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Immunoglobulin genotypes and cognitive functions in schizophrenia

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Abstract

Exposure to neurotropic viruses, such as herpes simplex virus type 1 and human cytomegalovirus, has been reported to be associated with cognitive impairment in schizophrenia. These viruses have evolved highly sophisticated strategies for decreasing the efficacy of the host immune response and interfering with viral clearance. Particular immunoglobulin GM (γ marker) genotypes modulate these viral immunoevasion strategies, influence antibody responsiveness to viral proteins, and are also associated with susceptibility to schizophrenia, providing an excellent rationale for determining their possible involvement in the cognitive functions in this highly heritable neurodevelopmental disorder. In this investigation, we assessed the cognitive functions (verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function) in 145 patients with schizophrenia and characterized their DNA for several GM and KM (γ marker) alleles. Particular KM and GM genotypes were significantly associated with verbal memory and attention and processing speed scores, respectively ($p = 0.01$ and 0.001). Epistatic effects of GM and KM genotypes on attention and processing speed, verbal fluency, and motor speed were also noted ($p = 0.031$, 0.047, 0.003). These results, for the first time, show that hitherto understudied immunoglobulin GM and KM genotypes—individually and epistatically—contribute to the magnitude of interindividual variability in the cognitive functions in patients with schizophrenia. Additional studies involving these highly polymorphic genes of the immune system are needed.

Keywords

Neurotropic viruses; Immunoglobulin allotypes; Cognitive functions; Schizophrenia

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Immunoglobulin GM (γ marker) allotypes are encoded by immunoglobulin heavy chain G1 (*IGHG1*), *IGHG2*, and *IGHG3* genes on chromosome 14q32 (Oxelius and Pandey 2013). Although most GM alleles are common within a racial group (some with gene frequency >70%), they are not being evaluated in the genome wide association studies (GWAS) of schizophrenia or cognitive function, because these determinants are not included in the commonly employed genotyping platforms (Schizophrenia Working Group 2014; Trampush et al. 2017). Furthermore, since GM allotypes were not typed in the HapMap project, they cannot be imputed. Even in the 1000 Genomes project the coverage of this region is very low, resulting in poor quality of imputation. Therefore, a candidate gene approach is necessary for evaluating the role of GM genes in the etiology of schizophrenia.

In a recent study, using a candidate gene approach and a large sample size, we found a highly significant association between a GM genotype and susceptibility to schizophrenia (Pandey et al. 2016). The subjects with this genotype were over 3 times as likely to develop schizophrenia as those without this genotype. The mechanisms underlying this association are not known. Since almost all GM alleles are expressed in the Fc region of immunoglobulin γ chains (Oxelius and Pandey 2013), the putative mechanisms are likely to include Fc-mediated host immunosurveillance mechanisms against infectious pathogens implicated in the pathology of schizophrenia. Exposure to neurotropic viruses, such as herpes simplex virus 1 (HSV1) and human cytomegalovirus (CMV), has been reported to be associated with cognitive impairment in schizophrenia (Shirts et al. 2008). These viruses have evolved highly sophisticated strategies for decreasing the efficacy of the host immune response and interfering with viral clearance. One strategy involves encoding decoy Fcγ receptors (FcγRs), which thwart the host's Fc-mediator effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) (Corrales-Aguilar et al. 2014). Interestingly, GM alleles modulate this viral strategy, by differentially binding to the viral FcγR (Atherton et al. 2000; Namboodiri and Pandey 2011; Pandey et al. 2015; Pandey et al. 2017). Additionally, GM alleles contribute to the magnitude of humoral immunity to certain viral proteins and to the cytotoxicity of virally infected cells (Pandey et al. 2014; Moraru et al. 2015).

The association of GM alleles with susceptibility to schizophrenia and their contribution to immunity to herpesviruses, coupled with the reported association of the latter with cognitive impairment, provide a strong rationale for investigating whether or not these polymorphic genes are associated with cognitive functions in this disease. Therefore, in the present investigation, we aimed to determine the contribution of GM genotypes to the magnitude of cognitive functions in patients with schizophrenia. Additionally, we investigated whether particular KM (κ marker) allotypes—encoded by the *IGKC* (immunoglobulin kappa constant) gene on chromosome 2p12—also influence the magnitude of cognitive functions. Like GM, the KM allotypes also influence immunity to certain herpesviruses, which are implicated in the cognitive decline of patients with schizophrenia (Biggar et al. 1984; Shim et al. 2017).

The study population consisted of 145 Japanese schizophrenia patients recruited from the University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan. The study was approved by the University Ethics Committee, using the ethical standards of the

Declaration of Helsinki. The diagnosis of schizophrenia was established based on the Structured Clinical Interview for DMS-IV (SCID) and a comprehensive review of the patient medical records. The inclusion and exclusion criteria and demographic characteristics of the participants have been described in detail elsewhere (Hori et al. 2016).

Cognitive function was assessed by trained psychiatrists using the Brief Assessment of Cognition in Schizophrenia (BACS) in a Japanese-language version (BACS-J) (Kaneda et al. 2007). This metric includes brief assessments of verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function. The primary measures from each subtest of the BACS-J were standardized by creating *z*-scores, as described in detail elsewhere (Hori et al. 2016).

IgG1 markers GM 3 and 17 (arginine to lysine), were determined by a pre-designed TaqMan® genotyping assay from Applied Biosystems Inc. (Foster City, CA), employing the following primers and probes:

Forward primer: 5′ CCCAGACCTACATCTGCAACGTGA-3′

Reverse primer: 5′ CTGCCCTGGACTGGGACTGCAT-3′

Reporter 1 (GM 17-specific): VIC-CTCTCACCAACTTTCTTGT-NFQ

Reporter 2 (GM 3-specific): FAM-CTCTCACCAACTCTCTTGT-NFQ

IgG2 markers GM 23− and 23+ (valine to methionine), a G to A substitution in the CH2 region of the γ2 gene—were determined by a nested PCR-RFLP method. In brief, a 915 bp region of the γ2 gene that incorporates the sites for the allelic substitutions was amplified as described by Brusco et al., (1995), using the following primers: 5′ AAATGTTGTGTCGAGTGCCC 3′ and 5′ GGCTTGCCGGCCGTGGCAC 3′. A 197 bp segment was further amplified from this 915 bp fragment using the following primers:

5′ GCACCACCTGTGGCAGGACC 3′and 5′ TTGAACTGCTCCTCCCGTGG 3′. After digestion of the amplified product with the restriction enzyme NlaIII, the following products corresponding to the three genotypes were obtained:

GM 23+	90 bp, 63 bp, 44 bp
GM 23−	134 bp, 63 bp
GM 23+,23−	134 bp, 90 bp, 63 bp, 44 bp

Three alleles—KM 1, KM 1,2, and KM 3—segregate at the KM (*IGKC*) locus. Over 98% of the individuals positive for KM 1 are also positive for KM 2; KM 1 allele, without KM 2, is extremely rare. Thus, in this and in most other investigations, positivity for KM 1 includes both KM 1 and KM 1,2 alleles. The KM alleles were determined by a previously described PCR-RFLP method (Moxley and Gibbs, 1992).

General linear models (GLMs) were used to test associations between cognitive function domain scores and each of the GM and KM loci of interest. Separate models were constructed to examine the main effects of each locus, followed by another series of models to assess epistasis. For each test, we considered 4 different genetic models (genotypic, additive, dominant, and recessive), which correspond to different approaches to examining

the recessive homozygotes, heterozygous, and dominant homozygotes for each locus. When comparing the various epistasis models, Akaike Information Criteria (AIC) was used to determine the best fitting model. All statistical tests were 2-sided, and we used an alpha level of 0.05. Analyses were conducted with SAS v9.4 (Cary, NC).

The nominal *p*-values are provided in the results. They were not adjusted for multiple testing, in order that the reader can make an informed judgment. Adjustments for multiple testing are controversial (Perneger 1998). Instead of performing such adjustment in this work, we believe the best approach would be to perform similar testing in an independent sample. It is relevant to point out that, because of significant linkage disequilibrium within GM loci, not all tests performed in this study were independent. Thus, associations at 2 independent loci—GM and KM—were explored.

Cognitive function data were not available for 21 patients. Therefore, statistical analyses involved GM genotype and cognitive function data from 124 patients.

All genotypes were in Hardy-Weinberg equilibrium. Table 1 presents the mean verbal memory z-scores in relation to various GM and KM genotypes. Allelic variation at the KM locus contributed to the interindividual variation in the verbal memory scores. The association was significant for the genotype, additive, and dominant, but not for the recessive, model of inheritance. The verbal memory scores were significantly lower in KM 1/1 homozygotes and KM 1/3 heterozygotes than in KM 3/3 homozygotes (−0.85 and −0.96 vs. −0.34; $p = 0.01$). The GM genotypes were not associated with this cognitive function domain. Table 2 presents the mean attention and processing speed z-scores in relation to various GM and KM genotypes. Allelic variation at the GM 3/17 locus contributed to the interindividual variation in the attention and processing speed. The association was significant for the genotype, additive, and dominant, but not for the recessive, model of inheritance. Attention and processing speed scores were significantly lower in GM 17/17 homozygotes than in GM 3/3 homozygotes and GM 3/17 heterozygotes (−1.12 vs. −0.19 and −0.43; $p = 0.001$). The GM 23 and KM genotypes were not significantly associated with this cognitive function.

No other significant associations were found.

Table 3 presents three significant epistatic interactions involving the 3 loci of interest and the cognitive function domains. Although multiple epistasis models were assessed, only ones with significant findings are presented. When more than one type of model yielded significant findings, only the best fitting model (as determined by AIC) was presented. The reference alleles in these analyses were GM 3 and KM 1. For attention processing z-scores, there was a significant ($p = 0.031$) interaction between KM 1/3 and GM 3/17 (genotype × dominant model); the presence of the GM 3 allele was associated with lower mean scores among subjects with KM 1/1 (−1.45 vs. −0.44), but higher mean scores among subjects with KM 1/3 (−0.53 vs. −1.38) or KM 3/3 (−0.10 vs. −1.07).

For verbal fluency z-scores (Table 3), there was a moderately significant ($p = 0.047$) interaction between KM 1/3 and GM 3/17 (recessive × additive). Among subjects without the KM 3 allele, having the GM 3 allele was associated with higher z-scores, but among

subjects with the KM 3 allele, having more copies of the GM 3 allele was associated with lower scores.

For motor speed z-scores (Table 3), there was a significant ($p = 0.003$) interaction between KM 1/3 and GM 23. Although there were no GM 23 +/+ homozygotes in this study population and no subjects with both KM 1/1 and GM 23 +/−, having GM 23 +/− was associated with higher mean scores among subjects with KM 1/3 (0.33 vs. −0.99) but lower mean scores among subjects with KM 3/3 (−1.91 vs. −0.61).

The results presented here show that GM and KM genotypes—individually and in particular epistatic combinations—contribute to the magnitude of various cognitive functions in patients with schizophrenia. There are several immunological mechanisms through which these polymorphic genes could impact cognitive functions. The most likely mechanisms would involve antibodies to self or non-self antigens that have been implicated in brain pathology (Brimberg et al. 2015).

As stated earlier, exposure to neurotropic viruses CMV and HSV1 has been implicated in cognitive impairment in patients with schizophrenia. GM alleles have been shown to modulate immunoevasion strategies of both viruses. The HSV1-encoded FcγR, as well as those encoded by the CMV genes *UL119-UL118* and *RL13,* has significantly higher affinity for IgG1 proteins expressing the GM 17 allotype than for those expressing the allelic GM 3 allotype (Atherton et al. 2000; Pandey et al. 2015; Pandey et al. 2017). These results predict that subjects expressing the high affinity GM 17 allele would be more likely to have their Fc domains scavenged, thereby reducing their immunological competence to eliminate the virus through ADCC and other Fc-mediated effector mechanisms. Consequently, they would be expected to have higher degree of virally-induced/spurred cognitive impairment than those expressing the low affinity allele. Consistent with this prediction, we found a highly significant association between homozygosity for the GM 17 allotype and low scores for attention and processing speed.

Molecular mimicry—immune response against antigens shared by the host and an environmental trigger (e.g. gliadin)—could provide another mechanism for the GM gene involvement in cognitive functions in schizophrenia. Non-celiac gluten sensitivity—characterized by the presence of antibodies to gliadin but the absence of other biomarkers of celiac disease—is significantly associated with a variety of neurological disorders, including schizophrenia. The GM 23 allotype—which epistatically with the KM alleles influences the motor speed in the present investigation—has been shown to be associated with antibody responsiveness to gliadin (Weiss et al. 1983). There is immune cross-reactivity between gliadin and synapsin 1 (Alaedini et al. 2007), a cytosolic phosphoprotein that is found in most neurons and is involved in the regulation of neurotransmitter release (Li et al. 1995; Humeau et al. 2001; Hilfiker et al. 2005). It is possible that anti-synapsin 1 antibodies expressing particular GM alleles could differentially influence the magnitude of neurotransmitter release and thus contribute to the interindividual variability in the cognitive functions.

Another mechanism for the GM gene involvement in cognitive functions could be through the complement system, which has been implicated in synaptic pruning in schizophrenia (Sekar et al. 2016; Presumey J et al. 2017). The C1q complex, which triggers the complement cascade, has been shown to bind differentially to the IgG antibodies expressing different GM alleles (Bruggemann et al. 1987). It is possible that allelically different anti-gliadin/synapsin1 antibodies have differential affinity to C1q and thus differentially influence the magnitude of the complement-mediated synaptic pruning, which could influence the cognitive functions.

Allelically disparate IgG antibodies to neurotropic viruses, gliadin/synapsin 1, or to any other cross-reacting brain antigen, if generated in the mother, could be transferred to the developing fetal brain before the blood-brain barrier is formed. They could also gain access to the brain antigens if the integrity of the blood-brain barrier is compromised (Brimberg et al. 2015). These IgG antibodies could interact with allelically different FcγRs expressed on neural cells (Okun et al. 2010) and cause ADCC, resulting in varying levels of cognitive impairment. We have presented evidence for allelic interaction between the IgG (GM) and FcγR loci in the ADCC of HSV1-infected cells (Moraru et al. 2015).

It is also possible that there are other loci (on chromosomes 14 and 2) that regulate cognitive functions in schizophrenia, distinct from GM and KM, whose alleles are in significant linkage disequilibrium with those of the GM and KM loci. This putative linkage disequilibrium could give rise to the associations observed.

This is the first report implicating GM and KM genes in the cognitive functions. It needs to be replicated in an independent and larger multiethnic study population. It is hoped that the results presented here would inspire further studies to investigate the role of (hitherto understudied) the GM and KM genes in the immunobiology of schizophrenia.

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References

Alaedini A, Okamoto H, Briani C, Wollenberg K, Shill HA, et al. Immune cross-reactivity in celiac disease: anti-gliadin antibodies bind to neuronal synapsin I. J Immunol. 2007; 178:6590–6595. [PubMed: 17475890]

Atherton A, Armour KL, Bell S, Minson AC, Clark MR. The herpes simplex virus type 1 Fc receptor discriminates between IgG1 allotypes. Eur J Immunol. 2000; 30:2540–2547. [PubMed: 11009087]

Biggar RJ, Pandey JP, Henle W, Nkrumah FK, Levine PH. Humoral immune response to Epstein-Barr virus antigens and immunoglobulin allotypes in African Burkitt lymphoma patients. Int J Cancer. 1984; 33:577–580. [PubMed: 6327537]

Brimberg L, Mader S, Fujieda Y, Arinuma Y, Kowal C, et al. Antibodies as mediators of brain pathology. Trends Immunol. 2015; 36:709–724. [PubMed: 26494046]

Brüggemann M, Williams GT, Bindon CI, Clark MR, Walker MR, et al. Comparison of the effector functions of human immunoglobulins using a matched set of chimeric antibodies. J Exp Med. 1987; 166:1351–1361. [PubMed: 3500259]

Brusco A, de Lange GG, Boccazz C, Carbonara AO. Molecular characterization of G2m(n+) and G2m(n-) allotypes. Immunogenetics. 1995; 42:414–417. [PubMed: 7590976]

Corrales-Aguilar E, Trilling M, Hunold K, Fiedler M, Le VT, et al. Human cytomegalovirus Fcγ binding proteins gp34 and gp68 antagonize Fcγ receptors I, II and III. PLoS Pathog. 2014; 10:e1004131. [PubMed: 24830376]

Hilfiker S, Benfenati F, Doussau F, Nairn AC, Czernik, et al. Structural domains involved in the regulation of transmitter release by synapsins. J Neurosci. 2005; 25:2658–2669. [PubMed: 15758176]

Hori H, Yoshimura R, Katsuki A, Atake K, Igata R, et al. Relationships between serum brain-derived neurotrophic factor, plasma catecholamine metabolites, cytokines, cognitive function and clinical symptoms in Japanese patients with chronic schizophrenia treated with atypical antipsychotic monotherapy. World J Biol Psychiatry. 2016; 15:1–8.

Humeau Y, Doussau F, Vitiello F, Greengard P, Benfenati F, et al. Synapsin controls both reserve and releasable synaptic vesicle pools during neuronal activity and short-term plasticity in Aplysia. J Neurosci. 2001; 21:4195–4206. [PubMed: 11404405]

Kaneda Y, Sumiyoshi T, Keefe R, Ishimoto Y, Numata S, et al. Brief assessment of cognition in schizophrenia: validation of the Japanese version. Psychiatry Clin Neurosci. 2007; 61:602–609. [PubMed: 18081619]

Li L, Chin LS, Shupliakov O, Brodin L, Sihra TS, et al. Impairment of synaptic vesicle clustering and of synaptic transmission, and increased seizure propensity, in synapsin I-deficient mice. Proc Natl Acad Sci U S A. 1995; 92:9235–9239. [PubMed: 7568108]

Moraru M, Black LE, Muntasell A, Portero F, López-Botet M, et al. NK cells and immunoglobulins interplay in defense against herpes simplex virus type 1: epistatic interaction of CD16A and IgG1 allotypes of variable affinity modulates antibody-dependent cellular cytotoxicity and susceptibility to clinical reactivation. J Immunol. 2015; 195:1676–1684. [PubMed: 26179905]

Moxley GM, Gibbs RS. Polymerase chain reaction-based genotyping for allotypic markers of immunoglobulin kappa shows allelic association of Km with kappa variable segment. Genomics. 1992; 13:104–108. [PubMed: 1349568]

Namboodiri AM, Pandey JP. The human cytomegalovirus *TRL11/IRL11*-encoded FcγR binds differentially to allelic variants of immunoglobulin G1. Arch Virol. 2011; 156:907–910. [PubMed: 21311920]

Okun E, Mattson MP, Arumugam TV. Involvement of Fc receptors in disorders of the central nervous system. Neuromolecular Med. 2010; 12:164–178. [PubMed: 19844812]

Oxelius VA, Pandey JP. Human immunoglobulin constant heavy G chain (IGHG) (Fcγ) (GM) genes, defining innate variants of IgG molecules and B cells, have impact on disease and therapy. Clin Immunol. 2013; 149:475–486. [PubMed: 24239836]

Pandey JP, Kistner-Griffin E, Radwan FF, Kaur N, Namboodiri AM, et al. Immunoglobulin genes influence the magnitude of humoral immunity to cytomegalovirus glycoprotein B. J Infect Dis. 2014; 210:1823–1826. [PubMed: 24973460]

Pandey JP, Namboodiri AM, Radwan FF, Nietert PJ. The decoy Fcγ receptor encoded by the cytomegalovirus *UL119-UL118* gene has differential affinity to IgG proteins expressing different GM allotypes. Hum Immunol. 2015; 76:591–594. [PubMed: 26382248]

Pandey JP, Namboodiri AM, Elston RC. Immunoglobulin G genotypes and the risk of schizophrenia. Hum Genet. 2016; 135:1175–1179. [PubMed: 27393575]

Pandey JP, Namboodiri AM, Mohan S, Nietert PJ, Peterson L. Genetic markers of immunoglobulin G and immunity to cytomegalovirus in patients with breast cancer. Cell Immunol. 2017; 312:67–70. [PubMed: 27825564]

Perneger TV. What's wrong with Bonferroni adjustments. BMJ. 1998; 316:1236–1238. [PubMed: 9553006]

Presumey J, Bialas AR, Carroll MC. Complement system in neural synapse elimination in development and disease. Adv Immunol. 2017; 135:53–79. [PubMed: 28826529]

Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421–427. [PubMed: 25056061]

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, et al. Schizophrenia risk from complex variation of complement component 4. Nature. 2016; 530:177–183. [PubMed: 26814963]

Shim SM, Cheon HS, Jo C, Koh YH, Song J, Jeon JP. Elevated Epstein-Barr virus antibody level is associated with cognitive decline in the Korean elderly. J Alzheimer's Dis. 2017; 55:293–301. [PubMed: 27589534]

Shirts BH, Prasad KM, Pogue-Geile MF, Dickerson F, Yolken RH, et al. Antibodies to cytomegalovirus and herpes simplex virus 1 associated with cognitive function in schizophrenia. Schizophr Res. 2008; 106:268–274. [PubMed: 18801645]

Trampush JW, Yang ML, Yu J, Knowles E, Davies G, Liewald DC, et al. GWAS meta-analysis reveals novel loci and genetic correlates for general cognitive function: a report from the COGENT consortium. Mol Psychiatry. 2017; 22:336–345. [PubMed: 28093568]

Weiss JB, Austin RK, Schanfield MS, Kagnoff MF. Gluten-sensitive enteropathy. Immunoglobulin G heavy-chain (Gm) allotypes and the immune response to wheat gliadin. J Clin Invest. 1983; 72:96–101. [PubMed: 6409931]

Table 1

Tests of associations between GM 3/17, GM 23 +/−, and KM 1/3 genotypes and verbal memory scores in patients with schizophrenia

Locus (allele*)	Genotype	n	Verbal Memory Mean ± SD	P-value genotypic	P-value additive	P-value dominant	P-value recessive
GM 3/17	3/3	11	−0.82 ± 1.65	0.40	0.51	0.27	0.67
(3)	3/17	53	−0.48 ± 1.10				
	17/17	60	−0.79 ± 1.33				
GM 23	−/−	112	−0.71 ± 1.27	0.24	N/A	N/A	N/A
	+/−	12	−0.25 ± 1.21				
KM 1/3	1/1	13	−0.85 ± 1.01	0.03	0.02	0.008	0.57
(1)	1/3	53	−0.96 ± 1.35				
	3/3	58	−0.34 ±1.18				

* Dominant and recessive models are based on this reference allele in the parenthesis.

Table 2

Tests of associations between GM 3/17, GM 23 +/−, and KM 1/3 genotypes and the scores for attention and processing speed in patients with schizophrenia

Locus (allele*)	Genotype	n	Attention/Processing Speed Mean ± SD	P-value genotypic	P-value additive	P-value dominant	P-value recessive
GM 3/17	3/3	11	−0.19 ± 1.38	0.005	0.002	0.001	0.14
(3)	3/17	53	−0.43 ± 1.09				
	17/17	60	−1.12 ± 1.33				
GM 23	−/−	112	−0.78 ± 1.29	0.29	N/A	N/A	N/A
	+/−	12	−0.37 ± 1.19				
KM 1/3	1/1	13	−0.83 ± 1.12	0.23	0.16	0.09	0.79
(1)	1/3	53	−0.95 ± 1.30				
	3/3	58	−0.53 ±1.28				

*Dominant and recessive models are based on this reference allele in the parenthesis.

Table 3

Epistasis effects of GM 3/17, GM 23 +/−, and KM 1/3 genotypes on cognitive functions in patients with schizophrenia

Epistasis (Model)	Genotype Combination		N	Z-score		P Value
				Mean	(SD)	
Attention Processing (KM 1/3 Genotype × GM 3/17 Dominant)	KM 1/3	GM 3/17				0.031
	1/1	3/3 or 3/17	5	−1.45	0.61	
	1/1	17/17	8	−0.44	1.21	
	1/3	3/3 or 3/17	27	−0.53	1.13	
	1/3	17/17	26	−1.38	1.34	
	3/3	3/3 or 3/17	32	−0.10	1.10	
	3/3	17/17	26	−1.07	1.31	
Verbal Fluency (KM 1/3 Recessive × GM 3 Additive)	KM 1/3	GM 3/17				0.047
	1/1	3/3	0	N/A	N/A	
	1/1	3/17	5	−0.68	0.65	
	1/1	17/17	8	−1.87	0.85	
	1/3 or 3/3	3/3	11	−1.37	1.38	
	1/3 or 3/3	3/17	48	−0.86	1.11	
	1/3 or 3/3	17/17	52	−0.92	1.09	
Motor Speed (KM 1/3 Genotype × GM 23 Genotype)	KM 1/3	GM 23				0.003
	1/1	−/−	13	−0.69	1.28	
	1/1	+/−	0	N/A	N/A	
	1/3	−/−	47	−0.99	1.70	
	1/3	+/−	6	0.33	0.77	
	3/3	−/−	52	−0.61	1.13	
	3/3	+/−	6	−1.91	1.91	

N/A: not applicable