの生物学的なモデルとして提唱した．彼らは連続クリック音に対する聴覚誘発電位P50を測定したところ，健常者ではP50の振幅は第一刺激に比べ第二刺激では抑制されるが，統合失調症者ではあまり抑制されないことを示した．その結果を彼らは，健常者では連続した音刺激に対しては慣れによる抑制機構，すなわち“フィルタリング機構”が1回目の刺激により活性化するが，統合失調症者では感覚に対する抑制機構が，より不明瞭もしくは欠損していると解釈した．統合失調症者では，“フィルタリング機構”が障害されており，彼らはこのパラダイムが感覚フィルタリング機構の指標になると提唱した．以下にこの聴覚フィルタリング機構に関する神経生理学的所見（主に脳波および脳磁図）を紹介し，さらに感覚フィルタリング機構の機序，遺伝子との関連，統合失調症以外の精神疾患での知見を述べることとする．

脳波での知見

脳波は神経細胞の活動に沿って発生する集合電位をみているので，脳血流や脳の代謝産物を計測するfMRIやPET，SPECTなどと異なり，よりダイレクトに脳活動を調べることができる．さらにミリ秒単位の優れた時間分解能を持つため，刻々と変化する知覚や認知活動を詳細に記録し評価する場合に優れた測定法である．そのなかでも誘発電位は，ある外的刺激に対して脳波上で誘発されるその刺激に特異的な活動電位であり，たとえば聴覚刺激に関連した聴覚誘発電位を計測することで音刺激に対する脳の反応を調べることができる．音刺激提示後50ミリ秒後に陽性頂点を示す反応はP50と呼ばれているが，Adler[2]らは500ミリ秒の間隔で2つのクリック音刺激を被験者に提示した際にみられる，健常者と統合失調症者のP50の抑制度の違いに注目した．健常者では2回目の刺激に対するP50の誘発電位（S2）は1回目の刺激に対する電位（S1）に比して小さくなるが，統合失調症者ではそのS1とS2にほとんど違いがみられず，この連続クリック音を使用したパラダイムが統合失調症の感覚フィルタリング障害に関する重要な指標となり得ると提唱した．Waldo[1]らは，このパラダイムを使用したS2に対するS1の抑制度（S2/S1）について，ほとんどの健常者でS2/S1が40%以下であるのに対して，多くの統合失調症者ではS2/S1が50%以上あり，しばしば90%もしくはそれ以上になると報告している．さら

に多くの追試による検討が行われ[5]-[7]，このパラダイムを用いたS2に対するS1の抑制度は統合失調症における神経生理学的指標の一つであると考えられるようになった[8]．Boutros[9]らは，このパラダイムを使用し，解体型統合失調症と妄想型統合失調症の2群を健常者と比較検討した．その結果，解体型統合失調症群は他の2群に比べS1自体の振幅が小さく，S2/S1も有意に低かった．一方，妄想型統合失調症群と健常者群では有意差はなかったと報告した．彼らは，このパラダイムを用いた感覚フィルタリング障害は，妄想型よりむしろ解体型統合失調症に特徴的であるとし，統合失調症におけるサブタイプでの検討が必要であることを示した．

この感覚フィルタリング機構の異常は，多くの認知機能障害と関連しているという仮説が提唱されており[10]-[14]，神経心理的な検討も行われている．Cullum[10]らは，神経心理的指標のなかでも，統合失調症で障害されているとされる注意機能と記憶に注目し，心理検査と連発クリック音を用いたP50抑制度との関連を検索した．その結果，注意機能と記憶のほぼすべての項目で統合失調症群は低い値を示し，そのなかでも特に持続的注意を反映するテストにおいて特に長い時間を必要とした．また，この持続的注意機能の障害の程度とP50障害とに有意な相関が認められ，統合失調症における神経生理学的な障害の指標が，持続的注意機能の障害と関係していたと報告した．しかしながら，統合失調症の症状として特異的といえる陽性症状（幻覚や妄想など）や陰性症状（感情の平板化，思考の貧困，意欲の欠如や引きこもり）との比較においては，脳波を用いた感覚フィルタリング機構の障害と症状に明らかな関連はみられなかった[11][15]．また，最近では統合失調症者のP50抑制異常に関する膨大な知見をもとに，メタ解析[16]が行われ，この異常は罹病期間や抗精神病薬の影響を受けないと報告されており，P50抑制障害が統合失調症に特異的な指標となり得ることが示唆されている．

脳磁図での知見

脳波と同様に脳磁図（magnetoencephalography：MEG）は，ある時点での脳の状態もしくは変化を表すCT, MRI, fMRI, PET, SPECT等の脳画像検査に比べ，優れた時間分解能をもつ．MEGは，刻々と変化する脳の電気活動をミリ秒単位でとらえることが可能であり，知覚や識別などの感覚情報処理過程を検索する際には非常に有用である．さらに，MEGで測定する磁場は，脳波のように頭蓋骨や脳脊髄液などの生体組織による影響を受け測定データが減衰し歪むことがないため，より正確なデータを得ることができる．その結果，正確で歪みのないない磁場信号に基づいた脳内活動源を数ミリメートル以内の誤差で計測でき，脳波に比べより優れた空間分解能を有す．さらに，脳波では皮質下構造を含めた広範囲の活動も混在してとらえてしまうが[17][18]，MEGは皮質における活動を選択的にとらえることが可能であり，より正確で鋭敏な測定結果が得られる．このようにMEGは高精度の時間的ー空間的な解析が可能でるため，一連の脳機能（脳活動）を追いかけながらそれを脳構造に反映するためには重要な検査法であるといえる．

近年，精神科の領域では，統合失調症をはじめとした精神疾患において，脳構造異常および脳機能異常[19]-[24]に対する多くの報告がなされており，脳の機能（知覚や認知）と，構造（左右差や脳の各部位における差異）の両者に対するアプローチの重要性が増してきた．ごく最近になり，前記のMEGの特徴を生かした統合失調症者における感覚フィルタリング機構の研究がなされており，脳の機能異常と構造異常を裏づける知見がいくつか報告されている．たとえば，Thoma[25]らは，20人の統合失調症者と15人の健常者を対象に，MEGと脳波にてスタンダードな連続クリック音を用いたパラダイムでの検討を行った．その結果，聴覚誘発電位P50に対応する聴覚誘発磁場P50mが左右両半球の上側頭回（聴覚皮質）に電源推定され，

感覚フィルタリング機構の障害が統合失調症者群の左半球に認められたと報告した．また，P50mに加え，より後期の成分であるN100m（刺激提示後100ミリ秒後に生じる聴覚誘発磁場）におけるフィルタリング機構について検索した報告もある．Hanlon[26]らは，25人の統合失調症者と26人の健常者を対象に同様のパラダイムを使用し聴覚誘発磁場の結果を比較検討したところ，健常者に比べ統合失調症者では左半球のP50mおよび両半球のN100mの抑制に障害が認められたと報告した．さらに左右のP50mおよびN100mの抑制度の相関を調べたところ，左半球のN100mと左半球のP50mの抑制度が有意に相関していた．一方で，右半球のN100mとはいずれの半球のP50mの抑制度とも相関はなかった．

またThoma[27]らは，22人の統合失調症者と11人の健常者を対象に，同じパラダイムで聴覚誘発電位および聴覚誘発磁場のP50およびP50mの振幅の同時測定を行い，S1に対するS2の抑制度（S2/S1）を指標に，MRIにて測定した聴覚皮質（上側頭回）の厚さとの比較検討を行った．それによると，統合失調症者は健常人に比べP50と左のP50mの感覚フィルタリング機構が有意に障害されていた．また，統合失調症者の両半球の聴覚皮質は健常人に比べより薄く，統合失調症者には左右それぞれのP50mの感覚フィルタリング機構障害と聴覚皮質の厚さとの間に負の相関が認められることを報告した．彼らは，統合失調症の両半球の聴覚皮質の構造異常が，聴覚フィルタリング機構の障害をもたらしている可能性があると結論づけている．

さらに彼ら[28]は，20人の統合失調症者を対象に，同様のパラダイムで聴覚誘発電位および聴覚誘発磁場の同時測定を行い，精神症状の評価項目との相関を検討した結果，聴覚誘発電位では他の報告[11][15]同様に有意な相関はなかったが，聴覚誘発磁場においてはP50mの右半球における抑制障害と陰性症状の重症度に有意な相関がみられたと報告している．これは，Adler[11]らの脳波を用いた研究では，P50の抑制度と陰性症状に有意な相関が認められなかったという所見と異なっており，高い空間分解能を有し皮質における活動を選択的にとらえるMEGでは，新たな知見が得られる可能があることを示唆している．

これら感覚フィルタリングの研究は，連続クリック音を用いたパラダイムがスタンダードな方法であるが，われわれは，統合失調症の幻聴のほとんどが言語性であること[29]と，言語音は社会生活で重要あることを考慮し，刺激音に言語音（母音「ア」）を用いて，2連発言語音に対する聴覚誘発磁場を測定した．図1はその一例であり，29歳の健常者と30歳の統合失調症者の左側聴覚野におけるS1およびS2に対する誘発磁場反応を示している．健常者ではS1に対してS2のP50mの振幅が小さく明らかに抑制されているのに対し，統合失調症者ではS1とS2のP50mの振幅にあまり変化がないことがわかる．

このように，MEGではその特性を生かし，脳構造異常を反映した微妙な統合失調症者の聴覚情報処理過程の異常を検出できる．今後MEGを用い，精神疾患における感覚フィルタリング機構をはじめとした脳活動を記録し，脳構造との関連を検索することが，新たな病態解明につながると期待されている．

感覚フィルタリング機構の機序

聴覚フィルタリング機構の機序に関して，神経解剖学的または神経化学的な解明が試みられているが，一貫した結果は得られていない．神経解剖学的には主にFreedman[13]らの知見が多く引用されている．彼らは，ヒトを対象とした研究（硬膜下電極での測定等）と動物実験の結果の集積により，海馬が感覚フィルタリング機構にかかわる主要な部位であり，統合失調症者の感覚フィルタリング機構の障害には海馬のなんらかの異常が関与すると述べている．これは，脳画像研究にて，統合失調症者には海馬に形態学的異常がある[30][31]との知見を反映しているといえる．

神経化学的な見解としては，感覚フィルタリン

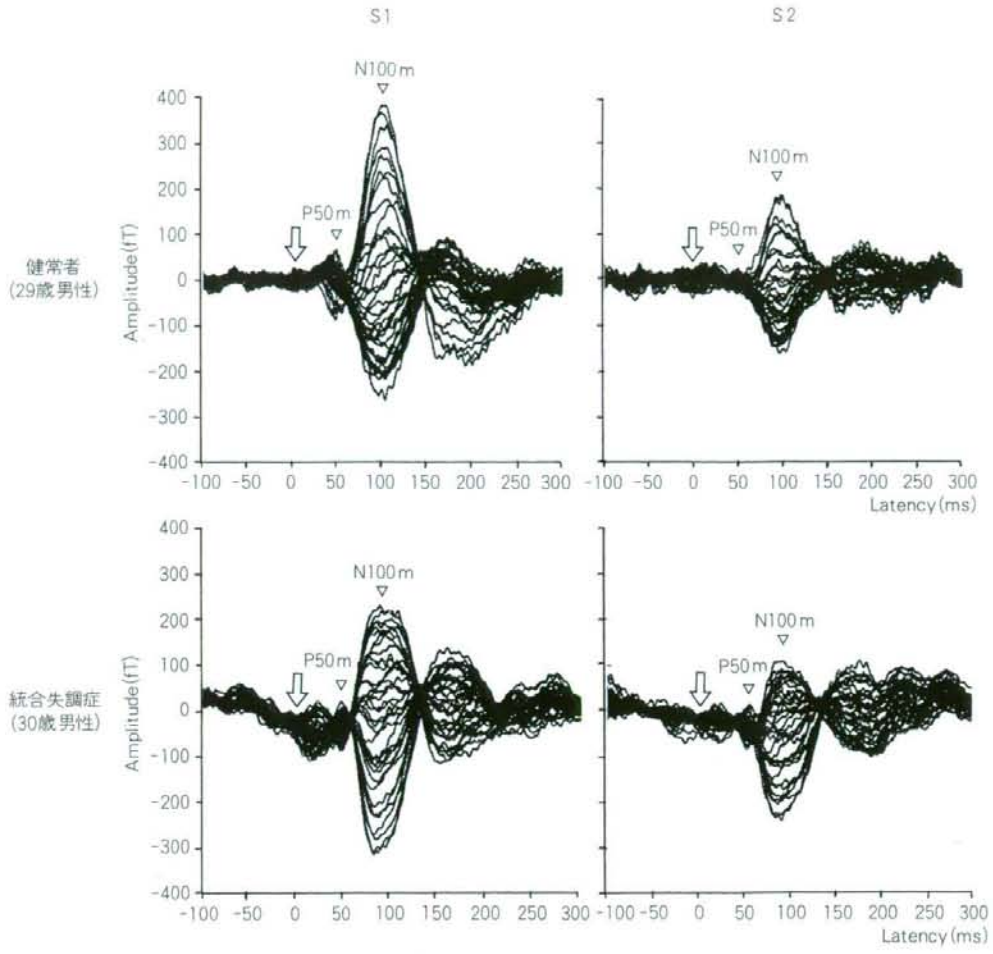

図1　2連発言語音に対する左側聴覚野の聴覚誘発磁場（37チャンネル分の記録を重ね合わせた波形）
健常者では，第一刺激（S1）に比べ第二刺激（S2）のP50mの振幅は小さく抑制されているが，統合失調症者ではS1とS2のP50mの振幅に変化がなくS2が抑制されていないことがわかる．

グ機構には，コリン作動性，ドーパミン作動性，GABA作動性，グルタミン酸作動性，ノルアドレナリン作動性，セロトニン作動性のシステムといった，複数の神経伝達物質の関与が報告されている[31][32][33]．さらに最近ではアデノシンの関与も報告されている[34][35]．これら多くの神経化学的研究からは一貫した知見は得られていないが，複数の神経伝達物質が感覚フィルタリング機構に関与していることが示唆される．Carlsson[36][37]は，“統合失調症の精神症状は，単一の神経伝達物質のみの不足や過剰により起こるのではなく，複数の神経伝達物質（ドーパミン，セロトニン，グルタミン酸，GABA）の不均衡により生じる”と提唱しており，感覚フィルタリング機構障害にも複数の神経伝達物質の不均衡が基盤にある可能性が示唆される．

遺伝との関連

感覚フィルタリングの指標であるP50抑制障害と遺伝についての報告はいくつかあり，統合失調症者の一親等家族においてもP50抑制異常が認められたという[38][39]．双生児研究[40]においてもP50抑制と遺伝の関連が示唆されている．また，P50

抑制障害と特定の関連遺伝子についての報告があり，15番染色体のα7ニコチン受容体遺伝子との関連[41]や，そのプロモーター領域との関連[42]も報告されている．これらの遺伝性および関連遺伝子の知見は，P50抑制障害が遺伝医学研究において統合失調症のエンドフェノタイプ（疾患脆弱性遺伝子多型と臨床的表現型を反映）[43]になり得ることを示唆しており，統合失調症の精神症候学的な診断基準とともに，重要な生物学的マーカーとしての役割を果たすと考えられており，今後さらなる研究が期待されている．

他の精神疾患における所見

このパラダイムを用いたP50抑制障害が，精神疾患の中で統合失調症に特異的か否かの検討もなされている．Baker[44]らは，他の精神疾患と比較しP50抑制障害は統合失調症に特異的であり，trait markerと考えられると主張した．一方でJessen[45]らは，アルツハイマー病においても同様のP50抑制障害がみられたことを報告している．彼らはこの理由として前述のα7ニコチン受容体の減少がアルツハイマー病にある[46]ためではないかと推測した．またFranks[47]らは，双極性障害では，症状の安定時期には健常人と同様にP50抑制がみられるが，躁状態の急性期には統合失調症者と同様にP50抑制障害が認められたと報告した．Olincy[48]らは，同様に双極性障害の症状に注目し，精神病症状（幻覚・妄想）の既往がある患者群にP50抑制異常がみられたと報告し，統合失調症と精神病症状を伴う双極性障害との間に，何らかの病態生理学的な関連性があると推測した．

一方，過覚醒や聴覚過敏を有する心的外傷後ストレス障害（Posttraumatic stress disorder：PTSD）にもP50抑制障害が認められたという報告も散見される[49]-[52]．また，パニック障害[53]においてもP50抑制障害が認められたという報告がある．さらに最近では健常者のなかでも，音楽家は非音楽家に比べ，P50抑制が少なかったという報告もある[54]．

P50抑制障害を改善する物質や要因についての報告も散見される．そのなかでも，嗜好品であるタバコとコーヒーの成分（ニコチン，カフェイン）に関する報告は興味深い．Adler[55]-[57]らはニコチンにより一過性に統合失調症者のP50抑制障害が正常化することを報告し，前述のP50抑制障害とα7ニコチン受容体遺伝子との関連性[41]を示した．彼らは，α7ニコチン受容体に作用する薬物によりP50抑制障害が改善することで，統合失調症者の精神症状の改善につながる可能性があると説明し，統合失調症者の喫煙率が健常者や他の入院患者に比べはるかに高いのは，自ら精神症状の改善のためタバコを服用しているのかもしれないと指摘している[55]．またGhisolfi[35]らは，健常者でカフェインの摂取量が多い群でP50抑制が有意に大きいことを報告し，カフェインが非選択的なアデノシン受容体のアンタゴニストであることを考慮し，P50抑制機構にアデノシンが関与していると推測した．また，短い睡眠が統合失調症者のP50抑制障害を一時的に改善したとの報告や[58]，統合失調症に対する治療薬である抗精神病薬のなかでは，クロザピン投与群のみがP50抑制障害を示さなかったという報告[59]がある．

これらの知見は，必ずしもP50抑制障害が統合失調症に特異的ではない可能性と，P50抑制に関与する薬物が抗精神病薬以外に考えられることを示唆しており，今後も疾患群での再検討や遺伝解析も含めたさらなる検討の余地があると考えられる．

おわりに

本稿では，聴覚フィルタリング機構とその異常に関して，最近の知見をもとにレビューを行った．前半では脳波および脳磁図での聴覚フィルタリング障害に関する知見をそれぞれの特徴をもとに紹介した．後半では，感覚フィルタリング機構の機序，遺伝との関連，統合失調症以外での知見やその他の最近の知見を紹介した．

統合失調症者のP50抑制障害に関する報告が数

多く蓄積されており，聴覚P50は統合失調症のエンドフェノタイプとして重要な生物学的マーカーとして期待されている．一方で，P50抑制障害が統合失調症に特異的ではない可能性や，P50抑制障害における複数の神経伝達物質の関与も示唆されており，その解釈が複雑になっている．それゆえ，今後は疾患群での再検討や新たなアプローチによる多角的で慎重な検討が必要であると思われる．

その一手段として，近年では脳波に加え，脳磁図での計測が可能となり，症状や脳の形態異常との関連が報告されるようになった．また，遺伝性や特定遺伝子との関連性の解明も進み，以前に比べ詳細な解析が可能となっている．さらに最近の知見ではP50抑制障害を改善する物質や薬物が明らかになりつつある．今後はさらなる研究により，病態の解明のみならず，評価，治療といった臨床的な応用が期待されている．

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Genetic structure of the dopamine receptor D4 gene (*DRD4*) and lack of association with schizophrenia in Japanese patients

Hiroshi Mitsuyasu [a], Hiroaki Kawasaki [a,*], Hideaki Ninomiya [b], Naoko Kinukawa [c], Takeharu Yamanaka [d], Tomoko Tahira [e], Vincent P. Stanton Jr. [f], Gregory M. Springett [g], Kenshi Hayashi [e], Nobutada Tashiro [a], Shigenobu Kanba [a]

[a] *Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan*
[b] *Fukuoka Prefetural Dazaifu Hospital, Psychiatric Center, 3-8-1, Gojoh, Dazaifu, Fukuoka 818-0125, Japan*
[c] *Department of Medical Information, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan*
[d] *Institute for Clinical Research, National Kyushu Cancer Center, 3-1-1, Notame, Minami-Ku, Fukuoka 811-1395, Japan*
[e] *Division of Genome Analysis, Research Center for Genetic Information, Medical Institute of Bioregulation, Kyushu University, 3-1-1, Maidashi, Higashi-Ku, Fukuoka 812-8582, Japan*
[f] *Genome Science Division, RCAST, Tokyo University, 4-6-1, Komaba, Meguro-Ku, Tokyo, 153-8904, Japan*
[g] *Drug Discovery Program, Department of Interdisciplinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL 33612, USA*

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Abstract

In order to investigate the contribution of genetic variation in the human dopamine receptor D4 gene (*DRD4*) to the risk of developing schizophrenia, we carried out a genetic analysis of 27 polymorphisms in 216 schizophrenic patients and 243 healthy controls from the Kyushu region of Japan. Twenty-two single nucleotide polymorphisms (SNPs) and five insertion/deletion polymorphisms were analyzed in this study, including four novel SNPs and a novel mononucleotide repeat. Linkage disequilibrium (LD) and haplotype analyses reveal weak LD across the *DRD4* gene. In univariate analysis female individuals with allele −521C had a higher risk for schizophrenia. However, this finding was not significant after correction for multiple hypothesis testing. No other polymorphisms or haplotypes differed between schizophrenic patients and controls. Likewise, multivariate analyses did not reveal any statistically significant associations.

Keywords: Schizophrenia; Genetic association; Polymorphism; Dopamine receptor D4; Linkage disequilibrium; Haplotype

1. Introduction

Schizophrenia is the most prevalent of the major psychotic disorders with 1% of the population affected worldwide. Although family, twin and adoption studies strongly suggest that genetic variation contributes to the etiology of schizophrenia (Gottesman, 1991; Kendler and Diehl, 1993), the underlying molecular basis and pathophysiological mechanisms leading to the development of schizophrenia are still unclear. Several lines of clinical and pharmacological evidence suggest the possible involvement of dopaminergic neurotransmission systems in the pathogenesis of schizophrenia (reviewed by Willner, 1997). The "dopamine hypothesis" is supported by the observation that dopamine receptor antagonists modulate the symptoms of schizophrenia and the observation of altered dopamine levels in the striatum, prefrontal cortex and limbic system of schizophrenic patients. Accordingly dopamine receptors have been a focus of genetic studies aimed at finding abnormalities associated with schizophrenia. In particular, the *DRD4* gene, a member of the D2-like dopamine receptor family, has been considered a strong candidate gene for schizophrenia. This is partly based on the finding that the atypical antipsychotic drug, clozapine, has a relatively high affinity for DRD4 (Van Tol et al., 1991), and

* Corresponding author. Tel.: +81 92 642 5626; fax: +81 92 642 5644.
E-mail address: hiroakik@npsych.med.kyushu-u.ac.jp (H. Kawasaki).

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that elevated levels of DRD4 protein and mRNA were found postmortem in the brains of schizophrenia patients (Seeman et al., 1993; Stefanis et al., 1998). The DRD4 gene has also been investigated in attention deficit hyperactivity disorder (ADHD) and in relation to personality traits such as novelty seeking.

The *DRD4* locus is highly polymorphic (Cichon et al., 1995; Mitsuyasu et al., 2001; Mitsuyasu et al., 1999; Okuyama et al., 2000; Paterson et al., 1996; Seaman et al., 1999; Van Tol et al., 1992; Wang et al., 2004; Wong et al., 2000).

Association between various polymorphisms and schizophrenia have been reported by some investigators, however, efforts to replicate those results have generally been unsuccessful. Only three studies reported positive association results (Okuyama et al., 1999; Weiss et al., 1996; Xing et al., 2003). Among the polymorphisms analyzed for association with schizophrenia, the −521T/C polymorphism is one of the most extensively studied, not only in relation to schizophrenia (Jonsson et al., 2001; Jonsson et al., 2003; Mitsuyasu et al., 2001; Okuyama et al., 1999; Xing et al., 2003), but also ADHD (Bellgrove et al., 2005; Kirley et al., 2004; Lowe et al., 2004; Mill et al., 2003) and personality traits (Bookman et al., 2002; Ekelund et al., 2001; Joyce et al., 2003; Lakatos et al., 2002; Lee et al., 2003; Mitsuyasu et al., 2001; Okuyama et al., 2000; Ronai et al., 2001; Strobel et al., 2002; Strobel et al., 2003). However, although several studies suggest that the 48-base pair (bp) variable number of tandem repeat (VNTR) polymorphism in exon 3 of *DRD4* is associated with ADHD and personality traits (Faraone et al., 2005; Jonsson et al., 2003; Savitz and Ramesar, 2004; Schinka et al., 2002), the overall results of these extensive investigations are inconsistent.

Previously, we reported nine novel polymorphisms in the upstream region of the *DRD4* gene in the Japanese population (Mitsuyasu et al., 1999). Our analysis of five single nucleotide polymorphisms (SNPs), including −521T/C, in 208 schizophrenia patients and 210 normal controls revealed no significant association (Mitsuyasu et al., 2001).

In this report, we describe a more exhaustive analysis of polymorphism in the *DRD4* gene by carrying out LD and haplotype analyses with a total of 27 polymorphisms including the polymorphic 120-bp tandem repeat (TR) in the 5′ UTR and the 48-bp VNTR in exon 3. Both SNP and haplotype based association analyses, using uni- and multivariate statistical methods, were carried out to clarify the relationship between schizophrenia and polymorphisms of *DRD4*.

2. Materials and methods

2.1. Study population

Two hundred sixteen schizophrenic patients fulfilling the DSM-IV diagnostic criteria for schizophrenia (121 male and 95 female), aged 18–82 (mean 51.5 ± 13.7, male 50.5 ± 14.0, female 52.7 ± 13.3), were recruited from nine hospitals in the northern area of Kyushu. 243 controls (138 male and 105 female), aged 30–71 years (mean 50.2 ± 4.6, male 52.1 ± 1.2, female 47.7 ± 6.1), were recruited from the personnel of the Japanese Self-Defense Forces and the staff of three hospitals in Fukuoka prefecture, Kyushu. All patients and controls were ethnically Japanese. There are no significant differences between the ages of the schizophrenic and control populations, or between male schizophrenics and controls, total female and total male populations or female and male schizophrenic populations. In contrast, there are significant age differences between female and male control populations and between female patients vs. controls: the average female control is 4.3 years younger than the average male control ($p < 0.0001$) and 5.0 years younger than the average female schizophrenic ($p = 0.001$).

The controls were selected based on information acquired from a questionnaire that interrogated various aspects of socio-economic, physical and mental status, as well as neuro-psychiatric and psychological characteristics. This questionnaire provides information similar to that obtained from batteries such as the Temperament and Character Inventory (Cloninger et al., 1993; Kijima et al., 1996), the Beck Depression Inventory (Beck et al., 1961), the State-Trait Anxiety Inventory (Spielberger et al., 1970), the Maudsley Obsessive-Compulsive Inventory (Hodgson and Rachman, 1977), and the Kurihama Alcoholism Screening Test (Saito and Ikegami, 1978). The inclusion criteria for controls were: (1) over 30 years old, (2) no physical or psychiatric history, (3) good social adjustment with occupation, and (4) no intellectual deficit. All control subjects were assessed for mental and physical illness by administering the Japanese edition of the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan and Lecrubier, 1998).

All subjects gave informed consent. This study was approved by and performed in accordance with the guidelines of the Ethics Committee of the Graduate School of Medical Sciences, Kyushu University.

2.2. Genotyping methods

Genomic DNA was purified from peripheral blood leukocytes as previously described (Lahiri and Nurnberger, 1991; Mitsuyasu et al., 2001). Genotyping experiments were performed using polymerase chain reaction (PCR) and/or direct sequencing methods. The amplified fragments and primer pairs for PCR are summarized in Table 1 and Fig. 1. Both the 120-bp TR and 48-bp VNTR polymorphisms were genotyped by detecting the length of each amplified fragment. The 26 other polymorphisms were genotyped by sequencing two PCR amplified fragments.

The 120-bp TR polymorphism was genotyped using a previously reported PCR-based typing method (Seaman et al., 1999). Genotypes were read based on the presence of 429-bp and/or 549-bp fragments.

Table 1
List of primers for genomic DNA fragment amplification and sequencing reactions

Name of primer	Sequence (5′–3′)	Direction	Position[c]		Product size (bp)	Purpose
D4-120F[a]	GTTGTCTGTCTTTTCTCATTGTTTCCATTG	Sense	−1726	−1697	429, 549	Amp[f]
D4-120R[a]	GAAGGAGCAGGCACCGTGAGC	Antisense	−1179	−1199		Amp
D4iF3	CACACCTGTCCCTGGTGCAGG	Sense	−1256	−1236	606	Amp, Seq[g]
D4iR3	CCCACCCGTTGCACAGTTGATC	Antisense	−651	−672		Amp, Seq
D4iiF3	TACCTAGCTCACGGTCTTGGGC	Sense	−765	−744	1160	Amp
D4ivR2	CTGGAAGCTCCGCACCAGAAAG	Antisense	395	374		Amp
D4iiF5	GCTGTCCGCCCAGTTTCGGAG	Sense	−706	−686		Seq
D4pos3[b]	CTCAGGTCTTTCTGCGTCTGGC	Sense	−472	−451		Seq
D4EX1F[c]	CGCCATGGGGAACCGCAG	Sense	−4	14		Seq
D4iiiR1	GTGGCCACGCTCACGCACACG	Antisense	182	162		Seq
D4iiiR2	CGCTGAGCACCGCGGACAACG	Antisense	−17	−37		Seq
D4iiR1	TCGACGCCAGCGCCATCCTAC	Antisense	−346	−366		Seq
D4neg3[a]	CAGGTCACAGGTCACCCCTCTT	Sense	−947	−926	792	Amp, Seq
D4neg4[a]	TTGCTCATCTTGGAATTTTGCG	Antisense	−156	−177		Amp, Seq
D4-48F[d]	AGGTGGCACGTCGCGCCAAGCTGCA	Sense	2612	2636	$174 + (48 \times N^{h})$	Amp
D4-48R[d]	TCTGCGGTGGAGTCTGGGGTGGGAG	Antisense	2929	2905		Amp

[a] Seaman et al. (1999).
[b] Mitsuyasu et al. (1999, 2001).
[c] Catalano et al. (1993).
[d] Nanko et al. (1993).
[e] Relative position to the first nucleotide of initiation codon of the genomic sequence (GenBank Accession No. AC021663).
[f] Amp, these primers were used for PCR amplification.
[g] Seq, these primers were used for direct sequencing.
[h] *N*, number of repeats of the 48-bp sequence in exon 3.

The 48-bp VNTR was genotyped according to published methods (Nanko et al., 1993; Van Tol et al., 1992). PCR products were electrophoresed on an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc., USA). The size of the amplified fragments was 174 bp plus 48 bp multiplied by the repeat number.

DNA sequencing was used to genotype 26 polymorphisms. First DNA sequencing templates were generated by PCR amplification of two DNA fragments (606-bp and 1160-bp) from genomic DNA of each individual (Fig. 1). PCR primers (Table 1) were designed based on GenBank Accession No. AC021663. The 606-bp fragment was amplified in a 10 μl reaction mixture that contained 1 μM of each primer, 0.2 mM of dNTPs (Amersham Biosciences Corporation, USA), 50 ng template DNA, 0.025 U/μl of AmpliTaq polymerase (Applied Biosystems, USA), 5.5 ng/μl of TaqStart Antibody (Clontech, USA), 50 mM KCl, 10 mM Tris–HCl (pH 8.3), 1.5 mM $MgCl_2$ and 10% of dimethylsulfoxide (DMSO) (Wako Pure Chemical Industries, Ltd., Japan). Thermal cycling profile was 1 min at 95 °C for initial denaturation, followed by 40 cycles of 30 s at 95 °C, 30 s at 60 °C and 1 min at 72 °C, followed by a final incubation at 72 °C for 5 min. The 1160-bp fragment was amplified in 1 μM of each primer, 0.2 mM of dNTPs, 50 ng template DNA, 0.025 U/μl of KOD Dash polymerase (Toyobo, Japan), KOD Dash PCR buffer supplied by the manufacturer and 10% of DMSO in a total volume of 20 μl. The thermal cycling profile was 1 min at 96 °C for the initial denaturation, followed by 33 cycles of 30 s at 95 °C, 2 s at 63 °C and 30 s at 74 °C followed by a final incubation at 74 °C for 5 min.

These two DNA fragments were then used for 26 minisequencing reactions. First the template fragments were treated with two units of shrimp alkaline phosphatase (Roche Diagnostics Corporation, USA) and exonuclease I (New England Biolabs, USA) at 37 °C for 1 h. Both enzymes were heat inactivated at 80 °C for 15 min. Cycle sequencing was carried out by BigDye Terminator Cycle Sequencing Ready Reaction Kit ver 2.0 (Applied Biosystems, USA) according to the manufacturer's instructions. Depending on the fragments and primers used (Table 1 and Fig. 1), the protocols were slightly modified. Extension products were purified by Multiscreen 96-Well Filter Plates (Millipore, USA). Sample electrophoresis and data analysis were performed on the ABI PRISM 3100 and/or 3700 DNA Analyzer (Applied Biosystems, USA). Duplicate genotypes were generated from 133 individuals using as sequencing template a 792-bp fragment located between position −947 and −156, as previously described (Mitsuyasu et al., 2001). This fragment contains 12 polymorphisms (−713C/T, −616G/C, −615A/G, −603del/T, −600G/C, −598G/T, $-597(G)_{2-5}$, −521T/C, −376C/T, −364A/G, −291C/T and −234C/A) (Table 1 and Fig. 1) and was used to confirm results generated from the 1160-bp fragment.

2.3. Population genetic analyses

Hardy–Weinberg equilibrium of each bi-allelic polymorphism was assessed by χ^2 test. Pairwise LD statistic D' and r^2 were calculated with unphased genotype data by Haploview 3.2 software (Barrett et al., 2005). LD calculations were done for a total of 17 polymorphisms including 14

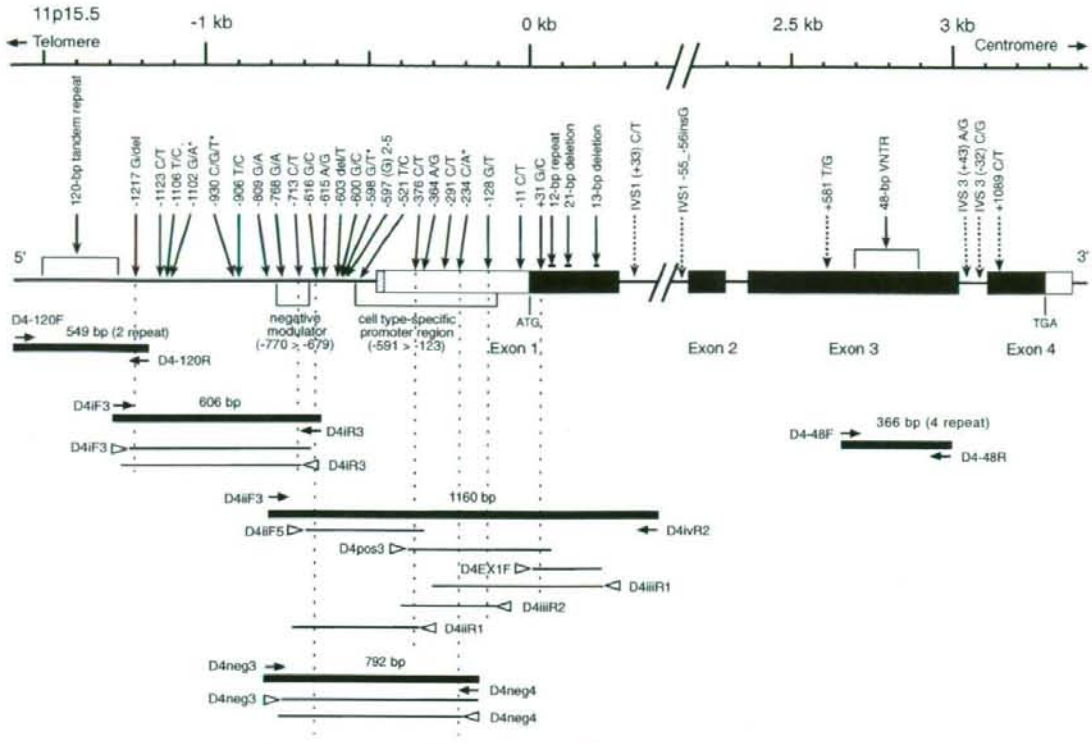

Fig. 1. Schematic representation of polymorphisms of the *DRD4* gene. The *DRD4* gene spans approximately 3.9 kbp consisting of four exons (black boxes: coding regions; white boxes: untranslated regions; hatched box: multiple transcription start sites). The region between position −1217 and +31 nucleotide (the numbering is relative to the first nucleotide of the initiation codon (ATG)) was extensively searched for novel or published SNPs. In total 34 polymorphisms (arrows) were collected from databases (dbSNP; Sherry et al., 1999) and JSNP (Hirakawa et al., 2002), published resources (PubMed) and our experiments. 28 polymorphisms (closed arrows) out of 34 were genotyped, including four novel polymorphisms (asterisks) first reported in this study. For genotyping, five fragments (bold lines) (549-bp, 606-bp, 1160-bp, 792-bp and 366-bp in length) were amplified by five primer sets (closed arrows; details are shown in Table 1) and sequenced by primers as indicated (open arrowheads). Thin lines next to open arrows indicate sequenced regions and orientation of primers. Exact positions of genotyped markers on each sequenced fragment are shown by longitudinal dotted lines. The reference sequence was AC021663 (GenBank).

biallelic polymorphic markers (120-bp TR, −1217G/del, −1106T/C, −906T/C, −809G/A, −768G/A, −713C/T, −616G/C, −603del/T, −600G/C, −521T/C, −376C/T, −291C/T and 12-bp repeat) for which minor allele frequencies exceeded 0.01, and three multi-allelic polymorphisms (−930C/G/T, $-597(G)_{2-5}$ and 48-bp VNTR). Since the Haploview software can analyze only bi-allelic data, we excluded individuals with allele T for −930C/G/T, and individuals with allele $(G)_2$ or $(G)_5$ for $-597(G)_{2-5}$. For the same reason, only individuals with genotype 4/4, 2/4, or 2/2 at the 48-bp VNTR were included. LD blocks were defined according to the confidence intervals described by Gabriel et al. (2002). Haploview LD analysis was carried out by selecting confidence intervals as specified in the software.

LD blocks in the 4.4-kb region of the *DRD4* gene were investigated and tag-SNPs (haplotype tagging markers) selected using Tagger software in Haploview. Markers whose r^2 values were more than 0.8 were selected by Tagger as part of an LD block.

Tag-markers selected using Tagger were used for haplotype estimation by PHASE ver 2.1 software (Stephens and Donnelly, 2003; Stephens et al., 2001). The distribution of the predicted haplotypes was compared between: (i) all schizophrenic patients vs. all controls, (ii) female schizophrenic patients vs. female controls, and (iii) male schizophrenic patients vs. male controls by χ^2 test.

We also carried out a sliding window haplotype analysis using the HTR (Haplotype Trend Regression) program (http://statgen.ncsu.edu/zaykin/htr.html) (Zaykin et al., 2002). This program estimates haplotype frequencies and performs a sliding window mode of haplotype association analysis between cases and controls. In this study, window size was set to be from 2 to 6 markers.

2.4. Statistical methods

Genotype frequencies of 17 polymorphic markers were compared between: (i) all schizophrenic patients vs. all controls, (ii) female schizophrenic patients vs. female controls,

and (iii) male schizophrenic patients vs. male controls by χ^2 test. When the expected number of any cell in a contingency table was less than 5, we employed Fisher's exact test. The significance level (α) for all statistical tests was two sided 0.05. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs).

Following univariate analysis, stepwise logistic regression analyses were carried out using gender, age and the 17 polymorphic markers as independent variables. The binary dependent variable was "schizophrenia affected" = 1 or "control" = 0.

A modified Bonferroni procedure was used to correct for multiple hypothesis testing. According to Bonferroni, since multiple tests were performed, the α level of 0.05 should be divided by the number of tests. However, this correction is almost certainly too strict because of the existence of LD between some of the polymorphisms. Therefore we also used a modified Bonferroni correction (Nyholt, 2004). According to this method, an effective number of independent marker loci is calculated and used in the denominator of the Bonferroni correction. Another adjustment to Bonferroni's method (Li and Ji, 2005) was also used to calculate an effective number of polymorphisms.

Statistical calculations were performed using BMDP statistical software (BMDP Statistical Software, Inc., USA) and SPSS 13.0J software (SPSS Japan Inc., Japan). StatXact (Cytel Software Corporation, USA) was used to compute Fisher's exact test, except for 2×2 contingency tables.

Our sample size had a post-hoc power of 0.848 to detect an effect size of $w = 0.10$ (weak) at the 0.05 significance level (two-tailed), as calculated by software program G*Power (http://www.psycho.uni-duesseldorf.de/aap/projects/gpower/how_to_use_gpower.html) (Erdfelder et al., 1996).

3. Results

3.1. Polymorphism detection and genotyping

Fig. 1 shows the structure of the *DRD4* gene and the locations of all reported polymorphisms (see also Table 2). We collected data on 34 polymorphisms including 28 SNPs and six insertion/deletions within an approximately 4.9 kbp region. The data was obtained from dbSNP (Sherry et al., 1999) (http://www.ncbi.nlm.nih.gov/SNP/snp_summary.cgi), JSNP (Haga et al., 2002; Hirakawa et al., 2002), other published reports and our experiments. As shown in Fig. 1, there are 27 polymorphisms, including 22 SNPs, in the 1.8 kbp region starting 1.5 kbp upstream of the 3′ end of exon 1. This is a much higher SNP density (12.2 SNPs/kbp) than the genome-wide average SNP density [reported to be 0.827 SNPs/kbp in dbSNP or 1.91 kbp/SNP by Sachidanandam et al. (2001)]. Table 2 summarizes data on 27 *DRD4* polymorphisms genotyped in this study, including four novel SNPs (−1102G/A, −930C/G/T, −598G/T and −234C/A) and one novel mononucleotide repeat polymorphism: $-597(G)_{2-5}$. The $-597(G)_{2-5}$ polymorphism was previously reported in the database as either −602G/del or $-602(G)_{8-9}$ (Mitsuyasu et al., 2001; Mitsuyasu et al., 1999; Okuyama et al., 2000). The $-602(G)_7$ and $-602(G)_{10}$ alleles were also identified in our experiments. In addition, a novel SNP (−598G/T) was found within the mononucleotide repeat of $-602(G)_{7-10}$. Thus, the $-602(G)_{8-9}$ polymorphism appears to be a combination of a guanine mononucleotide repeat with 2–5 units ($-597(G)_{2-5}$), together with a SNP at −598G/T and an invariant four guanine nucleotide repeat immediately upstream. Thus we suggest a designation of $-597(G)_{2-5}$ for this polymorphism instead of −602G/del or $-602(G)_{8-9}$. The −598G/T SNP was registered as −598G/A/del in the dbSNP database, however, our study showed only the −598G and T genotypes. For this reason, we classified this SNP as novel.

In order to understand the relationship between these polymorphisms, including the four novel SNPs, and the well studied 120-bp TR and 48-bp VNTR polymorphisms we include data on the latter in this study. The 120-bp TR is located approximately 0.8 kb upstream of the 5′ end of exon 1. The 48-bp VNTR is in exon 3. It has been reported that two adjacent intronic SNPs (IVS3(+43)A/G and IVS3(−32)C/G) are in strong LD with the 48-bp VNTR 4 repeat allele (Ding et al., 2002). Based on that data we typed the 48-bp VNTR polymorphism as a representative marker for variation in the 3′ region of the gene.

Twenty-seven polymorphisms were genotyped. (The 13-bp deletion in exon 1 could not be analyzed for technical reasons.) Twenty-one were biallelic SNPs (19 substitution, two insertion/deletion), one triallelic. Five SNPs (−1123C/T, −615A/G, −364A/G, −11C/T and +31G/C) were monomorphic in the study population, as was the 21-bp deletion (Table 2). Four markers (−1102G/A, −598G/T, −234C/A and, −128G/T) were singletons. These polymorphisms were not analyzed for disease association. The seven repeat allele of the 48-bp VNTR was rare; only four heterozygous genotypes (4/7) were found.

The genotype distribution of each biallelic polymorphism was consistent with Hardy–Weinberg equilibrium (data not shown).

3.2. Association with schizophrenia

Uni- and multivariate analyses were carried out with 17 polymorphisms to assess the effect of polymorphism on risk of developing schizophrenia. Specifically, 12 known SNPs (−1217G/del, −1106T/C, −906T/C, −809G/A, −768G/A, −713C/T, −616G/C, −603del/T, −600G/C, −521T/C, −376C/T, and −291C/T), three repeat polymorphisms (120-bp TR, 12-bp repeat, and 48-bp VNTR) and two novel polymorphisms (−930C/G/T and $-597(G)_{2-5}$) were analyzed. Results from univariate statistical analyses are shown in Table 2.

No polymorphisms differed in frequency between the schizophrenic patients and the controls, even before adjusting for multiple hypothesis testing (Table 2). Comparing the female schizophrenic patients with the female controls, we

Table 2
Comparison of genotype frequencies of polymorphisms of the *DRD4* between schizophrenic patients and controls in Japanese population

Polymorphism[a]		Genotype frequency									db SNP[c]	JSNP[d]	References
		All			Female			Male					
		Control	Schizophrenia	p^b	Control	Schizophrenia	p	Control	Schizophrenia	p			
120-bp tandem repeat	n[f]	239	214	0.827	105	95	0.369	134	119	0.798	–	–	Paterson et al. (1996)
(−1480 to −1240)	2/2	0.582	0.603		0.524	0.621		0.627	0.588				Seaman et al. (1999)
	2/1	0.364	0.350		0.429	0.347		0.313	0.353				
	1/1	0.054	0.047		0.048	0.032		0.060	0.059				
−1217G/del[e]	n	238	209		105	93		133	116		rs12720364	–	Okuyama et al. (2000),
	G/G	0.685	0.718	0.713[g]	0.695	0.688	0.566[g]	0.677	0.741	0.497[g]			Wang et al. (2004)
	G/del	0.294	0.258		0.295	0.280		0.293	0.241				
	del/del	0.021	0.024		0.010	0.032		0.030	0.017				
−1123C/T	n	241	215		105	94		136	121		–	–	Okuyama et al. (2000)
	C/C	1.000	1.000		1.000	1.000		1.000	1.000				
	C/T	0.000	0.000		0.000	0.000		0.000	0.000				
	T/T	0.000	0.000		0.000	0.000		0.000	0.000				
−1106T/C	n	242	215		105	94		137	121		rs936460	IMS-JST111981	Wang et al. (2004)
	T/T	0.798	0.800	1.000[g]	0.838	0.777	0.226[g]	0.766	0.818	0.488[g]			
	T/C	0.190	0.186		0.162	0.202		0.212	0.174				
	C/C	0.012	0.014		0.000	0.021		0.022	0.008				
−1102G/A	n	239	214		103	94		136	120		–	–	Present study
	G/G	0.996	1.000		0.990	1.000		1.000	1.000				
	G/A	0.004	0.000		0.010	0.000		0.000	0.000				
	A/A	0.000	0.000		0.000	0.000		0.000	0.000				
−930C/G/T	n	240	214		104	94		136	120		–	–	Present study
	C/C	0.979	0.967	0.396[g]	0.981	0.979	0.793[g]	0.978	0.958	0.365[g]			
	C/G	0.017	0.023		0.019	0.011		0.015	0.033				
	C/T	0.000	0.009		0.000	0.011		0.000	0.008				
	G/G	0.004	0.000		0.000	0		0.007	0				
−906T/C	n	239	214		104	94		135	120		rs3758653	IMS-JST111982	Wang et al. (2004)
	T/T	0.669	0.645	0.714	0.654	0.670	0.801[g]	0.681	0.625	0.289			
	T/C	0.280	0.313		0.317	0.287		0.252	0.333				
	C/C	0.050	0.042		0.029	0.043		0.067	0.042				
−809G/A	n	241	215		104	94		137	121		rs936461	IMS-JST111983	Mitsuyasu et al. (1999)
	G/G	0.643	0.605	0.486	0.654	0.606	0.097[g]	0.635	0.603	0.867			Okuyama et al. (2000)
	G/A	0.299	0.349		0.308	0.394		0.292	0.314				Mitsuyasu et al. (2001)
	A/A	0.058	0.047		0.038	0.000		0.073	0.083				
−768G/A	n	240	215		104	94		136	121		rs4987058	–	Mitsuyasu et al. (1999)
	G/G	0.963	0.977	0.544	0.952	0.979	0.449[g]	0.971	0.975	1.000[g]			Mitsuyasu et al. (2001)
	G/A	0.038	0.023		0.048	0.021		0.029	0.025				
	A/A	0.000	0.000		0.000	0.000		0.000	0.000				
−713C/T	n	240	215		104	94		136	121		rs11246224	–	Present study
	C/C	0.996	0.977	0.105[g]	1.000	0.957	0.049[g]	0.993	0.992	1.000[g]			
	C/T	0.004	0.023		0.000	0.043		0.007	0.008				
	T/T	0.000	0.000		0.000	0.000		0.000	0.000				
−616G/C	n	240	210		103	94		137	116		rs747302	–	Mitsuyasu et al. (1999)
	G/G	0.467	0.486	0.503	0.515	0.543	0.486	0.431	0.440	0.876			Okuyama et al. (2000)
	G/C	0.408	0.424		0.359	0.383		0.445	0.457				Mitsuyasu et al. (2001)
	C/C	0.125	0.090		0.126	0.074		0.124	0.103				