d 肝臓疾患

肝臓疾患の主要なものに肝硬変が挙げられる。肝硬変は肝細胞の壊死を伴う肝機能不全状態である。成因の大半をウイルス性肝炎が占め(C型肝炎約60%，B型肝炎約15%)，アルコール性が1割強である。

ウイルス肝炎には，A型，B型，C型，D型，E型の5種類が確認されている。A型肝炎は食物(生牡蠣など魚介類)・飲料水等からの経口感染により平均約30日の潜伏期ののち急激に発症するが，慢性化せず予後は良好である。症状は，発熱，悪心・嘔吐，腹痛，全身倦怠感，黄疸などである。

B型肝炎は血液，唾液などを通して感染し，乳幼児が感染した場合は持続感染者(キャリア)となりやすいが，成人が感染した場合慢性化することはまれとされる。かつては出産時における母子感染等が多かったこともあり，B型肝炎ウイルスキャリアは推定110～140万人いるが，昭和60年度から妊婦検診でHBs抗原検査を行い，子に対するワクチン投与などの適切な予防措置を講じたため(B型肝炎母子感染防止事業)，キャリアの数は減少している。

一方，C型肝炎は血液により感染し(輸血，入れ墨，注射器等)，感染年齢にかかわらず高率に慢性化しキャリアとなる。日本には推定200～240万人のキャリアがおり，そのうち一定の割合(6割という推定もある)が20年をかけて肝硬変に移行し，さらに肝がんへと移行する。したがって，C型慢性肝炎患者にはインターフェロンやリバビリン，ペグインターフェロンによりウイルスを駆除する治療等が必要となる。感染予防のためには，日常生活において剃刀，歯ブラシ，爪切り等の共用を避けることが重要である。

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。このような精神疾患の増加を受け同省は2011(平成23)年7月6日に精神疾患を，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，重点的対策を行う方針を示している。

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(日本の定期／任意予防接種スケジュール(20歳未満)，国立感染症研究所，4種混合ワクチンの導入に関する方針について(案)，厚生労働省健康局結核感染課)。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勝ちとなっていた。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，一般の人が本来持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)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，外傷を思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」をさし，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

プ」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。

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)。日本では，警察庁生活安全局の報告によると，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32,000～33,000人前後で推移している。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2010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, 2010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。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，2008年の不慮の事故で最も多かったのは窒息9,419，次いで交通事故7,499，転倒転落7,170，溺死6,464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2006(平成18)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，2006年は37,323に達し，深刻な社会問題となっている。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)

7

Impact of Epidemiology on Molecular Genetics of Schizophrenia

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'To grasp the full meaning of the *obvious* is a better basis for the understanding than the confused knowledge of the *obscure*.'
(Engels)

1. Introduction

Schizophrenia is a common deleterious psychosis that begins typically in late adolescence or early adulthood (Gottesman, 1991; Jablensky, 1995). Although it has a strong genetic component in its etiology, no susceptibility genes conferring a large proportion of heritability have been identified (Allen et al., 2008; Need et al, 2009). Results of association studies including genome-wide scans have been inconsistent, and schizophrenia-associated genes including copy number variations differ across populations or even across individuals of a same ethnicity (Allen et al., 2008; Xu et al., 2008; Need et al, 2009). Thus, situation of molecular genetics of schizophrenia has become rather perplexing just contrary to our expectation.

In this chapter, we describe the consistent major epidemiological findings of schizophrenia, and show how these evident macroscopic aspects shed light to the confused microscopic aspects of schizophrenia genetics today, proposing a new hypothesis for this puzzling disorder.

2. Devil's triangle of human genetics – Epidemiological facts of schizophrenia

We describe here three epidemiological facts of schizophrenia - high prevalence, high heritability and low reproductive fitness. These properties form a Devil's triangle; any combination of the two tends to exclude the third, and in this triangle most diseases vanish except for schizophrenia, suggesting that schizophrenia has a unique etiological basis among the many human diseases.

2.1 Schizophrenia as a common disease

Substantial evidence of epidemiology shows that schizophrenia crosses all cultures and tribes in different continents at a relatively high prevalence (approximately 0.7%; 95%

Confidence Interval 0.3% - 2.7%) (Saha et al., 2005); the prevalence of schizophrenia, at the macro-level, varies within narrow limits (Jablensky, 1995), and appears to be stable across generations in several countries (Harrison et al., 1991; Osby et al., 2001). This epidemiological fact suggests that schizophrenia has an ancient origin.

2.2 Schizophrenia as a heritable disease

It has long been known that schizophrenia runs in families (McGue & Gottesman, 1991). Adoption studies demonstrate an increased risk of schizophrenia in biological relatives of adoptees with schizophrenia, suggesting that genetic components play an important role in the etiology of schizophrenia (Kendler & Dichl, 1993). Now it has been established by twin studies that heritability of schizophrenia is ~0.85 (Cannon et al., 1998; Cardno et al., 1999).

Although the mode of transmission of schizophrenia is still unknown, several reports suggest a higher maternal transmission of schizophrenia (Shimizu et al., 1987; Goldstein et al., 1990; Valero et al., 1998; Li et al., 2007).

2.3 Schizophrenia as a low fitness disease

It has been well documented that the fertility of patients with schizophrenia, particularly of males, is remarkably reduced compared to healthy individuals (Böök, 1953; Larson & Nyman, 1973; Ødegård, 1980; Nanko & Moridaira, 1993; Fãnanás & Bertranpetit, 1995; Nimgaonkar, 1998; McGrath et al., 1999; Haukka et al., 2003; Svensson et al., 2007). The latest meta-analysis (Bundy et al., 2011) shows that fertility ratio (patients/controls) is ~0.39 and that the reduction of fertility is more pronounced in males (male/female ratio is ~0.54).

Because schizophrenia is an early onset disease (late adolescence ~ early adulthood), psychotic symptoms of the disease such as autistic way of life and abnormal behaviors may make mating unsuccessful. This tendency may be more pronounced in males because the age at onset is significantly lower in males than in females (Jablensky, 1995; Kulkarni & Fink, 2000). Thus, unsuccessful mating, coupled with an increased mortality (McGrath et al., 2008), may remarkably reduce the fertility of patients with schizophrenia.

2.4 Schizophrenia and the Devil's triangle of human genetics

The three epidemiological characteristics of schizophrenia - high prevalence, high heritability and low fitness - form a Devil's triangle; any combination of the two tends to exclude the third, and in this triangle most diseases vanish except for schizophrenia (**Fig. 1**). Diseases with high prevalence and high heritability such as type 2 diabetes and adult cancers are late-onset diseases and exhibit almost normal reproductive fitness. Diseases with high heritability and low reproductive fitness such as most harmful Mendelian diseases in childhood are rare. Diseases with low reproductive fitness and high prevalence such as poor nutrition, severe injuries and infections in childhood or early adulthood are mainly due to the environmental factors.

This may lead us to strongly suspect that schizophrenia has a unique etiological basis among the many human diseases.

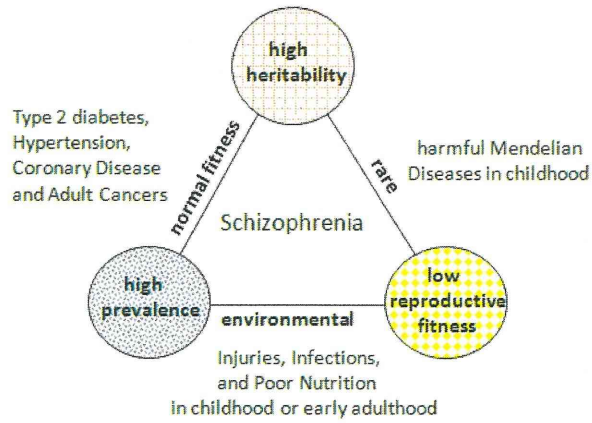

Fig. 1. Devil's triangle of human genetics (Doi et al., 2009)

3. Persistence problem and mutation-selection balance in schizophrenia

The three epidemiological characteristics of schizophrenia mentioned above give a paradox. How has a highly heritable disease associated with a remarkable biological disadvantage never been extinct in the long human history? And how can it persist at a relatively high prevalence? This 'persistence problem of schizophrenia' (or 'schizophrenia paradox') has puzzled scientists for long years (Huxley et al., 1964; Crow, 1995; Brüne, 2004; Keller & Miller, 2006).

In this section, we discuss that the only plausible mechanism for the persistence is mutation-selection balance with or without heterozygote advantage. Based on the consistent epidemiological findings on the fertility of patients with schizophrenia and their family members, we show that heterozygote advantage works in the mitochondrial genome model but not in the nuclear genome model.

3.1 Mutation-selection balance is the only plausible mechanism for the persistence

From an evolutionary viewpoint, four explanations are possible for the persistence: (i) ancestral neutrality, (ii) negative frequency-dependent selection, (iii) heterozygote advantage (balancing selection or pleiotropy), and (iv) mutation-selection balance.

'Ancestral neutrality' assumes that reproductive fitness of affected individuals and/or their relatives was higher in ancient environments and that selection coefficients of pathogenic alleles were close to zero. Because the effective population size in ancient times might be much smaller than now, pathogenic but neutral or almost neutral alleles could be fixed by genetic drift. While this hypothesis explains that schizophrenia has not been extinct in the long human history, ancestral neutrality itself provides no explanation for the apparently stable prevalence of the disease across generations today; although 'ancestral neutrality' might be plausible, it needs another mechanism to account for the persistence in modern environments, where the effective population size has been expanded and the influence of negative selection pressure may be much stronger than ever before.

'Negative frequency-dependent selection' explains the persistence only when the fitness of the affected individuals increases as the prevalence in the general population decreases, which seems not to be the case with schizophrenia.

Thus, the remaining possibility for persistence mechanism is mutation-selection balance with or without heterozygote advantage.

3.2 Heterozygote advantage works in the mitochondrial genome model but not in the nuclear genome model for schizophrenia

'Heterozygote advantage' assumes that the susceptibility alleles increase the fitness of the unaffected gene carriers, thereby sustaining the gene frequencies. This line of explanations may include: (i) physiological advantage (resistance to shock, infections, and poor nutrition etc.), (ii) a higher sexual activity and/or attractiveness, and (iii) creative intelligence or a higher trait creativity including 'everyday creativity'.

This hypothesis needs two lines of confirmation: (a) that unaffected gene carriers have such advantages, and (b) that such advantages really contribute to sufficiently increase their reproductive fitness.

It seems to gain the confirmation (a). For example, Erlenmeyer-Kimling (1968) reported an increased survival rate of *female* children of parents with schizophrenia, proposing a possible physiological advantage associated with schizophrenia. Kinney et al. (2001), in a well-designed and methodologically sophisticated study, showed that an advantage of everyday creativity was linked to a subtle clinical picture (schizotypal signs) in a non-psychotic sample of schizophrenia offspring.

However, it lacks the confirmation (b) in the nuclear genome model. This hypothesis, although theoretically plausible and fascinating, has not been supported by most epidemiological studies, which show a decreased reproductive fitness of unaffected siblings of patients with schizophrenia. Although recent large-sampled epidemiological studies (Bassett et al., 1996; McGrath et al., 1999; Haukka et al., 2003; Svensson et al., 2007) have consistently shown that the reproductive fitness of unaffected *female* siblings of patients with schizophrenia is slightly but significantly increased (1.02-1.08), it is not large enough to compensate for the gene loss due to the decreased reproductive fitness of patients (0.2-0.3 in males and 0.4-0.5 in females) and their unaffected male siblings (0.9-1.0) in the nuclear genome model. On the other hand, the latest meta-analysis (Bundy et al., 2011) shows no significant difference between the fertility of parents of patients with schizophrenia and healthy controls, although there is a trend towards parents having more offspring. Therefore, heterozygote advantage seems not to work in the nuclear genome model.

On the other hand, it works in the mitochondrial genome model because mitochondrial DNA (mtDNA) is transmitted to the next generation only through females. Indeed, we can see that this slightly elevated reproductive fitness of the unaffected female siblings, coupled with the less pronounced decreased reproductive fitness of female patients, is sufficient to compensate for the gene loss; when we calculate $-\Delta$, the cross-generational reduction of the frequency of females with a putative pathogenic mtDNA in the general population, using the data in the largest-sampled cohort study to date (Haukka et al., 2003), we have $-\Delta < 5.06 \times 10^{-3}$ (**Note**). This figure implies that the gene loss can be balanced by *de novo*

mutation in the mtDNA which occurs at a rate of $8.8\times10^{-4}\sim1.3\times10^{-2}$ per locus per generation (4.3×10^{-3} on average) (Sigurđardóttir et al., 2000).

4. Persistence criterion for nuclear susceptibility genes for schizophrenia

As is shown in the previous section, putative pathogenic genes, if located in the mtDNA, are sustained by mutation-selection balance with heterozygote advantage. On the other hand, if located in the ncDNA, they should be sustained by mutation-selection balance without heterozygote advantage. In this section, we introduce our previous work (Doi et al., 2009), in which we carefully re-examined the necessary conditions for putative nuclear susceptibility genes for schizophrenia and deduced a criterion (persistence criterion, or 'P-criterion') that every nuclear susceptibility gene should fulfill for persistence of the disease, and present its applications to association studies for schizophrenia.

4.1 Three basic assumptions

At first we describe our three basic assumptions.

4.1.1 An ideal human population

We assume here a random-mating human population with a sufficiently large effective population size at equilibrium, where negative selection pressures on the susceptibility alleles for schizophrenia are predominant and the effect of genetic drift is negligibly small. The prevalence p of schizophrenia in this ideal human population is assumed to be stable across generations by mutation-selection balance. Therefore, the gene frequency in the general population (m_G) is given in terms of the gene frequencies in the affected population (m_A) and in the unaffected population (m_U):

$$m_G = pm_A + (1-p)m_U \text{ , or } m_A - m_G = (1-p)d \ . \ \ d \equiv m_A - m_U \ ) \tag{1}$$

4.1.2 Mutation-selection balance in each risk locus

We assume here that the total of the population frequencies of the pathogenic alleles at *each risk locus* is preserved by mutation-selection balance. Therefore, $-\Delta m_G$,the cross-generational reduction of the frequency of a pathogenic allele should not be more than the rate of mutations that produce pathogenic variants at the locus. On the other hand, since mutations at the locus include mutations of two directions that produce pathogenic or non-pathogenic variants, the mutation rate at the locus (μ) should be greater than the rate of mutations that produce pathogenic variants at the locus.

Thus we have:

$$\mu > -\Delta m_G \, . \tag{2}$$

4.1.3 Multifactorial threshold model

We assume the multifactorial threshold model, in which quantitative traits such as liability to the disease are determined by multiple genetic and non-genetic factors including a

stochastic and/or an epigenetic effect. Under this assumption, the relative fitness as a quantitative trait in the affected population is determined by multiple factors and approximately follows a gamma distribution with a mean $(1-s)$. (s is the selection coefficient of schizophrenia; the mean relative fitness in the normal population is 1.)

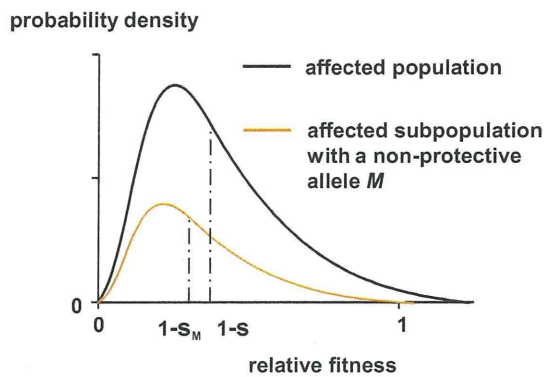

Fig. 2. Distribution curve of the reproductive fitness in the affected population

Distribution curve of the reproductive fitness in the affected subpopulation with a schizophrenia-associated allele M never shifts to the right unless M has a strong protective effect (i.e. an effect of elevating carrier's reproductive fitness by reducing severity of and liability to the disease). Therefore, we can assume that s_M, the selection coefficient in the affected subpopulation with a schizophrenia-associated allele M, is not smaller than s ($s \le s_M < 1$) for a susceptibility allele (**Fig. 2**). The inequality $s > s_M$ implies that M is a resistance gene that reduces severity and risk of the disease.

No special assumptions else are required on the allelic structure in each locus, penetrance of each susceptibility gene, and possible interactions among the loci.

4.2 Deduction of the P-criterion

Now we proceed to deduce the P-criterion. From the assumptions, m'_G, the population frequency of the schizophrenia-associated allele M in the next generation, is given by:

$$m'_G = \frac{p \cdot m_A \cdot (1-s_A) + (1-p) \cdot m_U \cdot 1}{p \cdot (1-s_M) + (1-p) \cdot 1} = \frac{m_G - s_M p m_A}{1 - s_M p}.$$

Therefore the reduction of the population frequency of the schizophrenia-associated allele M per generation is:

$$-\Delta m_G = m_G - m'_G = \frac{s_M p(m_A - m_G)}{1 - s_M p} = p(1-p)d \cdot \frac{s_M}{1 - s_M p}. \quad (3)$$

From (2) and (3) we have:

$$\mu > p(1-p)d \cdot \frac{s_M}{1-s_M p} \tag{4}$$

Since $\frac{s_M}{1-s_M p}$ is monotonically increasing for s_M $(0 < s_M < 1)$ and $s \le s_M < 1$ holds for the susceptibility allele M, we have:

$$\mu > p(1-p)d \cdot \frac{s}{1-sp}, \text{ or } \frac{(1-sp)\mu}{(1-p)sp} > d. \tag{5}$$

On the other hand, the principle of association studies demands: $0 < d$.

Thus we have the criterion for a susceptibility gene:

$$0 < d < \nu, \text{ where } \nu \text{ is defined as } \nu \equiv \frac{(1-sp)\mu}{(1-p)sp}. \tag{6}$$

From the observation (5), we can see that $d \ge \nu$ implies $s > s_M$ for any schizophrenia-associated variant M which is sustained by mutation-selection balance.

4.3 Parameter estimate for schizophrenia

Mutation rates on autosomes and the X chromosome almost always fall within the range between 10^{-6} and 10^{-4} per locus per generation (usually < 10^{-5}; one generation = 20 years) (Nachman & Crowell, 2000) and can be approximated by a linear function of the parental age at least under 30 years for maternal age and under 40 years for paternal age (Risch et al., 1987). Large-sampled cohort studies in Israel, Sweden and Denmark show that the mean age of parents in the general population is ~ 28 years for mothers and ~31 years for fathers; the mean age of both parents is < 29.6 years (Malaspina et al., 2001; El-Saadi et al., 2004). Therefore we assume here:

$$10^{-6} < \mu < \frac{29.6}{20} \times 10^{-4} = 1.48 \times 10^{-4}.$$

According to the epidemiological data by Haukka et al. (2003), the estimated values for p and s are $p = 1.29 \times 10^{-2}$ and $s = 6.54 \times 10^{-1}$. Therefore, we have $\nu = 1.76 \times 10^{-3}$ for the average mutation rate (1.48×10^{-5}), $\nu = 1.76 \times 10^{-2}$ for the highest mutation rate (1.48×10^{-4}), and $\nu = 1.76 \times 10^{-4}$ for a relatively low mutation rate (1.48×10^{-6}).

4.4 Implications for association studies of schizophrenia

We present here some applications of the P-criterion to association studies of schizophrenia. The results suggest that common disease/common variant hypothesis is unlikely to fit schizophrenia and that an enormous sample size is required to detect a nuclear susceptibility gene for schizophrenia.

4.4.1 Calculation of an upper bound of the effect size of a putative susceptibility gene of a given frequency

Using the P-criterion, we can calculate an upper bound of the effect size of a putative susceptibility gene of a given frequency.

Effects size of a susceptibility gene M is expressed by odds ratio defined as

$$OR = \frac{m_A(1-m_U)}{(1-m_A)m_U},$$

which is monotonically increasing for m_A and monotonically decreasing for m_U. Since the criterion demands $m_U < m_A < m_U + \nu$, we have

$$\frac{m_U(1-m_U)}{(1-m_U)m_U} < OR < \frac{(m_U+\nu)(1-m_U)}{(1-m_U-\nu)m_U}, \text{ or } 1 < OR < 1 + \frac{\nu}{m_U(1-\nu-m_U)} \quad (7)$$

for $0 < m_U < 1-\nu$.

And since the criterion demands $m_A - \nu < m_U$, we have

$$1 < OR < \frac{m_A(1-m_A+\nu)}{(1-m_A)(m_A-\nu)} = 1 + \frac{\nu}{(1-m_A)(m_A-\nu)} \quad (8)$$

for $1-\nu \le m_U < 1$.

Thus, we have an upper bound of the effect size for a given frequency.

From the above we can easily see that the common disease/ common variant hypothesis, which proposes that common alleles at a handful of loci interact to cause a common disease, is unlikely to fit schizophrenia. No common alleles with population frequency between 0.05 and 0.95 can have large effects for schizophrenia: the odds ratio of every common risk allele is less than 1.04 for the average mutation rate, less than 1.58 for the highest mutation rate, and less than 1.004 for a relatively low mutation rate (**Table 1**).

4.4.2 Calculation of range of the frequency of a putative susceptibility gene of a given effect size

By solving the inequality (7) or (8), we can estimate the range of gene frequency for a given effect size. Thus, we can see that susceptibility genes of the average mutation rate and a moderate effect that meet the criterion are limited to 'very rare variants' or 'very common variants'. For example, suppose $\mu = 1.48 \times 10^{-5}$ and OR=5.0, then we have: $\nu = 1.76 \times 10^{-2}$ and

$$4 < \frac{\nu}{m_U(1-\nu-m_U)}.$$

Solving this inequality, we get either $0 < m_U < 0.00044$ (that is, $0 < m_A < m_U + 0.00176 < 0.0022$) or $m_U > 0.9977$.

m_U	$\mu = 1.48 \times 10^{-6}$	$\mu = 1.48 \times 10^{-5}$	$\mu = 1.48 \times 10^{-4}$
0.01	< 1.02	< 1.18	< 2.81
0.02	< 1.009	< 1.09	< 1.92
0.05	< 1.004	< 1.04	< 1.38
0.1	< 1.002	< 1.02	< 1.20
0.3	< 1.0009	< 1.009	< 1.09
0.5	< 1.0008	< 1.008	< 1.08
0.7	< 1.0009	< 1.009	< 1.09
0.9	< 1.002	< 1.02	< 1.24
0.95	< 1.004	< 1.04	< 1.58
0.98	< 1.009	< 1.10	< 8.49

Table 1. Upper bounds of odds ratio for given allele frequencies in the unaffected population

4.4.3 Calculation of the required sample size and the power of an association study

Using the P-criterion we can calculate a lower bound of sample size required in an association study of a given power as well as an upper bound of the power of an association study of a given sample size.

Concerning the required sample size $2N$ (N case-control pairs) and the power $1-\beta$ of an association study, we have the well-established formulae (Ohashi & Tokunaga, 2002):

$$N \cong \frac{1}{2}\left(\frac{z^*_\alpha \sqrt{2x(1-x)} + z_\beta \gamma}{d}\right)^2,$$

and

$$1-\beta \cong \Phi\left(\frac{\sqrt{2N}d - z^*_\alpha \sqrt{2x(1-x)}}{\gamma}\right).$$

Here, Φ, z^*_α, and z_β denote the cumulative distribution function of the standard normal curve, the two sided a point (a: a significant level) and the upper β point of the standard normal curve, and x (population frequency of the allele) and γ^2 are defined as follows.

$$x \equiv \frac{1}{2}(m_A + m_U) \qquad \gamma^2 \equiv m_A(1-m_A) + m_U(1-m_U) = 2x(1-x) - \frac{1}{2}d^2$$

For the average mutation rate $\mu = 1.48 \times 10^{-5}$, we have $\nu = 1.76 \times 10^{-3}$. Suppose $0.0005 < x < 0.9995$, then we have $2x(1-x) > 0.9995 \times 10^{-3}$. From the P-criterion, we have:

$$\frac{1}{2}d^2 < \frac{1}{2}\nu^2 < 1.6 \times 10^{-6} < 2x(1-x) \times 0.002.$$

Therefore, we have the following approximation with an error smaller than 0.2 %:

$$\gamma^2 = 2x(1-x) - \frac{1}{2}d^2 \cong 2x(1-x), \text{ or } \gamma \cong \sqrt{2x(1-x)}.$$

Thus, we have:

$$N \cong \frac{1}{2}\left(\frac{z^*_\alpha \sqrt{2x(1-x)} + z_\beta \gamma}{d}\right)^2 \cong \left(\frac{z^*_\alpha + z_\beta}{d}\right)^2 x(1-x) > \left(\frac{z^*_\alpha + z_\beta}{\nu}\right)^2 x(1-x)$$

$$1-\beta \cong \Phi\left(\frac{\sqrt{2N}d - z^*_\alpha \sqrt{2x(1-x)}}{\gamma}\right) \cong \Phi\left(\sqrt{\frac{N}{x(1-x)}}d - z^*_\alpha\right) < \Phi\left(\sqrt{\frac{N}{x(1-x)}}\nu - z^*_\alpha\right)$$

Let us calculate the required sample size in a genome-wide association study ($\alpha = 2.5 \times 10^{-7}, 1-\beta = 0.95$). Since we have $z^*_{0.00000025} + z_{0.05} = 6.79$,

$$N > \left(\frac{z^*_\alpha + z_\beta}{\nu}\right)^2 x(1-x) = \left(\frac{6.79}{1.76 \times 10^{-3}}\right)^2 x(1-x) = 3.72 \times 10^6$$

for $x = 0.5$. Therefore, more than 3.7 million case-control pairs are required in a genome-wide association study with a power 0.95 to detect a susceptibility variant of the average mutation rate and a population frequency between 0.0005 and 0.9995.

Similarly we can see that more than 37,000 case-control pairs are required in a genome-wide association study with a power 0.95 to detect a susceptibility variant of the highest mutation rate ($\mu = 1.48 \times 10^{-4}$) and a population frequency between 0.005 and 0.995.

Finally, let us consider the case with a relatively low mutation rate $\mu = 1.48 \times 10^{-6}$, which corresponds to $\nu = 1.76 \times 10^{-4}$. In this case, more than 370 million case-control pairs are required in a genome-wide association study with a power 0.95 to detect a susceptibility variant of a population frequency between 0.000005 and 0.999995. Therefore it would take more than several hundred years to gather the required number of samples even if all of the affected individuals in the world were to be recruited to the study.

5. Mitochondrial DNA (mtDNA) hypothesis of schizophrenia

In this final section, we discuss on the nature of those schizophrenia-associated genes that do not meet the P-criterion, suggesting that these genes should be resistance genes that reduce the morbid risk and severity of the disease. We show that the results of association studies to date is compatible with the mitochondrial genome model but not with the nuclear genome model and propose a new hypothesis which assumes that the risk loci are in the mtDNA. We present eight major predictions of this hypothesis, and discuss that these predictions seem to accord with the other epidemiological findings and the results of the genetic and the pathophysiological studies to date.

5.1 Nature of schizophrenia-associated genes that do not meet the P-criterion

Now, let us consider the nature of those schizophrenia-associated genes that do not meet the persistence criterion. The inequality $d \geq \nu$ implies $s_M < s$, where s_M and s denote the selection

coefficient in the affected subpopulation with an allele M and in the affected population respectively. Therefore, such genes, if sustained by mutation-selection balance, cannot be susceptibility genes but resistance genes that reduce severity and risk of the disease (see 4.2). If they were not resistance genes, their frequencies in the affected population must have been reduced to the same level in the unaffected population.

5.2 The results of association studies to date accord with the mitochondrial genome model but not with the nuclear genome model

Since a resistance gene in the nuclear genome model cannot be associated with the disease unless it is linked with a susceptibility gene, resistance genes in the nuclear model should be located in the vicinity of susceptibility genes, which disagrees with the results of association studies to date.

For example, on the chromosome 1, all of the schizophrenia-associated genes that could meet the criterion (*RGS4, PLXNA2, DISC1*) are located on 1q, while four resistance genes (*MHTFR, GRIK3, PDE4B, GSTM1*) are on 1p (**Table 2**). Fifteen resistance genes are located on 2q, 5q, 7q, 10q, 11p, 12p, 12q, 13p, 13q, 16p, 17p, and 19q, where no schizophrenia-associated variants that could meet the criterion are located (data: not shown). Therefore, the results of association studies to date argue against the nuclear genome model.

A possible interpretation which accords with the nuclear genome model might be that many nuclear susceptibility genes of less than the highest mutation rates have not been detected by association studies to date due to lack of power. In this case, however, an enormous sample size (more than 3.7~370 million case-control pairs) would be required to identify them as was mentioned above. In other words, such an enormous sample size is required to prove the nuclear genome model.

On the other hand, every resistance gene on *any* chromosome can be associated with schizophrenia in the mitochondrial genome model; since mtDNA is transmitted only via females and there is no link between the nuclear genome and the mitochondrial genome, every nuclear genome which interacts with a pathogenic mitochondrial genome to alter severity and risk of the disease is subject to natural selections in the predisposed maternal lineage that succeeds to a same pathogenic mitochondrial genome. Therefore, every resistance gene for schizophrenia in the mitochondrial genome model is to be subject to a positive selection in the predisposed maternal lineage, thereby associating with schizophrenia.

Thus, the mitochondrial genome model is compatible with the results of the association studies to date.

It should be noted that in the mitochondrial genome model every facilitating gene (a gene that increases the severity and morbid risk in the predisposed population) on any chromosome may diminish in the predisposed matrilineal pedigrees by negative selection, thereby negatively associating with the disease.

Schizophrenia-associated variants listed in the top 45 in the SZGene Database (the version of 10th December, 2010) were selected. Based on the genotype distributions in meta-analyses, allele frequencies and the case-control differences were calculated. 4 variants at the 3 loci (*RGS4, PLXNA2, DISC1*) could meet the criterion under the assumption that the mutation

rates at those loci are near the upper limit in the autosomes. All of them are located on 1q, while 4 resistance genes (*MHTFR, GRIK3, PDE4B, GSTM1*) are on 1p. * schizophrenia-associated alleles; variants that could meet the criterion are shown in bold characters

Genes and SNPs	Location	Allele (minor/major)	m_A	m_U	*OR*	*d*
MHTFR	1p36.22					
rs1801133		T*/C	0.3532	0.3211	1.15	0.032
GRIK3	1p34.3					
rs6691840		G*/T	0.2600	0.2226	1.25	0.037
PDE4B	1p31.3					
rs910694		C/T*	0.5780	0.5477	1.30	0.030
GSTM1	1p13.3					
GSTM1*0		ins-allele/del-allele*	0.7546	0.7140	1.35	0.041
RGS4	**1q23.3**					
rs2661319		A/**G***	0.4920	0.4744	**1.08**	**0.0176**
IL10	1q32.1					
rs1800896		G*/A	0.3056	0.2657	1.42	0.040
PLXNA2	**1q32.2**	A/G				
rs841865		A/G*	0.8434	0.8001	1.32	0.043
rs1327175		G/**C***	0.92840	0.91243	1.32	**0.016**
DISC1	**1q42.3**					
rs3737597		**A***/G	0.03069	0.01735	1.80	**0.013**
rs999710		**A***/G	0.3989	0.3819	1.07	**0.0170**

Table 2. Schizophrenia-associated genes on the chromosome 1 that could meet the criterion

5.3 The mtDNA hypothesis for schizophrenia and its predictions

Thus we propose here a new hypothesis which insists that the risk loci for schizophrenia are in the mtDNA.

Mitochondria are involved in a variety of major cellular events such as oxidative phosphorylation, free radical production and Ca^{2+} buffering, and play an active role in apoptosis. They possess two classes of antioxidant defense system (non-enzymatic and enzymatic), and structurally and functionally intact mitochondria serve as a *net sink* rather than a *net source* of reactive oxygen species (ROS) (Andreyev et al., 2005). ROS-defenses are severely undermined in structurally compromised mitochondria (Andreyev et al., 2005). Thus, mitochondrial dysfunction, presumably through imbalance of ROS production and removal (Andreyev et al., 2005), raises ROS emission (Esposito et al., 1999; Senoo-Matsuda et al., 2001) and causes intracellular oxidative stress.

Because abnormal mtDNA may cause mitochondrial dysfunction, the hypothesis predicts: (1) enhanced oxidative stress and disturbed energy metabolism in predisposed individuals, which may cause various pathogenic alterations such as genomic instability, aberrations in neurodevelopment, and the brain dysfunction. Furthermore, because mtDNA can be transmitted only through females and there is no link between the nuclear genome and the

mitochondrial genome, the mtDNA hypothesis predicts: (2) a higher maternal transmission of schizophrenia, and (3) positive associations between resistance genes and schizophrenia as well as negative associations between facilitating genes and schizophrenia (see 5.2). These predictions seem to be consistent with other major epidemiological findings and the results of the genetic and the pathophysiological studies to date.

5.3.1 Mitochondrial dysfunction and enhanced oxidative stress in affected individuals

The hypothesis predicts that patients with schizophrenia show mitochondrial dysfunction and enhanced oxidative stress.

Indeed, in the past decade, mitochondrial dysfunction and oxidative stress in schizophrenia has been suggested by several independent lines of evidence (for review, see Marchbanks et al., 1995; Ben-Shaffer, 2002; Wood et al., 2009); those include mitochondrial hypoplasia, disturbed oxidative phosphorylation, and altered mitochondrial-related gene expression in several cell lines.

The pioneering works in this field may be noteworthy (Utena & Niwa, 1992). As early as 1950, Hayashi, in a longitudinal study on glucose metabolites in blood sampled from the superior bulb of the internal jugular vein of schizophrenics, observed a decreased carbonic dioxide production in the brain and a higher level of lactate and glutathione, the brain's dominant free radical scavenger, in patients in an acute exacerbation of the illness. Utena and Ezoe (1951) reported a decreased glucose consumption *in vitro* in cortical brain tissues sampled from patients with schizophrenia who underwent prefrontal leukotomy. Takahashi (1953) confirmed this finding and emphasized the necessity of further investigations on oxidative phosphorylation in the brain tissue of schizophrenics. In line with those findings was the report by Stabenau et al. (1969), who observed, in a biochemical study of discordant monozygotic twin pairs, that lactate production and the lactate-pyruvate ratio were higher in the affected twins than the unaffected cotwins. More recently, Prabakaran et al. (2004), in a large-scale functional genomics study, suggested a state of intermittent or chronic hypoxic stress and mitochondrial dysfunction in the brain of patients with schizophrenia.

5.3.2 The mode of transmission

The hypothesis predicts a higher maternal transmission of schizophrenia. Although there has been no convincing evidence for maternal transmission of schizophrenia, several reports suggest a higher maternal transmission of schizophrenia (Shimizu et al., 1987; Goldstein et al., 1990; Valero et al., 1998; Li et al., 2007).

Some researchers have proposed the hypothesis that schizophrenia is associated with *de novo* mutations arising in paternal germ cells (Malaspina et al., 2001; Zammit et al., 2003; Byrne et al., 2003; El-Saadi et al., 2004; Sipos et al., 2004). It is based on the observation ('paternal age effect') that the risk of schizophrenia in the offspring seems to increase as the paternal age advances from 20 years to over 50 years.

However, the difference in the mean ages of fathers between affected and unaffected individuals are not very large (< 1.7 years) (Malaspina et al., 2001; El-Saadi et al., 2004). Furthermore, the risk of schizophrenia was also increased in the offspring of younger men

(< 21 years) (Malaspina et al., 2001; El-Saadi et al., 2004; Sipos et al., 2004) as well as in the offspring of younger women (< 20 years) (El-Saadi et al., 2004). Therefore, major roles of paternally derived mutations in schizophrenia seem to remain unsubstantiated.

Indeed, no available data can exclude the possibility that the 'paternal age effect' has a 'maternal origin'; while women in many countries today may be usually supposed to bear children after the age of 20 years and not to marry much older men or too young men unless the men have special socio-economic benefits, a certain proportion of predisposed women might behave differently.

It should be noted that in the famous twin study by Gottesman and Bertelsen (1989) which included almost equal number of male and female monozygotic twins, most schizophrenic twins whose offspring are affected are females (12 out of 14), implying that the transmission was mainly via females ($p = {}_{14}C_{12} \times 0.5^{14} + {}_{14}C_{13} \times 0.5^{14} + {}_{14}C_{14} \times 0.5^{14} < 0.007$). While this gender effect might be due to non-genetic factors such as stronger psychological interactions between mother and child, we must also consider the possibility that it is due to the closer genetic relationship between mother and child, i.e. the mtDNA.

5.3.3 Sex difference and a protective effect of estrogen in schizophrenia

The hypothesis predicts that endogenous antioxidants exhibit a protective effect against schizophrenia, and may give a plausible explanation for sex difference of the disease.

A consistent and specific finding for schizophrenia is that the age at onset is significantly lower in males than in females (Jablensky, 1995; Kulkarni & Fink, 2000); schizophrenia starts earlier on average in males and reaches its peak between 15 and 25 years of age, whereas in females it occurs almost between 20 and 30 years of age and shows a less steep curve after that age. It also appears that women are vulnerable to relapses or first episode of schizophrenia in the perimenoposal period (the second peak of onset for females) (Kulkarni & Fink, 2000), when estrogen production diminishes. A close association between premenstrual or menstruation phase and exacerbation of the illness in females has been well documented (Kulkarni & Fink, 2000). In addition, less negative symptoms, less brain morphological changes, and better response to neuroleptic medication are relatively consistent finding in female patients with schizophrenia (Jablensky, 1995; Goldstein & Lewine, 2000).

These observations lead to the concept that estrogen protects predisposed females (Kulkarni & Fink, 2000), which seems to accord with the hypothesis; estrogen has been shown to have antioxidant activity due to its intrinsic antioxidant structure that lies in the phenolic moiety of the steroidal compound (Behl, 2002), to increase antioxidant enzyme activities (Strehlow et al., 2003; Pajović et al., 2003), and to have neuroprotective effect against oxidative stress (Behl, 2002; Brann et al., 2007). Furthermore, mitochondrion has estrogen binding sites (Monje & Boland, 2001; Chen et al., 2004) and estrogen increases mitochondrial efficiency and reduces intracellular oxidative stress (Stirone et al, 2005).

5.3.4 Low comorbidity between schizophrenia and rheumatoid arthritis

The hypothesis predicts that diseases predisposed by facilitating genes, if present, would be negatively associated with schizophrenia. Rheumatoid arthritis could be one of such candidates.

A role of oxidative stress in the pathogenesis of rheumatoid arthritis has been suggested by several lines of evidence (for review, see Hitchon et al, 2004). In addition, it has been shown that chronic oxidative stress in the synovial T lymphocytes is not secondary to exposure to environmental free radicals but originates from intracellularly produced reactive oxygen species (Remans et al, 2005). Therefore, a presumptive susceptibility gene for rheumatoid arthritis, which may cause intracellular oxidative stress in several cell lines, could be a facilitating gene for schizophrenia in this model and is likely to be subject to a negative selection in the predisposed matrilineal pedigrees.

Indeed, robust evidence shows a negative association between schizophrenia and rheumatoid arthritis while the exact mechanism is still unknown (Vinogradov et al., 1991; Jablensky, 1995; Rubinstein, 1997; Oken 1999). According to the nuclear genome model, several hypotheses have been proposed such that pathogenic genes for schizophrenia may be protective genes for rheumatoid arthritis and vice versa.

Thus the mitochondrial genome model may offer a new explanation for the low comorbidity between schizophrenia and rheumatoid arthritis and the additional prediction: most of patients with both of the diseases would be females because the survival rate of males in early life stage must be remarkably reduced due to lack of the antioxidant defense by estrogen, and show more negative symptoms, poorer response to neuroleptic medication, and/or more morphological changes in the brain.

5.3.5 Prenatal risk factors for schizophrenia

The hypothesis predicts that early-life exposure to environments which induce strong oxidative stress can increase the risk of later development of schizophrenia in the predisposed population.

Indeed, prenatal environmental factors such as severe nutritional deficiency (Susser, et al., 1996), exposure to increased homocysteine (Brown et al., 2007) or lead (Opler & Susser, 2005), and infection of influenza virus (Limosin et al., 2003; Brown et al., 2004; Opler & Susser, 2005) and Toxoplasma gondii (Brown et al., 2005) have been suggested to increase the risk for schizophrenia. More recently, it has been suggested that central nervous system infections of cytomegalovirus or mumps virus in childhood may also increase the risk for schizophrenia (Dalman et al., 2008). All of these factors have been shown to affect mitochondria, inducing strong intracellular oxidative stress and/or apoptosis (Akaike et al., 1990; Edlund et al., 1994; Speir et al., 1998; He et al., 2003; Berger et al., 2004; Zaki et al., 2005; Gupta et al., 2004; Kruman et al., 2006; Wang et al., 2006; Poncet et al., 2006; Chang et al., 2007; Nishikawa et al., 2007).

5.3.6 Increased obstetric complications in the birth of patients with schizophrenia

It has been suggested that mitochondrial dysfunction may be involved in the etiology of preeclampsia (Shanklin et al., 1990; Barton et al., 1991; Furui et al., 1994). In addition, a high incidence of preeclampsia, eclampsia, and stillborn infants has been observed in a family with a known mitochondrial disorder (Torbergsen et al. 1989). Folgero et al. (1996) demonstrated two separate mtDNA point mutations in two families having a high incidence of preeclampsia and eclampsia.