**Table 1: Comparative Analysis of Studies on Genetic and Epigenetic Factors in Methamphetamine Addiction: Focus on SLC and COMT Genes**

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| **Author (Year)** | **Country** | **Sample Size** | **Population Characteristic** | **Genetic Factors Analyzed** | **Epigenetic Factors Analyzed** | **Key Findings** | **Methodology** | **Psychological Assessments Used** | | **Main Conclusions** | **Limitations** |
| Fang et al. (2024) | China | 189 | MAUD patients | DRD4, COMT | Methylation of DRD4 and COMT | Association of DRD4 rs1800955 C allele with lower paranoid symptoms and COMT rs4818 CC allele with lower motor-impulsivity scores | SNP and methylation analysis of DRD4 and COMT genes | Assessment of paranoid and motor-impulsive symptoms | SNP genotype and methylation status of DRD4 and COMT genes are indicators for high-risk psychotic symptoms | | Limited to preliminary findings, requires larger sample size and replication |
| Jugurnauth et al. (2011) | Taiwan | 925 | Methamphetamine users and controls | COMT gene polymorphisms (rs4680, rs165599) | Not analyzed | Significant haplotype effect involving rs4680 and rs165599 in methamphetamine addiction | Genotyping, allele and genotype distribution comparison between cases and controls | Not specified | COMT haplotypes, particularly A/G for rs4680/rs165599, may be associated with methamphetamine addiction | | No significant allele/genotype differences for rs165599, limited to Taiwanese population, lack of detailed psychological assessments |
| Al-Eitan et al. (2020) | Jordan | 1000 | SUD patients and healthy controls | DRD4 exon III VNTR, SLC6A4 (5-HTTLPR, rs25531) | Not analyzed | Significant association of DRD4 exon III VNTR polymorphism with SUD, no association with SLC6A4 polymorphisms | Genotyping using PCR and PCR-RFLP, statistical analyses including chi-square and ANOVA | Not specified | DRD4 exon III VNTR polymorphism contributes to SUD susceptibility in Jordanian Arab population, 5-HTTLPR does not | | Focus on specific polymorphisms, lack of psychological assessments, nominal significance |
| Johnson et al. (2010) | USA | 120 | METH-dependent adults of European descent | 5′-HTTLPR genotypes (L and S alleles) | Not analyzed | SS genotype associated with earlier onset of METH use in males, not females | Structured questionnaires, PCR-RFLP for genotyping | Not specified | SS genotype of 5′-HTTLPR linked to greater risk for earlier onset METH use in Caucasian males | | Focus on European descent, small sample size, preliminary findings |
| Hosák et al. (2004-2006) | Czech Republic | 37 | Czech Caucasians dependent on methamphetamine | COMT Val158Met polymorphism | Not analyzed | Met allele associated with higher novelty seeking scores in methamphetamine abusers | TCI questionnaire, DNA genotyping | Temperament and Character Inventory (TCI) | Met allele linked to high novelty seeking behavior due to low COMT activity and high dopamine levels | | Small sample size, preliminary results, limited to Czech Caucasian population |
| Li et al. (2004) | Taiwan | 851 | Han Chinese METH abusers and controls | COMT Val158Met, DRD4 120-bp VNTR, DRD4 exon 3 VNTR | Not analyzed | Excess of Val158 allele in METH abusers; significant haplotype association of DRD4 VNTRs with METH abuse | Genotyping, haplotype analysis, case/control design | Not specified | Genetic variation in COMT and DRD4 may encode additive effect on METH abuse risk | | Focus on specific population, lack of functional studies to confirm interactions |
| Saloner et al. (2020) | USA | 122 | 75 methamphetamine-dependent (METH+) and 47 non-dependent men | COMT Val158Met polymorphism | None | Significant interactions indicated METH+ had lower DA and higher HVA/DA ratios among Met/Met, but not Val/Met or Val/Val. Higher DA correlated with better EF in METH- Met/Met, but did not predict EF in the entire sample. | Neurocognitive testing, COMT genotyping, lumbar puncture for CSF DA and HVA assays, linear models, Pearson correlations | Executive function (EF) tests | Slow DA clearance exacerbates METH-associated DA dysregulation in Met/Met, with Met-carriers disproportionately vulnerable to METH-related perturbations of DA. Higher DA levels in METH- Met/Met, comparable DA levels among METH+ | | Preliminary findings, small sample size, lack of diversity in population (all male), and no epigenetic factors analyzed |
| Payer et al. (2012) | USA | 53 MA-dependent, 47 controls | Adults | SERT gene: SERT-LPR and STin2 VNTR polymorphisms | None reported | Higher aggression in MA users and those with high genetic risk for aggression. Lower amygdala activation in high genetic risk group. Differences in brain activation between MA and control groups, and high vs low genetic risk groups. | fMRI while viewing emotional faces, genotyping, self-report measures | Self-report measures of aggression | SERT risk allele loads comparable between MA and controls. MA and genetic risk influence aggression independently with minimal neural overlap. | | Cross-sectional design, no epigenetic factors examined |
| Chen et al. (2007) | Taiwan | 439 methamphetamine abusers (94 with suicide attempts, 294 without | Chinese methamphetamine abusers | 5-HTTLPR polymorphism in serotonin transporter gene | None reported | Suicide attempts related to female gender, methamphetamine-induced psychosis/depression, family history of psychosis. No association between 5-HTTLPR and suicidal behavior. | Interviews (Diagnostic Interview for Genetic Study, Family Interview for Genetic Study), genotyping | Assessment of psychiatric disorders, suicidal behavior | Clinical correlates but not 5-HTTLPR polymorphism associated with suicidal behavior in this sample. | | Small sample size for genetic analysis, no epigenetic factors examined |
| Ezaki et al. (2008) | Japan | 166 methamphetamine patients (95 transient psychosis, 71 prolonged psychosis), 197 controls | Japanese methamphetamine abusers | 5-HTTLPR polymorphism in serotonin transporter gene | None reported | Higher frequency of S allele in prolonged psychosis patients, especially those with spontaneous relapse, compared to controls. | Genotyping, clinical assessments | Assessment of psychosis type (transient vs prolonged) and relapse | 5-HTTLPR S allele may be a risk factor for prolonged methamphetamine psychosis, possibly due to reduced serotonin transporter levels and dysfunction. | | No epigenetic factors examined, limited sample size |
| Aoyama et al. (2006) | Japan | 213 MAP dependents, 443 controls, 96 healthy controls for LD | Japanese individuals with methamphetamine dependence | SLC22A3 polymorphisms (5 SNPs) | Not analyzed | SLC22A3 polymorphisms were not significantly associated with MAP dependence. However, significant differences in SNP2 and SNP3 genotype and allele frequencies between polysubstance and single-MAP users were found. | Single-marker and haplotype analyses on SLC22A3 polymorphisms | Not specified | Polymorphisms of SLC22A3 are related to the development of polysubstance use in Japanese patients with MAP dependence. | | Focus on SLC22A3; lack of psychological assessments; small sample for genetic association studies |
| Ujike et al. (2003) | Japan | 124 METH dependence/psychosis patients, 160 controls | Japanese individuals with methamphetamine dependence/psychosis | hDAT1 gene (SLC6A3) polymorphisms (242C/T, 1342A/G, 2319G/A, and VNTR) | Not analyzed | Patients with METH psychosis lasting 1 month or more after discontinuance showed a significant excess of nine- or fewer repeat alleles of the VNTR in the 3â€²UTR of the hDAT1 gene (P=0.0054, OR=4.24, 95% CI=2.46â€“7.31). | Genotypic and allelic distribution analysis of hDAT1 (SLC6A3) polymorphisms | ['Not specified | ['The presence of nine- or fewer repeat alleles of hDAT1 (SLC6A3) is a strong risk factor for a worse prognosis of METH psychosis. | | Focused only on hDAT1; did not consider other genetic factors or psychological assessments |
| Kishi et al. (2011a) | Japan' | 197 METH-induced psychosis patients, 337 controls | Japanese individuals with methamphetamine-induced psychosis | HTR6 gene polymorphisms (rs6693503, rs1805054, rs4912138, rs3790757, rs9659997) | Not analyzed | rs6693503 was associated with METH-induced psychosis in allele/genotype-wise analysis, remaining significant after Bonferroni correction. Associations were also found in haplotype-wise analysis between two markers (rs6693503, rs1805054) and three markers (rs6693503, rs1805054, rs4912138) in HTR6. | Genetic association analysis of caseâ€“control samples using five tagging SNPs in HTR6 | Not specified | HTR6 may play an important role in the pathophysiology of METH-induced psychosis in the Japanese population. | | Focus on HTR6; lack of broader genetic and psychological assessments |
| Cao et al. (2013) | Multi-cultural (European, Asian, Mexican, African populations) | 7999 cases, 8264 controls, 676 families or parent-offspring trios from 55 studies | Multi-cultural populations with substance use disorder'] | SLC6A4 gene (5-HTTLPR and STin2 polymorphisms)'] | Not analyzed | Meta-analysis showed significant associations of 5-HTTLPR with alcohol, heroin, cocaine, and methamphetamine dependence/abuse. Associations varied by substance and population, with different risk allele frequencies across European, Asian, Mexican, and African populations. | Comprehensive meta-analysis of 55 studies examining associations of 5-HTTLPR and STin2 polymorphisms with substance use disorder across multiple racial and ethnic populations | Not specified | The SLC6A4 gene is associated with substance use disorder, with the strength and direction of association varying by substance and population, especially for methamphetamine dependence/abuse. | | Inconsistencies due to population stratification, phenotype definition, and inadequate statistical power; further studies with larger sample sizes needed. |
| Ujike et al. (2011) | Japan | 231 methamphetamine dependence patients (214 with psychosis), 248 controls | Japanese individuals with methamphetamine dependence, majority with psychosis | HTR1B gene (3 SNPs: rs130058 (A-165T), rs1228814 (A-700C), rs1228814 (A+1180G)) | Not analyzed | No significant difference in allelic and genotypic distributions of HTR1B SNPs between methamphetamine dependence patients and controls. No association with clinical phenotypes such as age at first abuse or prognosis of psychosis. | Case-control genetic association study of HTR1B polymorphisms in methamphetamine dependence patients | Not specified'] | HTR1B does not play a major role in susceptibility to methamphetamine dependence or development of methamphetamine-induced psychosis. | | Focused only on HTR1B; did not analyze other genetic or environmental factors contributing to methamphetamine dependence |
| Yahya et al. (2023) | Malaysia | 285 METH-dependent male subjects, 251 male control subjects | Malaysian population consisting of four ethnic groups (Malay, Chinese, Kadazan-Dusun, and Bajau) | SLC1A2 gene polymorphism (rs4755404)'] | Not analyzed | Significant association between rs4755404 polymorphism and METH-induced psychosis in METH-dependent subjects (p = 0.041), particularly for those with the GG homozygous genotype. No significant association with METH dependence or METH-induced mania. | Genotyping of rs4755404 single nucleotide polymorphism (SNP) in METH-dependent and control subjects'] | Not specified | The SLC1A2 rs4755404 gene polymorphism may confer susceptibility to METH-induced psychosis, especially for individuals carrying the GG homozygous genotype. | | Limited to male subjects; lack of psychological assessments and other gene polymorphisms |
| Aoyama et al. (2006) | Japan | 213 MAP dependence subjects, 443 controls, 96 healthy controls for linkage disequilibrium (LD) analysis | Japanese individuals with methamphetamine dependence, including polysubstance and single-MAP users | SLC22A3 polymorphisms (5 haplotype tag SNPs) | Not analyzed | SLC22A3 polymorphisms were not significantly associated with MAP dependence in single-marker or haplotype analyses. However, significant differences in SNP2 and SNP3 genotype and allele frequencies were found between polysubstance and single-MAP users. | Single-marker and haplotype analyses on 5 SLC22A3 polymorphisms | Not specified | Polymorphisms of SLC22A3 may be related to the development of polysubstance use in Japanese patients with MAP dependence. | | Focus on SLC22A3; did not assess other genetic or psychological factors; small sample for subgroup analyses |
| Suzuki et al. (2006) | Japan | 143 patients with methamphetamine psychosis, 200 healthy controls | Japanese individuals with methamphetamine psychosis, divided into subgroups by clinical features | Catechol-O-methyl transferase (COMT) gene polymorphism (val158met) | Not analyzed | Significant difference in COMT allele frequency between patients with spontaneous relapse and controls (P=0.018, OR=1.67), indicating a 1.7-fold higher rate of low activity alleles (met) in the patient group. | Analysis of val158met polymorphism in COMT gene among methamphetamine psychosis patients and controls'] | Not specified'] | The met allele frequency of the COMT gene is associated with patients experiencing methamphetamine psychosis and spontaneous relapse, suggesting increased risk of adverse response to methamphetamine for individuals with the met allele. | | 'Focus on COMT; limited to a specific Japanese population; did not analyze other genetic factors or broader psychological aspects' |
| Sonia et al. (2021) | Bangladesh | 183 substance abused subjects, 175 healthy controls | Bangladeshi male individuals with substance abuse, including various substances | Catechol-O-methyltransferase (COMT) (Val158Met) and Dopamine receptor D4 (DRD4) (120 bp tandem duplication) gene polymorphisms | Not analyzed | The heterozygous COMT Val/Met variant (p<0.05, OR=1.66) and homozygous and heterozygous DRD4 120 bp tandem duplication variants were significantly associated with substance abuse risk. The Met/Met COMT variant showed a longer addiction period in heroin users. | Allele-specific PCR analysis of COMT and DRD4 polymorphisms among substance abuse subjects and controls | Not specified | Genetic variability in COMT and DRD4 may influence susceptibility to substance abuse and addictive characteristics in Bangladeshi males. | | Focused on male subjects; did not assess other genetic or psychological factors |
| Reclaw et al. (2024)'] | Poland | 107 men with gambling disorder and amphetamine dependency, 200 non-addicted controls | Polish men with gambling disorder and amphetamine dependency, compared to healthy controls | Catechol-O-methyltransferase (COMT) gene polymorphism (rs4680) | Not analyzed'] | Significant differences in rs4680 genotype frequency between subjects and controls (p = 0.03543). Subjects with gambling disorder and amphetamine use disorder scored higher on STAI trait/state scales and NEO-FFI Neuroticism, and lower on NEO-FFI Agreeability. | Genomic DNA extraction and real-time PCR technique to determine rs4680 polymorphism; psychometric evaluations using STAI and NEO-FFI inventories | State-Trait Anxiety Inventory (STAI) and NEO Five-Factor Personality Inventory (NEO-FFI) | The COMT rs4680 polymorphism influences the development of addiction, but it is multifactorial and should be considered alongside other factors such as personality traits. | | Focused on men with gambling disorder and amphetamine dependency; did not consider other genetic or environmental factors |
| Liu et al. (2020) | China | 207 male MA abusers (168 high addiction quality, 39 low addiction quality), 105 healthy controls | Male methamphetamine abusers with different addiction qualities compared to healthy controls'] | SLC1A6, BHLHB9, LYNX1, CAV2, and PCSK9 gene methylation levels'] | Genome-wide DNA methylation analysis using the Infinium Human Methylation 450 array | Seven pathways with abnormal methylation status identified, including circadian entrainment and glutamatergic synapse. SLC1A6, BHLHB9, LYNX1, CAV2, and PCSK9 showed differences in methylation. Only CAV2 had significantly higher methylated copies in the low addiction quality group. | Genome-wide DNA methylation scans with Infinium Human Methylation 450 array and verification using MethyLight qPCR'] | Not specified | The circadian entrainment pathway and caveolin-2 (CAV2) gene may play key roles in MA addiction quality, suggesting potential targets for drug intervention. | | Focus on male subjects; limited sample size for genome-wide analysis; further studies needed on functions and mechanisms |
| Heinzerling et al. (2012) | United States | 61 Non-Hispanic Caucasians and Hispanic Caucasians with methamphetamine dependence | Methamphetamine-dependent Hispanic and Non-Hispanic Caucasian individuals undergoing treatment | Catechol-O-methyltransferase (COMT) Val158Met, Brain-derived neurotrophic factor (BDNF) Val66Met, Mu opioid receptor (OPRM1) Asn40Asp polymorphisms | Not analyzed | Significant main effect for BDNF Val66Met on TES among Caucasians (p = 0.039) with higher TES among Val/Val genotype. No significant main effects for COMT Val158Met or OPRM1 Asn40Asp, though moderate effect sizes were observed. | Exploratory study using t-tests and linear regression models to assess TES in a randomized, double-blind, placebo-controlled trial of modafinil, with contingency management and cognitive behavioral therapy for MA dependence | Treatment Effectiveness Score (TES) via mean MA-negative urine drug screens | BDNF Val66Met polymorphism may be associated with better treatment response among Caucasians with methamphetamine dependence; COMT Val158Met and OPRM1 Asn40Asp showed no significant effects. | | Small sample size; limited to Hispanic and Non-Hispanic Caucasians; did not explore other genetic or psychological factors |
| Cherner et al. (2019) | United States | 149 non-Hispanic White men stratified by methamphetamine dependence and COMT genotype | Non-Hispanic White men with and without methamphetamine dependence, categorized by COMT Val158Met genotype | Catechol-O-methyltransferase (COMT) Val158Met polymorphism | Not analyzed | Methamphetamine group differences in executive function (EF) were significant only among Met/Met carriers (beta = -9.36, p < .001), indicating that Val allele carriers may have protective effects against methamphetamine-related executive dysfunction. | Analysis of executive function using WCST, Stroop, and Trails B tests, with the interaction of METH dependence and COMT Val158Met genotype examined | Wisconsin Card Sorting Test (WCST), Stroop Color-Word Test, Trail Making Test Part B | The Val allele of COMT Val158Met may confer protective effects against methamphetamine-related executive dysfunction, highlighting genetically driven differences in vulnerability to methamphetamine. | | Focused only on non-Hispanic White men; did not explore other genetic or environmental factors contributing to methamphetamine-related executive dysfunction |
| Hosak et al. (2011) | Czech Republic | 123 subjects with methamphetamine dependence, 67 parents of dependent individuals, 400 healthy controls | Methamphetamine-dependent individuals, their parents, and healthy controls in the Czech Republic | Catechol-O-methyltransferase (COMT) Val158Met polymorphism | Not analyzed | No significant association between the COMT Val158Met polymorphism and methamphetamine dependence was found. A trend toward more frequent psychotic symptoms in Val allele carriers compared to Met/Met homozygotes (p=0.062). | Population-based and family-based genetic association studies using the Chi-Square Test and UNPHASED program | Not specified | The study found no significant association between the COMT Val158Met polymorphism and methamphetamine dependence, suggesting the need for further research involving haplotype analysis and other dopamine-related genetic polymorphisms. | | Limited sample size; did not consider other genetic or environmental factors; potential variability in individual clinical subtypes of methamphetamine dependence |
| Bousman et al. (2010) | United States | 192 sexually active nonmonogamous men with methamphetamine dependence | Men with methamphetamine dependence and HIV infection, categorized by COMT Val158Met genotype | Catechol-O-methyltransferase (COMT) Val158Met polymorphism | Not analyzed | Main effects for executive dysfunction on number of sexual partners, but not COMT. A COMT x executive dysfunction interaction was found for risky sexual behavior, significant in Met/Met and Val/Met carriers but not Val/Val. | Genotyping, sexual behavior questionnaire, and executive functioning tests in men with methamphetamine dependence | Executive functioning tests; sexual behavior questionnaire | Dopaminergic overactivity in prefrontal cortex conferred by the Met/Met genotype may result in executive dysfunction and risky sexual behavior in men with methamphetamine dependence and HIV. | | Focused on men with methamphetamine dependence and HIV; did not assess other genetic or environmental factors influencing risky sexual behavior |