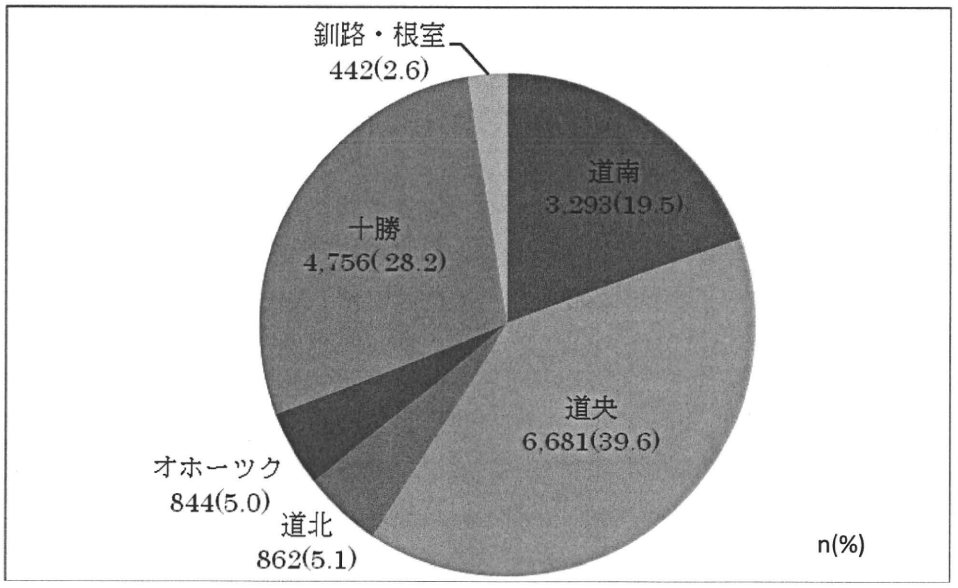


**図 1.北海道 6 医療圏別出産報告数（N=16878）**

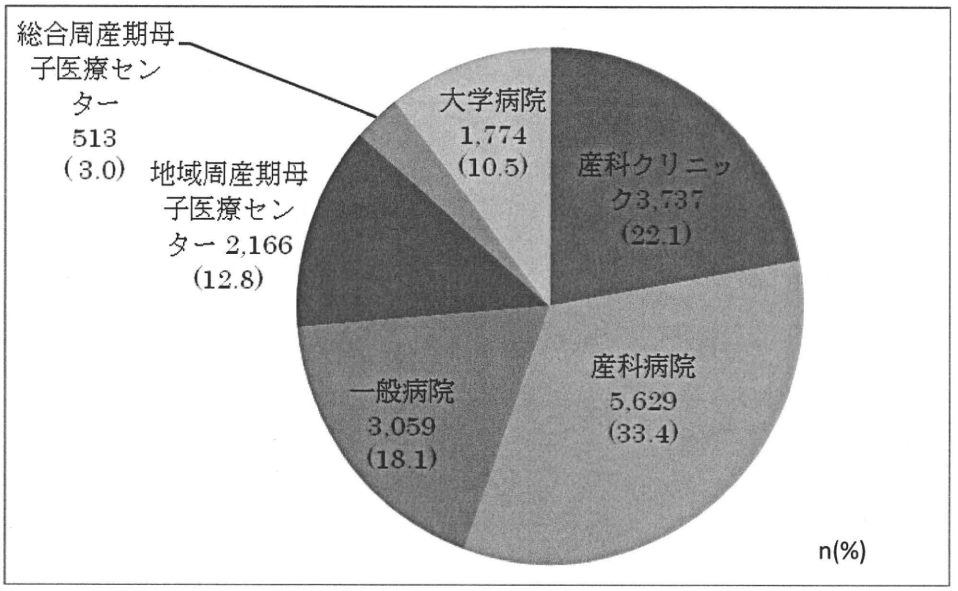


**図 2.医療施設別出産報告数（N=16878）**

## 表 1. 北海道 6 医療圏別・医療施設別の先天異常出産数

| 北海道医療圏 | 医療施設 | 先天異常 あり n | あり % | なし n | なし % | p値 |
|---|---|---|---|---|---|---|
| 道南地域 | 産科クリニック | 44 | 72.1 | 1710 | 52.9 | |
| | 産科病院 | 9 | 14.8 | 1055 | 32.6 | |
| | 一般病院 | 0 | 0.0 | 21 | 0.6 | |
| | 地域周産期母子医療センター | 3 | 4.9 | 59 | 1.8 | |
| | 総合周産期母子医療センター | 5 | 8.2 | 387 | 12.0 | 0.007* |
| | 小計 | 61 | 100.0 | 3232 | 100.0 | |
| 道央地域 | 産科クリニック | 26 | 17.4 | 1942 | 29.7 | |
| | 産科病院 | 41 | 27.5 | 2256 | 34.5 | |
| | 一般病院 | 7 | 4.7 | 483 | 7.4 | |
| | 地域周産期母子医療センター | 10 | 6.7 | 421 | 6.4 | |
| | 総合周産期母子医療センター | 0 | 0.0 | 77 | 1.2 | |
| | 大学病院 | 65 | 43.6 | 1353 | 20.7 | 0.000*** |
| | 小計 | 149 | 100.0 | 6532 | 100.0 | |
| 道北地域 | 一般病院 | 0 | 0.0 | 72 | 8.6 | |
| | 地域周産期母子医療センター | 9 | 31.0 | 0 | 0.0 | |
| | 総合周産期母子医療センター | 0 | 0.0 | 425 | 51.0 | |
| | 大学病院 | 20 | 69.0 | 336 | 40.3 | 0.006* |
| | 小計 | 29 | 100.0 | 833 | 100.0 | |
| オホーツク地域 | 産科クリニック | 0 | 0.0 | 15 | 1.8 | |
| | 産科病院 | 2 | 28.6 | 52 | 6.2 | |
| | 一般病院 | 5 | 71.4 | 703 | 84.0 | |
| | 地域周産期母子医療センター | 0 | 0.0 | 67 | 8.0 | 0.100 |
| | 小計 | 7 | 100.0 | 837 | 100.0 | |
| 十勝 地域 | 産科病院 | 37 | 58.7 | 2177 | 46.4 | |
| | 一般病院 | 12 | 19.0 | 1359 | 29.0 | |
| | 地域周産期母子医療センター | 14 | 22.2 | 1157 | 24.7 | 0.116 |
| | 小計 | 63 | 100.0 | 4693 | 100.0 | |
| 釧路・根室地域 | 一般病院 | 8 | 88.9 | 389 | 89.8 | |
| | 地域周産期母子医療センター | 0 | 0.0 | 1 | 0.2 | |
| | 総合周産期母子医療センター | 1 | 11.1 | 43 | 9.9 | 0.983 |
| | 小計 | 9 | 100.0 | 433 | 100.0 | |

* $p<0.05$ ** $p<0.01$ *** $p<0.001$

## 表 2. 対象母児の属性（全出産 N=16878）

| | | 全出産 | |
|---|---|---|---|
| | | n | % |
| 母親 | 母親年齢（歳） | 30.2±4.8[a] | |
| 新生児 | 在胎週数（週） | 38.4±3.3[a] | |
| | ＜22 | 221 | 1.3 |
| | 22–36 | 974 | 5.8 |
| | 37–41 | 15620 | 92.7 |
| | 42＜ | 35 | 0.2 |
| | 出産児数 | | |
| | 単胎 | 16530 | 98.3 |
| | 双胎 | 292(146組) | 1.7 |
| | 性別 | | |
| | 男 | 8440 | 50.2 |
| | 女 | 8240 | 49 |
| | 判別不能 | 128 | 0.8 |

[a]mean ± SD
*不明は除く

## 表 3. 死産・生産別による母児の属性（全出産 N=16878）

| | | 死産 | | | | | 生産 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 先天異常 | | | | p 値 | 先天異常 | | | | p 値 |
| | | あり | | なし | | | あり | | なし | | |
| | | n | % | n | % | | n | % | n | % | |
| 母親 | 母親年齢（歳） | 29.9±5.0[a] | | 30.8±5.2[a] | | 0.426 | 30.3±4.9[a] | | 30.2±4.8[a] | | 0.724 |
| 出産児 | 在胎週数（週） | 18.8±6.5[a] | | 17.3±7.4[a] | | 0.87 | 38.3±2.3[a] | | 38.8±1.6[a] | | 0.026* |
| | ＜22 | 40 | 85.1 | 172 | 78.5 | | 2 | 0.8 | 2 | 0 | |
| | 22–36 | 5 | 10.6 | 42 | 19.2 | | 20 | 7.5 | 899 | 5.5 | |
| | 37–41 | 2 | 4.3 | 5 | 2.3 | | 242 | 91.3 | 15319 | 94.2 | |
| | 42＜ | 0 | 0 | 0 | 0 | 0.30 | 1 | 0.4 | 34 | 0.2 | 0.000*** |
| | 出産児性別 | | | | | | | | | | |
| | 男児 | 18 | 39.1 | 77 | 35.8 | | 137 | 51.7 | 8180 | 50.4 | |
| | 女児 | 12 | 26.1 | 36 | 16.7 | | 127 | 47.9 | 8037 | 49.5 | |
| | 判別不能 | 16 | 34.8 | 102 | 47.4 | 0.19 | 1 | 0.4 | 7 | 0 | 0.045* |
| | 出生時体重（g） | 86.7±741.2[a] | | 463.7±691.6[a] | | 0.79 | 2899.6±534.0[a] | | 3031.0±504.6[a] | | 0.01* |

* p<0.05 ** p<0.01 *** p<0.001
[a]mean ± SD
不明は除く

表4. 先天異常発生数上位（平成22年10月末現在）

| 先天異常内訳 | 全出産 n=16,878 | | 在胎22週以降の出産 n=16,629 | | JAOG |
|---|---|---|---|---|---|
| | 人数 | 北海道（出産1万対） | 数 | 北海道（出産1万対） | 2002-2006年 |
| 心室中隔欠損症 | 27 | 16.0 | 27 | 16.24 | 27.7 |
| Down症候群 | 21 | 12.4 | 19 | 11.43 | 10.88 |
| 口唇口蓋裂 | 17 | 10.1 | 16 | 9.62 | |
| 多指症 | 16 | 9.5 | 16 | 9.62 | |
| 水腎症 | 14 | 8.3 | 13 | 7.82 | |
| 停留精巣・非触知精巣 ＊男児のみ全8,440人/22週以降8,356人） | 13 | 15.4 | 13 | 15.56 | |
| 心房中隔欠損症 | 10 | 5.9 | 10 | 6.01 | |
| 副耳 | 10 | 5.9 | 10 | 6.01 | |
| 口蓋裂 | 9 | 5.3 | 9 | 5.41 | 4.45 |

## 表5. マーカー奇形形症例数および有病率（平成22年10月末現在）

| 項目 | | | 全出産 n=16,878 | | 在胎22週以降の出産 n=16,629 | | JAOG |
|---|---|---|---|---|---|---|---|
| | | | 数 | 北海道（出産1万対） | 数 | 北海道（出産1万対） | 2002-2006年（出産1万対） |
| 頭部 | A1 | 無脳症 | 5 | 3.0 | 1 | 0.60 | 1.18 |
| | A2 | 脳瘤 | 1 | 0.6 | 0 | 0.0 | |
| | A3 | 小頭症 | 1 | 0.6 | 1 | 0.60 | 1.43 |
| | A4 | 水頭症 | 4 | 2.4 | 4 | 2.41 | 7.58 |
| | A5 | 全前脳胞症 | 2 | 1.2 | 2 | 1.20 | 1.45 |
| 眼部 | B1 | 眼瞼欠損 | 0 | 0.0 | 0 | 0.0 | |
| | B2 | 小眼球症・無眼球症 | 0 | 0.0 | 0 | 0.0 | |
| | B3 | 白内障 | 0 | 0.0 | 0 | 0.0 | |
| 耳部 | C1 | 小耳症 | 2 | 1.2 | 2 | 1.20 | |
| | C2 | 外耳道閉鎖 | 2 | 1.2 | 2 | 1.2 | |
| | C3 | 埋没耳 | 3 | 1.8 | 3 | 1.8 | |
| | C4 | 耳介低位 | 5 | 3.0 | 3 | 1.8 | |
| 口顔部 | D1 | 口唇裂 | 7 | 4.1 | 7 | 4.2 | |
| | D2 | 口蓋裂 | 9 | 5.3 | 9 | 5.41 | 4.45 |
| | D3 | 口唇口蓋裂 | 17 | 10.1 | 16 | 9.6 | |
| | D4 | 顔面裂 | 0 | 0.0 | 0 | 0.0 | |
| | D5 | 先天性歯 | 1 | 0.6 | 1 | 0.6 | |
| 上肢 | E1 | 多指症 | 16 | 9.5 | 16 | 9.6 | |
| | E2 | 合指症 | 6 | 3.6 | 5 | 3.0 | |
| | E3 | 裂手症 | 0 | 0.0 | 0 | 0.0 | |
| | E4 | 上肢の減数異常 | 0 | 0.0 | 0 | 0.0 | |
| | E5 | 上肢先天性絞扼輪症候群 | 0 | 0.0 | 0 | 0.0 | |
| | E6 | 橈骨側の異常 | 0 | 0.0 | 0 | 0.0 | |
| | E7 | 尺骨側の異常 | 0 | 0.0 | 0 | 0.0 | |
| 体幹 | F1 | 脊髄髄膜瘤（二分脊椎） | 5 | 3.0 | 3 | 1.80 | 5.28 |
| | F2 | 臍帯ヘルニア | 3 | 1.8 | 1 | 0.6 | 3.73 |
| | F3 | 腹壁破裂 | 4 | 2.4 | 0 | 0.0 | |
| | F4 | その他の腹壁異常 | 14 | 8.3 | 13 | 7.8 | |
| | | 横隔膜ヘルニア | 8 | 4.7 | 8 | 4.81 | 6.03 |
| | | 鼠径ヘルニア | 5 | 3.0 | 5 | 3.0 | |
| | | 不明 | 1 | 0.6 | 1 | 0.6 | |
| 心臓 | G1 | 先天性心疾患 | 62 | 36.7 | 62 | 37.3 | |

| 項目 | | | 全出産 n=16,878 | | 在胎22週以降の出産 n=16,629 | | JAOG |
|---|---|---|---|---|---|---|---|
| | | | 数 | 北海道（出産1万対） | 数 | 北海道（出産1万対） | 2002-2006年（出産1万対） |
| 消化器 | H1 | 食道閉鎖 | 2 | 1.2 | 2 | 1.20 | 4.58 |
| | H2 | 直腸肛門奇形 | 5 | 3.0 | 5 | 3.01 | 5.98 |
| | H3 | 小腸閉鎖 | 4 | 2.4 | 4 | 2.41 | 6.93 |
| | H4 | 十二指腸閉鎖 | 3 | 1.8 | 3 | 1.8 | |
| 泌尿器・生殖器 | I1 | 水腎症 | 14 | 8.3 | 13 | 7.8 | |
| | I2 | 異形成腎 | 3 | 1.8 | 2 | 1.20 | 2.33 |
| | I3 | 尿道下裂 ＊男児のみ 8,440人/22週以降8,356人 | 6 | 7.1 | 5 | 5.98 | 4.23# |
| | I4 | 停留精巣・非触知精巣 ＊男児のみ 全8,440人/22週以降8,356人 | 13 | 15.4 | 13 | 15.6 | |
| | I5 | 膀胱外反症・総排泄腔外反症 | 0 | 0.0 | 0 | 0.0 | 0.23 |
| | I6 | 陰核肥大 | 0 | 0.0 | 0 | 0.0 | |
| | I7 | 性別不分明 | 1 | 0.6 | 1 | 0.6 | |
| | I8 | 膣欠損 | 0 | 0.0 | 0 | 0.0 | |
| 下肢 | J1 | 多趾症 | 5 | 3.0 | 5 | 3.0 | |
| | J2 | 合趾症 | 8 | 4.7 | 6 | 3.6 | |
| | J3 | 裂足症 | 1 | 0.6 | 0 | 0.0 | |
| | J4 | 下肢の減数異常 | 0 | 0.0 | 0 | 0.0 | |
| | J5 | 下肢先天性絞扼輪症候群 | 0 | 0.0 | 0 | 0.0 | |
| 皮膚 | K1 | 6個以上または巨大な色素異常斑 | 3 | 1.8 | 3 | 1.8 | |
| | K2 | 継続する水疱・小水疱 | 2 | 1.2 | 2 | 1.2 | |
| 症候群・染色体異常 | L1 | Down症候群 | 21 | 12.4 | 19 | 11.43 | 10.88 |
| | L2 | 軟骨無形成症 | 1 | 0.6 | 1 | 0.6 | |
| | L3 | Apert症候群 | 0 | 0.0 | 0 | 0.0 | |
| | L4 | 先天性多発性関節拘縮症 | 0 | 0.0 | 0 | 0.0 | |
| | L5 | trisomy 18 | 3 | 1.8 | 2 | 1.20 | 8.18 |
| | L6 | trisomy 13 | 1 | 0.6 | 1 | 0.60 | 1.68 |
| 結合双生児 | M1 | 結合双生児 | 0 | 0.0 | 0 | 0.0 | |

＊JAOG: 国際先天異常モニタリングセンター

表6. 先天性心疾患の内訳 （平成22年10月末現在）

| | 項目 | 全出産 n=16,878 | | 在胎22週以降の出産 n=16,629 | | JAOG |
|---|---|---|---|---|---|---|
| | | 数 | 北海道（出産1万対） | 数 | 北海道（出産1万対） | 2002-2006年（出産1万対） |
| | 先天性心疾患全体 | 61 | 36.1 | 61 | 36.68 | |
| 1 | 心室中隔欠損症 | 27 | 16.0 | 27 | 16.24 | 27.7 |
| 2 | 心房中隔欠損症 | 10 | 5.9 | 10 | 6.01 | |
| 3 | 肺動脈（弁）狭窄症 | 6 | 3.6 | 6 | 3.61 | |
| 4 | ファロー四徴症 | 4 | 2.4 | 4 | 2.41 | 5.05 |
| 5 | 動脈管開存症 | 6 | 3.6 | 6 | 3.61 | |
| 6 | 大動脈縮窄症 | 2 | 1.2 | 2 | 1.20 | 3.45 |
| 7 | 肺動脈閉鎖症 | 4 | 2.4 | 4 | 2.41 | |
| 8 | 大血管転位症 | 3 | 1.8 | 3 | 1.80 | 4.03 |
| 9 | 単心室 | 1 | 0.6 | 1 | 0.60 | |
| 10 | 単心房単心室 | 2 | 1.2 | 2 | 1.20 | |
| 11 | 大動脈（弁）狭窄症 | 2 | 1.2 | 2 | 1.20 | |
| 12 | 心内膜床欠損症 | 2 | 1.2 | 2 | 1.20 | |
| 13 | 左室低形成症 | 1 | 0.6 | 1 | 0.60 | 3.53 |
| 14 | 右室低形成症 | 1 | 0.6 | 1 | 0.60 | |
| 15 | 両大血管右室起始 | 2 | 1.2 | 2 | 1.20 | |
| 16 | 右胸心 | 1 | 0.6 | 1 | 0.60 | |
| 17 | 総肺静脈還流異常症 | 1 | 0.6 | 1 | 0.60 | |
| 18 | 動脈管動脈瘤症 | 1 | 0.6 | 1 | 0.60 | |
| 19 | 三尖弁閉鎖（不全）症 | 1 | 0.6 | 1 | 0.60 | |
| 20 | 心室内結節 | 1 | 0.6 | 1 | 0.60 | |
| 21 | 大動脈逆流弁 | 1 | 0.6 | 1 | 0.60 | |
| 22 | 心奇形疑い | 5 | 3.0 | 5 | 3.01 | |

*JAOG: 日本産婦人科医会先天異常モニタリング

## 表7. その他の先天奇形症例数および有病率（平成22年10月末現在）

| 項目 | | | 総数 | 北海道（出産1万対） |
|---|---|---|---|---|
| 頭頸部 | 1 | 無頭蓋骨 | 1 | 0.6 |
| | 2 | 頭蓋骨形成不全 | 1 | 0.6 |
| | 3 | 脳室上衣下嚢胞 | 1 | 0.6 |
| | 4 | 透明中核欠損 | 1 | 0.6 |
| | 5 | 脳梁低形成 | 1 | 0.6 |
| | 6 | 小脳低形成 | 1 | 0.6 |
| | 7 | 頭部腫瘤（頭頂部に水腫瘍突起物(高さ1.2cm、幅0.9cm)） | 1 | 0.6 |
| | 8 | 眼球異常（網膜欠損ほか） | 1 | 0.6 |
| | 9 | 副耳 | 10 | 5.9 |
| | 10 | 片側難聴 | 1 | 0.6 |
| | 11 | 耳形状左右差、位置のアンバランス | 1 | 0.6 |
| | 12 | 耳瘻孔 | 2 | 1.2 |
| | 13 | 耳介水平 | 2 | 1.2 |
| | 14 | 小顎 | 1 | 0.6 |
| | 15 | 鰓弓症候群 | 2 | 1.2 |
| | 16 | 鰓弓遺残（左頸部） | 1 | 0.6 |
| | 17 | 歯槽のう胞 | 1 | 0.6 |
| | 18 | 頸部リンパ管腫 | 4 | 2.4 |
| | 19 | 左後頭部皮下水腫 | 1 | 0.6 |
| | 20 | 翼状頸 | 1 | 0.6 |
| 呼吸器 | 21 | 声門狭窄 | 1 | 0.6 |
| | 22 | 肺低形成 | 1 | 0.6 |
| 腹部 | 23 | 消化管穿孔 | 1 | 0.6 |
| | 24 | 乳び腹水 | 1 | 0.6 |
| | 25 | ヒルシュスプルング病 | 1 | 0.6 |
| 体幹 | 26 | 脊椎側弯 | 1 | 0.6 |
| | 27 | 脂肪腫（背部） | 1 | 0.6 |
| | 28 | 背部リンパ管腫 | 1 | 0.6 |
| | 29 | 腹部腫瘍(左前上腸骨棘付近の皮下1.5cm大) | 1 | 0.6 |
| | 30 | 仙尾部腫瘍 | 2 | 1.2 |
| | 31 | 体幹の変形（脊髄髄膜瘤に伴う麻痺性の変形） | 1 | 0.6 |
| 泌尿器・生殖器 | 32 | 尿膜管遺残症 | 1 | 0.6 |
| | 33 | 多嚢胞腎 | 1 | 0.6 |
| | 34 | 胎児水腎症 | 1 | 0.6 |
| | 35 | 両側腎盂拡張 | 1 | 0.6 |
| | 36 | 腎盂尿管移行部狭窄 | 1 | 0.6 |
| | 37 | 腎拡張 | 1 | 0.6 |
| | 38 | 巨大膀胱 | 1 | 0.6 |
| | 39 | 陰茎低形成 | 1 | 0.6 |

| 項目 | | | 総数 | 北海道（出産1万対） |
|---|---|---|---|---|
| 泌尿器・生殖器 | 40 | 陰のう水腫＊（男児8,442） | 1 | 1.2 |
| | 41 | 外陰のう胞＊＊（女児8,242） | 1 | 1.2 |
| | 42 | 卵巣のう腫＊＊（女児8,242） | 3 | 3.6 |
| | 43 | Skene腺のう症＊＊（女児8,242） | 1 | 1.2 |
| | 44 | Prune belly症候群 | 1 | 0.6 |
| 皮膚 | 45 | 先天性魚鱗癬症 | 1 | 0.6 |
| | 46 | 血管腫（顔面、頸部） | 2 | 1.2 |
| | 47 | 母斑（臀部） | 1 | 0.6 |
| | 48 | 痣（顔面） | 1 | 0.6 |
| | 49 | 神経皮膚黒色症疑い | 1 | 0.6 |
| | 50 | 皮膚欠損（頭部） | 2 | 1.2 |
| 症候群・染色体異常 | 51 | Pierre Robin症候群 | 1 | 0.6 |
| | 52 | 骨形成不全症候群 | 1 | 0.6 |
| | 53 | レッグリングハウゼン病 | 1 | 0.6 |
| | 54 | Campomelic dysplasia | 1 | 0.6 |
| | 55 | マーカー奇形以外の染色体異常症 | 9 | 5.3 |
| 四肢 | 56 | 手指形態異常 | 3 | 1.8 |
| | 57 | 手指の腫瘍 | 1 | 0.6 |
| | 58 | 内反足 | 2 | 1.2 |
| | 59 | 外反足 | 2 | 1.2 |
| | 60 | 手指爪欠損 | 1 | 0.6 |
| | 61 | 肢指爪欠損 | 1 | 0.6 |
| | 62 | 軟骨低形成症（四肢短縮症の疑い） | 1 | 0.6 |
| | 63 | 下肢の形態異常 | 2 | 1.2 |
| | 64 | 先天性下肢奇形(右足第5足の変形(短足)) | 1 | 0.6 |
| | 65 | 片側下肢低形成 | 1 | 0.6 |
| | 66 | 左膝関節脱臼 | 1 | 0.6 |
| | 67 | 骨形成不全 | 2 | 1.2 |
| | 68 | limb-body wall complex | 1 | 0.6 |
| | 69 | 関節拘縮 | 2 | 1.2 |
| | 70 | 四肢長の異常 | 3 | 1.8 |
| | 71 | 四肢短縮（軟骨無形成症、骨形成不全症を除く） | 4 | 2.4 |
| 他 | 72 | 内臓逆位 | 4 | 2.4 |
| | 73 | 単一臍帯動脈 | 2 | 1.2 |
| | 74 | ガスリー（副腎過形成） | 1 | 0.6 |
| | 75 | 羊膜索症候群 | 1 | 0.6 |
| | 76 | 胎児腹水/胎児水腫 | 9 | 5.3 |

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分担研究報告書

# 出生時体重に影響を及ぼす妊婦の喫煙と葉酸代謝酵素遺伝子多型との関連

**(Effects of Maternal 5,10-Methylenetetrahydrofolate Reductase C677T or A1298C Polymorphisms and Tobacco smoking on Infant Birthweight in a Japanese Population)**

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研究要旨

Folate is very essential for fetal growth and development. Having known that 5,10-methylenetetrahyrdofolate reductase (MTHFR) 677TT homozygosity and tobacco smoking are associated with low folate status, we investigated whether maternal smoking in the presence of 5,10-*MTHFR* C677T and A1298C polymorphisms may adversely reduce offspring's birthweight.

Results showed that maternal 5,10-*MTHFR* 1298AA was associated with low folate status. Smokers with 5,10-*MTHFR* 1298AA genotypes had reduced mean infant birthweight by 107g (95%CI, -180 to -34, p = 0.004) and the reduction was more in male infants by 117g (95%CI, -218 to -15, p = 0.025).

We concluded that maternal 5,10-*MTHFR* 1298AA may be associated with low folate status and more reduction in infant birthweight among tobacco smokers, especially in male infants.

研究協力者
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## A．研究目的

Maternal smoking in pregnancy is a well established risk factor for preterm delivery (PTD), intrauterine growth restriction (IUGR), low birthweight (LBW), small for gestational age (SGA) and other adverse pregnancy outcomes. More recently, smoking has been associated with nutritional deficiencies including folate[1].

Intracellular folate hemostasis depends on 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene which is located on chromosome 1p36. The gene codes for the enzyme *MTHFR* which catalyses the irreversible conversion of 5,10-*MTHFR* to 5-metyltetrahydrofolate, a substrate for methylation of homocysteine to methionine. So far, fourteen rare mutations in *MTHFR* have been described and these are associated with decrease in *MTHFR* enzyme activities. The two most common single nucleotide polymorphisms (SNPs) identified are 5,10-*MTHFR* C677T (dbSNP ID: rs1801133), a missense mutation in exon 4, characterised by alanine to valine substitution on codon 222 and 5,10-*MTHFR* A1298C (dbSNP ID: rs1801131), a point mutation in exon 7, characterised by a glutamate to alanine substitution on codon 429[2].

Biochemically, 5,10-*MTHFR* C677T polymorphism is associated with thermolability and reduced enzyme activity. The metabolic consequences are relative folate deficiency and mild hyperhomocysteinemia, a risk factor for thrombotic vascular diseases. Several studies

have identified maternal 5,10-*MTHFR* C677T polymorphisms as obstetric genetic risk factors for spina bifida, placenta-related vasculopathies, spontaneous fetal loss, PTD, LBW, SGA, neurodevelopmental delays and other congenital anomalies[3]. However, several other investigators have reported that no such associations exist[4]. Such confusing body of literature may be explained by the fact that phenotypic expression of this genetic trait is dependent on folate-related nutritional status and other environmental factors which do vary across geographical and ethnic diversities.

Although the 5,10-*MTHFR* A1298C variant is poorly characterised in terms of functional consequences, so far, it has been recognised as an additional risk factor for neural tube defects.

In Japan, only a few folate-related genetic association studies in relation studies in relation to obstetric events have been documented, and none considered infant birthsize. We therefore hypothesized that maternal smoking in the presence of 5,10-*MTHFR* C677T and/or A1298C polymorphisms may adversely reduce offspring's birthweight.

## B．研究方法

Participants were 1784 native Japanese mother-child pairs recruited between February 2003 to March 2006 from the ongoing "Hokkaido study on Environment and Children's Health". Data were acquired from baseline self-administered questionnaires, infants' hospital birth records and post–partum self-administered questionnaires. In addition, first trimester whole blood specimens were obtained for serum folate assays. Folate concentrations were assayed using an automated competitive protein binding (CPB) chemiluminescent enzyme immunoassay (CLEIA) technique by SRL, Inc. Tokyo, Japan. DNA amplifications were performed in batches of 96-well micro-amp reaction plates using validated Taqman® probes for *MTHFR* C677T (Assay ID: C_1202883_20) and A1298C (Assay ID: C_ 850486_20) on a Gene Amp 9700 thermal cycler (Applied Biosystems, Foster City, CA, USA). End-point allelic discrimination (AD) assay was carried out on the 7300/7500 Real time PCR System and the fluorescence was read on a sequence detection software (SDS) version 1.2.1. (Applied Biosystems, Foster City, CA, USA).

Overall smoking status was classified using both self-reported active tobacco smoking and passive exposure to environmental tobacco smoke (ETS) at home into three categories. Non-smokers were those who neither actively smoked nor passively inhaled at home. Non-smokers and quitters with passive exposure were classified as the passive smoking group, while smokers consisted of active smokers irrespective of ETS exposure status. Non-exposed quitters during the first trimester had mean infants' birthweights similar to nonsmokers hence added to nonsmoking group while quitters during the second and third trimesters were added to the active smoking group. 5,10-*MTHFR* C677T and A1298C genotypes were categorized based on AD assay's allele calling as dominant homozygous, heterozygous and recessive homozygous genotypes (677CC, 677CT and 677TT; 1298AA, 1298AC and 1298CC) respectively. These were abbreviated as

CC, CT and TT; AA, AC and CC genotypes respectively in the tables.

Statistical tests included univariate ANOVA with multiple comparison tests to explore main effects of maternal 5,10-*MTHFR* C677T and A1298C polymorphisms and smoking on serum folate levels and ANCOVA for interactive association between smoking and 5,10-*MTHFR* C677T and A1298C polymorphisms in relation to folate and infant birthweight. In the final regression analyses, known major predictors of infant birthweight were adjusted for (infant gender, gestational age at delivery, maternal age, maternal pre-pregnancy weight, maternal height, parity, and alcohol intake during pregnancy). In the preliminary analysis, folic acid supplement use highly positively correlated with serum folate levels, therefore, we included it as a covariate. Sub-groups with less than a 15-member sample size were excluded. *MTHFR* 677CC and 1298AC were the reference categories in the regression because the groups represented those with the desirable high folate status. Assessments of *MTHFR* C677T and A1298C genotypes for deviation from Hardy-Weinberg's equilibrium and other data quality check parameters were generated from Haploview version 4.2 Software. All other analyses were performed using SPSS version 16.00 for WINDOWS (SPSS Inc., Chicago, IL., USA). Level of statistical significance was set at $< 0.05$.

（倫理面への配慮）

This study was conducted with the informed consent of all subjects. The study protocol was approved by the institutional ethical board for human gene and genome studies of the Hokkaido University Center for Environmental and Health Sciences and the Hokkaido University Graduate School of Medicine.

## C．研究結果

Maternal mean serum folate was 16.4 ±1.5 nmol/L and mean infant birthweight was 3040±374 g. Prevalence of active smoking in pregnancy was 15.9% while that of passive smoking was 53.0%. Prevalence of folate deficiency (<6.8 nmol/L) status was very low (0.3%). The distributions of 5,10-*MTHFR* C677T and A1298C genotypes did not deviate from Hardy–Weinberg equilibrium (p=0.546 and 0.909) respectively. Frequencies of *MTHFR* 677CC, 677CT and 677TT were 37.3%, 46.7% and 16.0% respectively while that of *MTHFR* 1298AA, 1298AC and 1298CC were 62.7%, 33.1% and 4.2% respectively. A strong linkage disequilibrium (D'=0.943) between MTHFR C677T and A1298C was also observed and minor allele frequencies were 0.392 and 0.205 respectively (Table 1). These were similar to previous documentations from Japanese population.

Carrying the T allele was associated with a decrease in mean serum folate levels with the lowest score (14.1nmol/L) among the 677TT homozygous group. Tukey's honestly significant differences of 1.0nmol/L (p=0.008) and 3.8nmol/L (p <0.0005) were observed between 677CC versus 677CT and between 677CC versus 677TT respectively. On the other hand, carrying the 1298C allele was associated with increase in mean serum folate levels. Tukey's honestly significant difference of 1.5nmol/L (p<0.0005) was observed

between 1298AA versus 1298AC. Mean serum folate scores were generally lower in smokers across 5,10-*MTHFR* C677T genotypes with the lowest among 677TT homozygotes (11.8nmol/L, p for interaction =0.031). The lowest mean folate scores were identified among smokers with 1298AA homozygous genotypes, p for interaction = 0.046 (Figures 1, and 2).

To investigate whether the presence of maternal 5,10-*MTHFR* C677T and A1298C polymorphisms could be relevant in the determination of offspring's birthweight, we conducted a multiple regression analysis with adjustments for major known predictors of birthweight. For 5,10-*MTHFR* C677T, 677CT heterozygous genotype was observed to be associated with an increase in mean infant birthweight by 36.4g, (95%CI, 2.6 to 70.3, p=0.035). Polymorphism in 5,10-*MTHFR* A1298C showed no independent evidence of statistical significance in relation to offspring's birthweight. Infants of active tobacco smokers were 85.0g (95% CI, 133.3 to -36.8, p=0.001), lower than those born to nonsmokers (Table 2).

Further interactive analyses with tobacco smoking status, 5,10-MTHFR 677CT genotypes had male newborns with higher mean birthweight of 90.7g (95%CI, 6.0 to 175.5, p=0.036) (Table 3). 5,10-MTHFR 1298AA genotype was generally associated with decrease in mean infant birthweight in smokers by 107.0g (95%CI, -180.0 to -33.9, p=0.004). After stratification by infant gender, the effect was more pronounced in male infants with a reduction of 117.0g (95%CI, -218.6 to -14.7, p=0.025) (Table 4). In both cases, female infants never demonstrated any statistically significant changes in their mean birthweight.

## D．考察

### 1. Maternal 5,10-MTHFR C677T, MTHFR A1298C and serum folate status

5,10-*MTHFR* 677T allele was associated with low folate status, which agrees with other earlier reports[5]. 677TT homozygosity was associated with low folate status and these values were much lower among active and passive smokers. This observation revealed the independent effects exerted by tobacco smoke and 5,10-*MTHFR* C677T polymorphism on folate status. On the contrary, 5,10-*MTHFR* 1298AA genotype was found to be associated with low serum folate status. Although this SNP has not been fully characterized in terms of its metabolic and clinical impact, various investigators are recently exploring it. In a recent study conducted among Koreans, it was observed that mean plasma homocysteine value was highest among 1298AA homozygotes compared to those who carried 1298C allele[6]. Since serum folate is known to have an inverse correlation with plasma homocysteine, we inferred that our study population might have had similar patterns of plasma homocysteine distribution across genotypes. Another report from Portugal noted that 1298AC heterozygosity was associated with high plasma folate level with the lowest among the 1298CC homozygotes. That we had similar findings with a report from a Korean population sounds genetically plausible because racial, geographic and nutritional disparities may account for the differences in functional behaviors of 5,10-*MTHFR* SNPs.

### 2. Effects of maternal 5,10-MTHFR

A1298C polymorphism and tobacco smoke on infant birthweight

The birthweight reducing effect of maternal 5,10-*MTHFR* 1298AA genotype among tobacco smokers can be related to materno-fetal folate nutrition. Maternal 1298CC was observed to be associated with reduction in the risk of low birthweight than the 1298AA genotype[7]. 1298CC homozygous genotype was also reported to be protective against offspring's IUGR in Canadians[8]. In our study, we could not demonstrate the role of 1298CC genotype because of the low frequency in the population. Having observed the association between 5,10-*MTHFR* 1298AA genotype and lower serum folate status, additional chronic extracellular and intracellular folate deficits consequent to effects of tobacco smoke might have been severe enough to inflict nutritional stress. The consequence of hyperhomocysteinemia might have increased the risk of placental vasculopathies via oxidative stress, endothelial cell dysfunctions and coagulopathies leading to fetoplacental hypoperfusion. Among smokers, there might have been some form of nutritional deficiency including vitamin $B_{12}$, as a result, the methylation of homocysteine to methionine was further compromised with a sequel of impaired fetal growth. The minimal folate levels needed to silence the phenotypic expression of 1298AA among smokers was probably not met. Higher exogenous folate may be needed to correct deficits and maintain optimal levels for optimal fetal growth. Owing to the scarcity of literature about 5,10-*MTHFR* A1298C polymorphism especially among Japanese, further research is needed to verify this observation and uncover more biologic mechanisms associated with this SNP.

3. Effects of maternal 5,10-MTHFR C677T polymorphism and tobacco smoke on infant birthweight

Although 5,10-MTHFR 677T allele is known to be associated with low folate and high homocysteine status, we observed that carrying the 677CT genotype was protective against male offspring's birthweight reduction only in the absence of active or passive tobacco smoke. Such observation may be related to the fact that nonsmokers had higher serum folate status. Adequate folate status is said to silence the negative phenotypic expression of 5,10-*MTHFR* 677T allele. This observation underscores the need for smokers carrying the 677T allele modify their smoking lifestyle in order to benefit from the genetic trait.

4. Gender-specific response to MTHFR activities

Depending on the smoking status, only the male infants were more responsive to the gene-environment interplays eitherway. Nutritional needs are inherently higher for males than female fetuses, thus in a background of hyponutrinemia, the male fetus may be worst affected. Alhough the male fetus naturally thrives better under favourable conditions, it may not have withstood additional severe folate deficit among smokers with 1298AA genotype. Poorly understood phenomena on fetal gender-specific signals have been implicated in fetal growth especially in response to glucocorticoid activity which may modify fetal response to stress[9]

Japanese population genetics of 5,10-

MTHFR A1298C polymorphism shows that 1298AA genotype frequency is as high as >60.0%. The discovery of its association with low folate status may constitute a great public health burden especially in materno-fetal health.The recent threat of westernization on traditional dietary habits, deliberate dieting among young women to maintain low body mass indices and most importantly the increase in the annual prevalence of tobacco smoking among young Japanese women may adversely interact with this genetic susceptibility leading to increased morbidity and mortality. Healthy lifestyle modification like smoking cessation and encouragement towards targetted use of folic acid supplements could be very important tools of public health interest for this population especially the vulnerable smokers with genetic susceptibility.

## E．結論

Maternal 5,10-*MTHFR* 1298AA genotype may be associated with folate impairment. 5,10-*MTHFR* 677CT may be protective in non-smokers while 1298AA may interact with tobacco smoke to decrease offspring's birthweight. Male infants seemed to be more responsive to 5,10-*MTHFR* activities.

## F．研究発表

1.論文発表

None

2.学会発表

1)Thamar Ayo Yila, Seiko Sasaki, Toshiaki Baba, Chichiro Miyashita, Titilola Serifat Braimoh, Ikuko Kashino, Sumitaka Kobayashi, Emiko Okada, Eiji Yoshioka, Reiko Kishi: First Trimester Serum Folate Status of Japanese Women in Hokkaido -The Hokkaido Study on Environment and Children's Health (5) - (The 80th Annual Congress of the Japanese Society for Hygiene. 2010 May 9-11. Sendai, Japan).

2)Thamar Ayo Yila, Seiko Sasaki, Toshiaki Baba, Chichiro Miyashita, Titilola Serifat Braimoh, Ikuko Kashino, Sumitaka Kobayashi, Emiko Okada, Yuko Otake, Mariko Limpar, Eiji Yoshioka, Reiko Kishi: Effects of maternal smoking and 5, 10-MTHFR C677T polymorphism on infant's birthweight – the impact of folate supplementation – (Proceedings of The 3rd Annual Conference on Genomics of Common Diseases, 23rd – 26th Sept. 2009, Cambridge, UK.)

3)Thamar Ayo Yila, Susumu Ban, Motoyuki Yuasa, Ami Watanabe, Ayako Kanazawa, Eiji Yoshioka, Reiko Kishi: Association between folate supplementation, serum folate status, 5, 10-*MTHFR* gene polymorphisms and birth weight. (The 78th Annual Congress of the Japanese Society for Hygiene. 2008 March 28-31, Kumamoto).

## 参考文献

1. Brown KS, Kluijtmans LAJ, Young IS, Murray L, McMaster D, Woodside JV, Yarnell JWG, Boreham CA, McNulty H, Strain JJ, McPartlin J, Scott JM, Laura E, Mitchell LE, Whitehead AS. The 5,10-methylenetetrahydrofolate reductase C677T polymorphism interacts with smoking to increase homocysteine. *Atherosclerosis* 2004;174:315–322.

2. Weisberg I, Tran P, Christensen B. et al. A second genetic polymorphism in methylenetetrahydrofolate reductase

(MTHFR) associated with decreased enzyme activity. *Mol Genet Metab* 1998;64:169–172.

3. Tamura T, Picciano MF. Folate and human reproduction. *Am J Clin Nutr* 2006;83:993-1016.

4. Foka ZJ, Lambropoulos AF, Saravelos H, et al. Factor V Leiden and prothrombin G20210A mutations, but not methylene-tetrahydrofolate reductase C677T, are associated with recurrent miscarriages. *Hum Reprod* 2000;15:458–462.

5. Murakami S, Matsubara N, Saitoh M, Miyakaw S, Shoji M, Kubo T. The relation between plasma homocysteine concentration and methylenetetrahydro-folate reductase gene polymorphism in pregnant women. *J Obstet Gynaecol Res* 2001;27:349-352.

6. Kim NK, Choi YK, Kang MS, Choi DH, Cha SH, An MO, Lee S, Jeung M, Ko JJ, Oh D. Influence of combined methylenetetrahydrofolate reductase (MTHFR) and thymidylate synthase enhancer region (TSER) polymorphisms to plasma homocysteine levels in Korean patients with recurrent spontaneous abortion. *Thromb Res* 2006;117:653-658.

7. Nurk E, Tell GS, Refsum H, Ueland PM, Vollset SE. Associations between maternal methylenetetrahydrofolate reductase polymorphisms and adverse outcomes of pregnancy: the Hordaland Homocysteine Study. *Am J Med* 2004;117:26 –31.

8. Infante-Rivard C, Rivard GE, Yotov WV, Génin E, Guiguet M, Weinberg C, Gauthier R, Feoli-Fonseca JC. Absence of association of thrombophilia polymorphisms with intrauterine growth restriction. *N Engl J Med* 2002;347:19-25.

9. Murphy VE, Smith R, Giles WB, Clifton VL. Endocrine regulation of human fetal growth: the role of the mother, placenta, and fetus. Endocr Rev. 2006 ;27:141-69.

Table 1: Characteristics of 1784 mother-child pairs.

| Characteristic | N(%) |
|---|---|
| Maternal age (years) | 30.0 (4.3)[e] |
| Maternal height (cm) | 158.0 (5.1)[e] |
| Pre-pregnancy weight (kg) | 53.0 (9.3)[e] |
| Maternal serum folate (nmol/L) | 16.4 (1.5)[e] |
| Gestational age at delivery (weeks) | 38.9 (1.3)[e] |
| Infant birthweight (g) | 3040 (374)[e] |
| Infant gender | |
| Males | 873 (48.9) |
| Females | 911 (51.1) |
| Parity | |
| Nulliparous | 391 (21.9) |
| Parous | 1393 (78.1) |
| Alcohol intake during pregnancy | |
| No | 1499 (84.0) |
| Yes | 285 (16.0) |
| Tobacco smoking during pregnancy | |
| Nonsmoker | 555 (31.1) |
| Passive smoker | 946 (53.0) |
| Smoker | 283 (15.9) |
| Folic acid supplement use | |
| Nonuser | 1601 (89.7) |
| User | 183 (10.3) |
| Maternal *MTHFR* C677T genotypes[a, b] | |
| CC | 666 (37.3) |
| CT | 833 (46.7) |
| TT | 285 (16.0) |
| CT / TT | 1118 (62.7) |
| Maternal *MTHFR* A1298C genotypes[c,d] | |
| AA | 1118 (62.7) |
| AC | 591(33.1) |
| CC | 75 (4.2) |
| AC / CC | 666 (37.3) |

ETS = Environmental tobacco smoke, [e] Mean (SD)
*MTHFR* = Methylenetetrahydrofolate reductase gene
[a] HWE = Hardy-Weingberg's Equillibrium p value = 0.5463
[b] MAF = Minor allele frequency = 0.392
[c] HWE = Hardy-Weingberg's Equillibrium p value = 0.9091
[d] MAF = Minor allele frequency = 0.205

Table 2 : Association between maternal 5, 10-*MTHFR* C677T and A1298C genotypes and tobacco smoking on infant birthweight (N = 1784).

| Maternal 5,10-*MTHFR* genotypes / Smoking status | N | Crude Δ B (SE) [95%CI]g | Adjusted Δ B (SE) [95%CI]g |
|---|---|---|---|
| [a]*MTHFR* C677T | | | |
| CC | | | |
| CT | 666 | Reference | Reference |
| TT | 833 | 35.8 (19.5) [-2.5,74.1] | 36.4 (17.3) [2.6,70.3]* |
| | 285 | -10.7 (26.6) [-62.9,41.5] | 4.0 (23.5) [-42.2,50.1] |
| [a]*MTHFR* A1298C | | | |
| AA | 1118 | -13.0 (19.1) [-50.5,24.7] | -16.4 (17.0) [49.6,16.8] |
| AC | 591 | Reference | Reference |
| CC | 75 | -21.0 (46.1)[111.5,69.5] | -43.3 (40.8) [123.3,36.7] |
| [b]Smoking status | | | |
| Nonsmoker | 555 | Reference | Reference |
| Passive smoker | 946 | -19.0 (20.1) [-58.3, 20.5] | -14.4 (17.9)[-49.5, 20.6] |
| Smoker | 283 | -72.0 (27.4)[-125.7,-18.1] ** | -85.0(24.6)[-133.3,-36.8] ** |

**p < 0.01., *P < 0.05. Δ ( Change in mean birthweight) B (SE) = Unstandardized coefficient (standard error).
(CI) confidence interval. (*MTHFR*) Methylenetetrahydrofolate reductase. Grams (g).
[a]Multiple linear regression adjusted for gestational age, infant gender, maternal age, pre-pregnancy weight, height, parity, smoking during pregnancy and folic acid supplement use.
[b]Multiple linear regression adjusted for gestational age, infant gender, maternal age, pre-pregnancy weight, height, parity and folic acid supplement use.

Table 3: Association between maternal 5, 10-MTHFR C677T genotypes, tobacco smoking and infant's birthweight (N = 1784)

| 5,10-*MTHFR* C677T genotype | Smoking status | [a]Overall (N = 1784) | | | [b]Male newborns (N = 873) | | | [b]Female newborns (N = 911) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Crude Δ B (SE)[95%CI] g | Adjusted Δ B (SE)[95%CI]g | N | Crude Δ B (SE)[95%CI]g | Adjusted Δ B(SE)[95%CI]g | N | Crude Δ B (SE)[95%CI]g | Adjusted Δ B(SE)[95%CI]g |
| | Nonsmoker | 203 | Reference | Reference | 93 | Reference | Reference | 110 | Reference | Reference |
| CC | Passive smoker | 356 | 27.8 (33.0) [-36.9,92.5] | 9.5 (29.3) [-47.9,66.9] | 187 | -39.6 (46.3) [-130.6,51.3] | -39.6 (40.5) [-119.2,39.9] | 169 | 84.0 (46.3) [-6.8,174.7] | 59.3 (41.6) [-22.3,140.8] |
| | Smoker | 107 | 6.9 (44.0) [-80.9,94.8] | -38.7 (39.8) [-116.8,39.4] | 52 | 29.0 (63.2) [-95.1,153.1] | -37.7 (55.8) [-147.3,71.8] | 55 | -21.0 (62.4) [-143.4,101.4] | 55.3 (56.5) [-166.2,55.6] |
| | Nonsmoker | 262 | 83.7 (35.1) [15.0,152.5]* | 60.0 (31.0) [-.9,120.9] | 133 | 83.3 (49.4) [-13.6,180.2] | 90.7 (43.2) [6.0,175.5]* | 129 | 71.0 (49.0) [-25.1,167.2] | 34.1 (44.1) [-52.4,120.6] |
| CT | Passive smoker | 442 | 58.3 (31.8) [-4.0,120.7] | 47.5 (28.2) [-7.9,102.9] | 198 | 36.1 (45.9) [-54.0,126.2] | 21.2 (40.3) [-57.8,100.3] | 244 | 78.8 (43.4) [-6.3,163.9] | 62.1 (39.1) [-14.6,138.8] |
| | Smoker | 129 | -35.6 (42.2) [-118.4,47.2] | -53.1 (37.8) [-127.2,21.0] | 70 | -39.0 (57.8) [-152.4,74.4] | -39.8 (51.1) [-140.,60.4] | 59 | -55.7 (60.9) [-175.3,63.9] | -63.5 (55.2) [-171.9,44.9] |
| | Nonsmoker | 90 | 79.5 (47.5) [-13.6,172.6] | 59.1 (42.0) [-23.3,141.4] | 43 | 31.1 (67.3) [-101.1,163.2] | 15.1 (58.8) [-100.6,130.5] | 47 | 118.9 (65.8) [-10.3,248.0] | 91.7 (59.0) [-24.0,207.4] |
| TT | Passive smoker | 148 | -26.9 (40.5) [-106.4,52.6] | -14.4 (36.1) [-85.2,56.3] | 74 | -33.8 (56.9) [-145.5,77.8] | 11.1 (50.1) [-87.2,109.4] | 74 | -30.8 (56.8) [-142.3,80.6] | -39.7 (51.1) [-140.0,60.6] |
| | Smoker | 47 | -35.5 (60.7) [-154.6,83.5] | -49.1 (53.9) [-154.8,56.7] | 23 | -13.1 (85.0) [-179.9,153.8] | -53.7 (74.9) [-200.7,93.3] | 24 | -65.0 (85.1) [-231.9,102.0] | -48.3(76.7) [-198.8,102.2] |
| $P_{interaction}$ | | | 0.031 | | | | | | | |

*P <0.05. ETS (Environmental tobacco smoke). Δ ( Change in mean birthweight) B(SE) = Unstandadized coefficient (standard error). CI (Confidence interval). Grams (g).
[a]Multiple linear regression adjusted for infant's gender, gestational age at delivery, maternal age, maternal height, pre-pregnancy weight, parity, alcohol intake during pregnancy and folic acid supplement intake.
[b]Multiple linear regression adjusted for gestational age at delivery, maternal age, maternal height, pre-pregnancy weight, parity, alcohol intake during pregnancy and folic acid supplement intake.

Table 4: Association between maternal 5, 10-*MTHFR* A1298C genotypes, tobacco smoking and infant's birthweight ( N = 1778)

| 5,10-*MTHFR* A1298C genotypes | Smoking status | [a]Overall ( N = 1778) N | Crude Δ B (SE) [95%CI]g | Adjusted Δ B (SE) [95%CI]g | [b]Male newborns ( N =868) N | Crude Δ B (SE) [95%CI]g | Adjusted Δ B (SE) [95%CI]g | [b]Female newborns ( N = 910) N | Crude Δ B (SE) [95%CI]g | Adjusted Δ B (SE) [95%CI]g |
|---|---|---|---|---|---|---|---|---|---|---|
| | Nonsmoker | 342 | 14.7 (36.8) [-57.6, 86.8] | 0.7 (32.5) [-63.1, 64.4] | 169 | 32.8 (52.3) [-69.8,135.4] | -9.5 (45.7) [-99.3,80.3] | 173 | -10.3 (51.1) [-110.7,90.1] | 15.6 (45.7) [-74.2,105.4] |
| AA | Passive smoker | 589 | -23.0 (34.0) [-89.6, 43.8] | -27.7 (30.2) [-86.9, 31.4] | 266 | -41.3 (49.0)[-137.5,54.9] | 72.1 (43.1) [-156.7,12.5] | 323 | -7.1 (46.6) [-98.5,84.4] | 10.(41.8) [-71.4,92.7] |
| | Smoker | 187 | -85.4 (41.8) [-167.3, -3.4]* | -107.0 (37.2) [-180.0, -33.9]** | 94 | -64.8 (58.7)[-180.1,50.5] | -116.6 (51.9)[-218.6,-14.7]* | 93 | -115.1 (58.6) [-230.1,-0.1] | -99.8 (52.8) [-203.5,3.9] |
| | Nonsmoker | 182 | Reference | Reference | 83 | Reference | Reference | 99 | Reference | Reference |
| AC | Passive smoker | 319 | -7.4 (37.2) [-80.5, 65.7] | -12.6 (33.0) [-77.35, 52.5] | 173 | -38.0 (52.0) [-140.2,64.2] | -65.2 (45.6) [-154.6,24.3] | 146 | 10.9 (52.8) [-92.8,114.6] | 34.9 (47.5)[-58.2,128.2] |
| | Smoker | 90 | -32.3 (51.7) [-133.6, 69.1] | -57.5 (46.0) [-147.6, 325] | 46 | 10.5 (71.7)[-130.2,151.2] | -72.1 (63.2) [-196.3,52.0] | 44 | -87.7 (73.5) [-232.0,56.6] | -50.3 (66.4)[-180.7,80.1] |
| | Nonsmoker | 31 | 98.7 (78.0) [-251.6, 54.2] | -122.4 (69.1) [-257.9, 13.1] | 17 | 72.7 (103.8)[276.5,131.1] | -121.3 (91.0) [-300.0,57.3] | 14 | -149.8 (115.8)[-377.2,77.6] | -128.8(103.8)[-332.6,75.1] |
| CC | Passive smoker | 38 | 34.4 (71.5) [-105.9, 174.8] | 16.9 (63.3) [-107.2, 141.0] | 20 | 48.6 (97.1)[-142.1,239.2] | 0.6 (85.1) [-166.6,167.7] | 18 | 4.6 (103.9) [-199.4,208.7] | 20.3 (93.3)[-162.9,203.5] |
| $P_{interaction}$ | | | 0.046 | | | | | | | |

**p <0.01., *p <0.05. ETS (Environmental tobacco smoke). Δ ( Change in mean birthweight) B(SE) = Unstandadized coefficient (standard error). CI (Confidence interval) Grams (g).
[a]Multiple linear regression adjusted for infant's gender, gestational age at delivery, maternal age, maternal height, pre-pregnancy weight, parity, alcohol intake during pregnancy and folic acid supplement intake.
[b]Multiple linear regression adjusted for gestational age at delivery, maternal age, maternal height, pre-pregnancy weight, parity, alcohol intake during pregnancy and folic acid supplement intake.

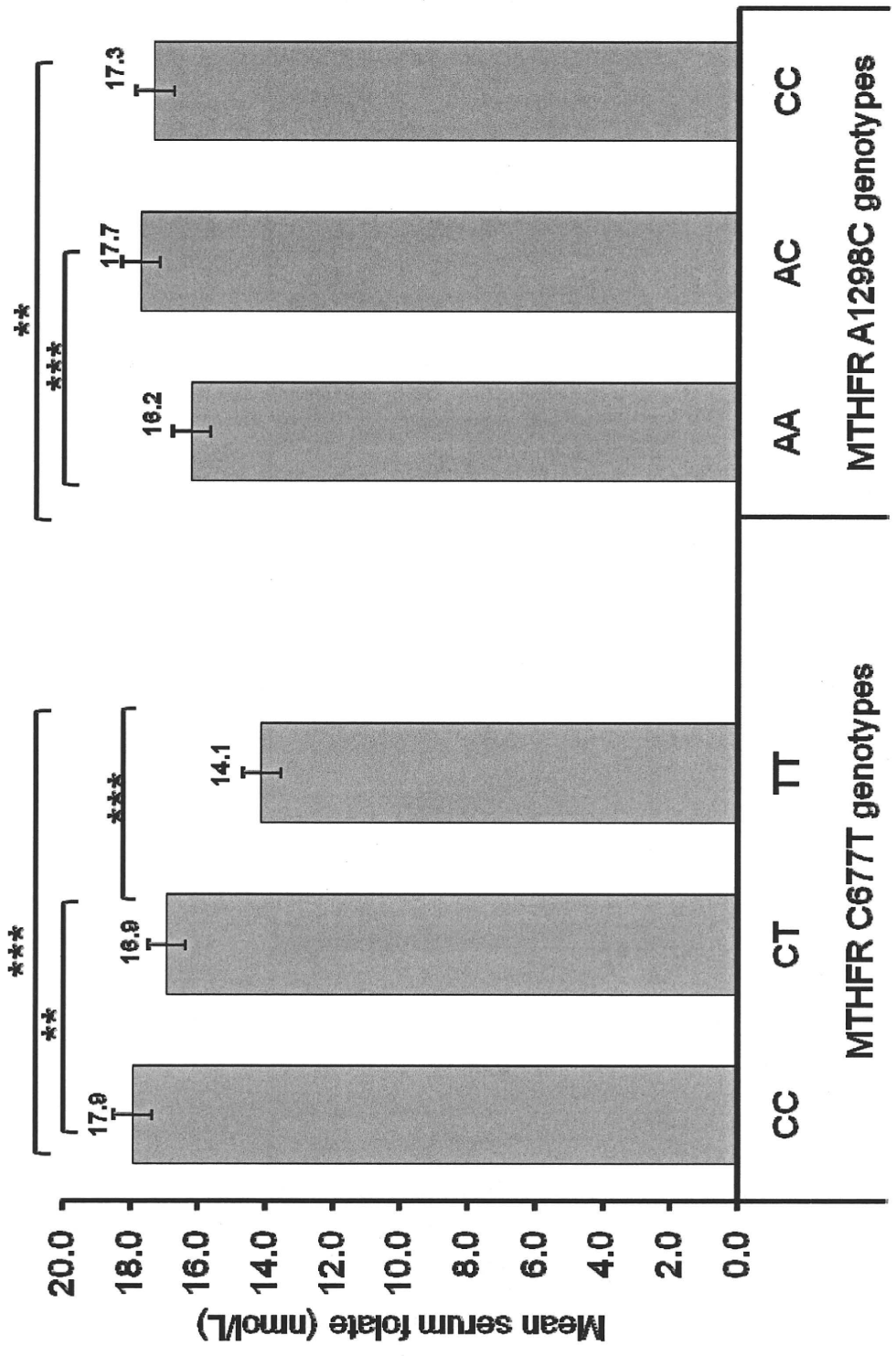


Figure 1: Maternal mean serum folate levels across MTHFR C677T and A1298C genotypes.

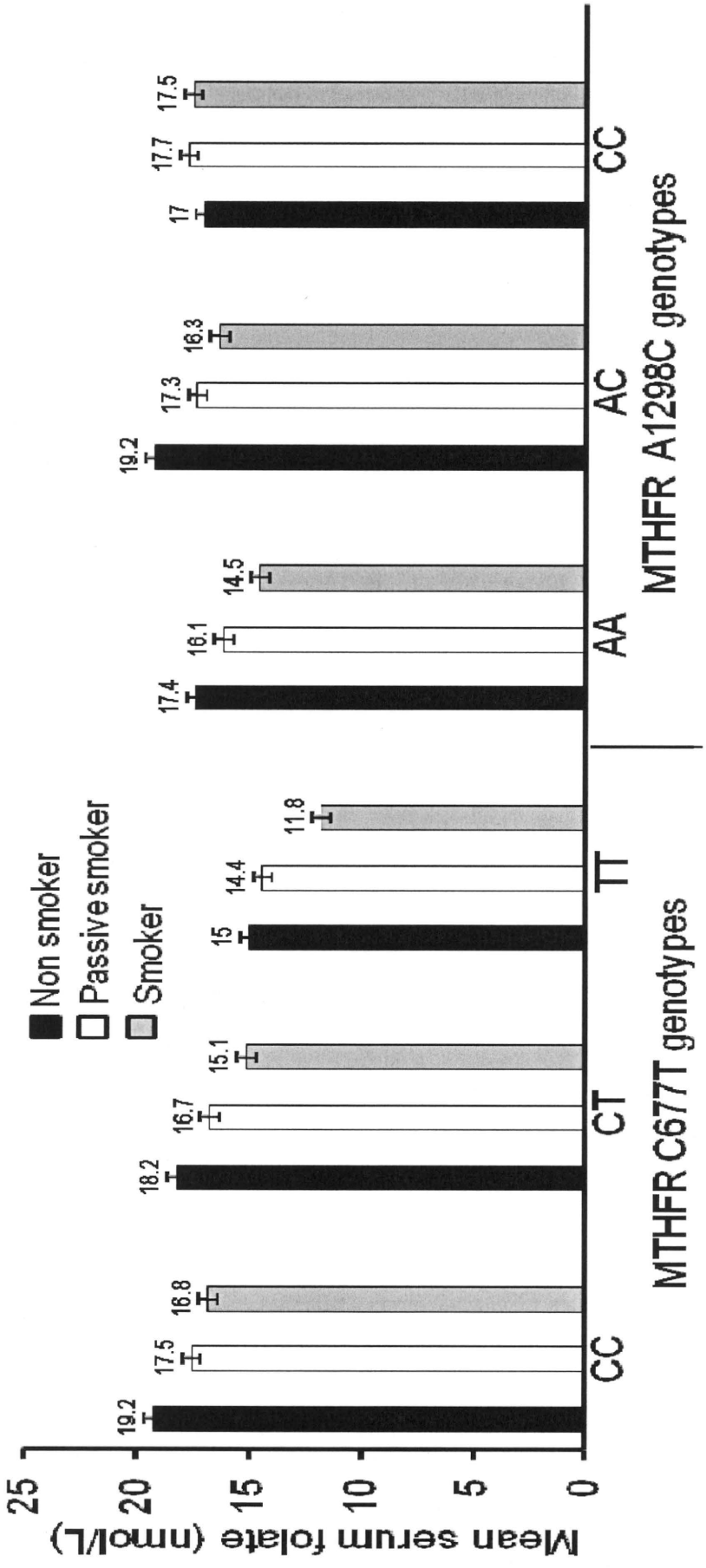


Figure 2: Maternal mean serum folate levels across MTHFR C677T and A1298C genotypes according to smoking status.