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Identifying new susceptibility genes on dopaminergic and serotonergic pathways for the framing effect in decision-making

[1,2] [3,4] [5] [6] [7,8]

[7,8] [1,7,9] [1,2,9,10,11]

100871 518060 710069 510631 -IDG/ 100871

104@

Abstract

(SLC6A4) (COMT) 26 1317 SLC6A4 COMT -L- (DDC)

Key words: DDC; COMT; SLC6A4

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Introduction

D - k- ( ) k- ( ), k ' (K , 1981; K , 1984; K et al., 1999). (K , 1979; , 1997), (et al., 1982; D k , 2004). . , ; (H et al., 2004; D et al., 2008). ( ) k (D et al., 2006; et al., 2009; et al., 2013; G et al., 2016). (D k D , 2008), , C , 2011). - k (K , 1979; , 1997; D et al., 2006; et al., 2009; G et al., 2016), (, 2011; C et al., 2012; C , 2012), . A k- k - - k k (C et al., 2009; D et al., 2009; K C , 2009; H et al., 2010; F et al., 2011; H et al., 2012; et al., 2013; et al., 2014), - - k (C et al., 2009, =36; et al., 2009, =30) 5-H L , (*SLC6A4*), ( ) 5-H L - ( ) k (=98) COMT COMT 158 - C / - , , (G et al., 2016). H , k - (, 2009; et al., 2010), H - . G (-L 2010; et al., 2010; et al., 2010; G et al., 2014). F COMT ( ) (et al., 1998; E et al., 2003; et al., 2003; G et al., 2004; k et al., 2005; D et al., 2006; K -K et al., 2007; et al., 2007; et al., 2008; et al., 2010; , H k , 2006). , - (MAOA MAOB) k - (D et al., 2009) - (K et al., 2007; et al., 2009) .

G (-L 2010; et al., 2010; B G , 2011; F et al., 2013; J L , 2014). , (/), ( ) 5-H L - (H et al., 2002; C et al., 2005; H et al., 2005) - (et al., 2014); k (B et al., 1998; L k, 2004; L k - et al., 2005; G , 2010), - 5-H L 5-H L LE k (et al., 2009). , , -L- - (*DDC*), , (C et al., 2010) (B et al., 2003).

C , k , J , (C), (A , 2008; H et al., 2011 ,) - (et al., 2007; et al., 2010) (G A) , - k , 26 . A . A KEGG (:// / k), (et al., 2011; et al., 2014; B et al., 2016). G k .

G ( ) G A , - - (LD) (A , 2008) k (et al., 2010). , C - (C) (, 2004; A , 2008).

(. ,) , 2004; K et al., 2008; A , 2008). C - , , (et al., 2010; et al., 2014) (A , 2008; H et al., 2011 ,).

Materials and methods

Participants

(G 2013) C , C , . C H (80.1% , 18.66 ± 0.90) . 15 . A 100 . - , , , , behavioral test; D et al., 2006; G et al., 1582 , 5 , . A 1317 . - , ( ). A (. <50, = 30.58, D = 5.35) - A (1971; et al., 1999) (. <50, = 33.3, D = 6.31) - - D (1965; et al., 1999), (51, 51, 53, 53, 53, 54, 54, 55 59,) (51, 51 56,) . G 12 . D H E C C , .

The behavioral test

G et al. (2016), D et al (2006) (et al., 2009; et al., 2013). A , . , - .

(.) , (.) (K 20 50') (.) (L 30 50'), . . F , . F , (K 80 100' *vs* K 100 40%'). - . . E 48 (16 , 16 - 16), . D et al. (2006). . A (500:1) . G et al. (2016) . - (<75%, - =57.9%±17.6%; 1317 , =90.5%±6.5%) . (4.44%±1.75%) 1317 (14.51%±0.34%), $t_{(1580)} = 9.16$, $P < 0.001$. F ( ). (=1591 , D=551) (=1601 , D=544) (=1776 , D=353 ; - =1872 , D=376), $t_{(1580)} = 6.639$, $P < 0.001$ $t_{(1580)} = 9.375$, $P < 0.001$, .

Genotyping

- D A kG 610L A I . I H -8 1 C I .

Gene selection and preprocessing

- K E G G (KEGG; :// /), ( ) (*TH*), -L- - (*DDC*), - (VMAT2) , ( ) (DRD1–5), ( ) - (*DAT1*,

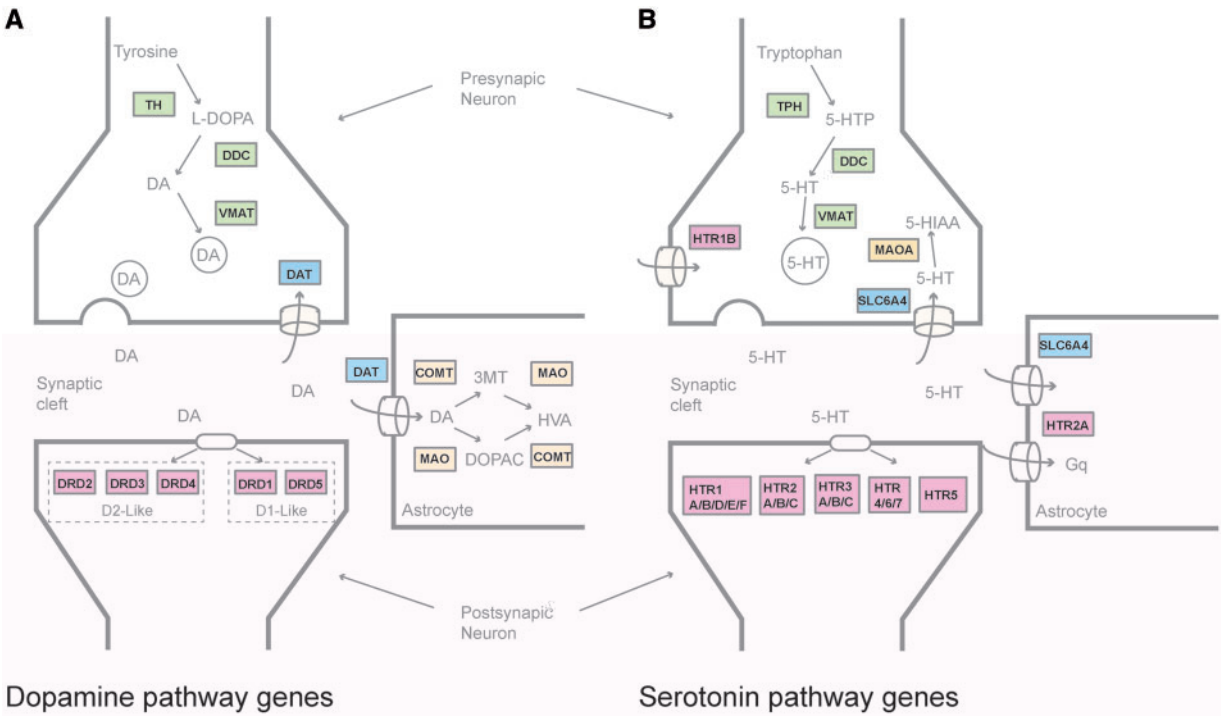


Fig. 1. D . D (A) (B) - , - , . A . A K E G G (KEGG; :// /K); , *et al.*, 2014.

SLC6A3), -O- (*COMT*), - A (*MAOA*) B (*MAOB*) (, *et al.*, 2011; *et al.*, 2014) ( ) 5- - (*TPH 1* *TPH2*) , ( ) 5- (*HTR1A/B/D/E/F*, *HTR2A/B/C*, *HTR3A/B/C/D/E*, *HTR4*, *HTR5A/B*, *HTR6-7*, *HTRA1-4*) , ( ) - - (*SLC6A4*) (B *et al.*, 2016) (F 1). *HTR3D* *HTR3E* K (*et al.*, 2003; B G E E , :// . /). *DRD4*, *DRD5*, *HTR1A/B/D/F*, *HTR5B*, *HTRA2* *HTRA4* G A LI K (*et al.*, 2007; *et al.*, 2014): ( ) , H E 10^{-4} (AF) 0.1 0.05; ( ) 0.05 ( ) . - , G A (D) - LI K (*et al.*, 2006; *et al.*, 2007) . LI K (*et al.*, 2007) (*et al.*, 2006). F 19 .

Principle component analysis

A C :// . - . LD , K . G A (CA) LD (A , 2008). , , (C) 90% (A , 2008; *et al.*, 2014). (LD), C . C LD (D *et al.*, 2001; *et al.*, 2001; G *et al.*, 2002), (1). F 6 90.2% DDC 47 G A .

Gene-behavior association analysis

-F (. K) (A , 2008; H *et al.*, 2011 ,). -F F .

Table 1.

F	G	C	%	R^2	A	R^2	Partial-F	p_{unc}	p_{perm}	p_{emp}
D	*TH*	2	2	100	0.001	<0.001	0.712	0.491	0.484	0.485
	DDC	47	6	90	0.010	0.006	2.329	0.031*	0.031*	0.038*
	VMAT2	17	9	90	0.003	<0.001	0.501	0.875	0.878	0.862
/	*DAT1*	16	6	91	0.005	<0.001	1.027	0.406	0.408	0.466
C	*COMT*	18	6	91	0.012	0.009	2.648	0.015*	0.014*	0.027*
	MAOA	6	3	90	0.003	<0.001	1.143	0.331	0.325	0.346
	MAOB	37	5	92	0.005	0.002	1.367	0.234	0.232	0.293
	DRD1	1	1	100	0.000	<0.001	0.097	0.756	0.756	0.780
	DRD2	16	8	90	0.004	<0.001	0.721	0.673	0.680	0.770
	DRD3	41	12	92	0.014	0.006	1.617	0.081	0.081	0.099
	TPH1	2	2	100	0.001	<0.001	0.719	0.487	0.476	0.477
	TPH2	6	4	93	0.002	<0.001	0.519	0.721	0.718	0.753
	SLC6A4	8	3	90	0.006	0.004	2.795	0.039*	0.038*	0.037*
	HTR1E	16	6	91	0.007	0.003	1.545	0.160	0.158	0.199
	HTR2A	44	12	90	0.013	0.005	1.492	0.120	0.121	0.123
	HTR2B	3	2	100	0.001	<0.001	0.596	0.551	0.551	0.519
	HTR2C	22	8	90	0.006	<0.001	0.920	0.499	0.499	0.517
	HTR3A	4	4	100	0.001	<0.001	0.364	0.834	0.831	0.833
	HTR3B	22	6	90	0.001	<0.001	0.228	0.968	0.967	0.970
	HTR3C	2	1	99	0.000	<0.001	0.124	0.725	0.724	0.677
	HTR4	46	14	91	0.015	0.005	1.422	0.135	0.136	0.075
	HTR5A	7	4	92	0.006	0.003	1.866	0.114	0.114	0.118
	HTR6	2	1	100	0.000	<0.001	0.000	0.990	0.992	0.982
	HTR7	22	6	93	0.006	0.002	1.316	0.247	0.242	0.301
	HTRA1	34	9	91	0.007	<0.001	0.974	0.460	0.456	0.441
	HTRA3	19	5	92	0.004	0.001	1.133	0.341	0.356	0.370

C , ; % , C ; p_{unc}, P F- ; p_{perm}, P p_{emp}, P

* P < 0.05.

-F ’ ( ) , (*Principle component analysis*) E F , -F (1) (H *et al.*, 2011). *k* ( )– ( ):

$$Fk, df(full) = \frac{RSS(reduced) - RSS(full)}{df(reduced) - df(full)} / \frac{RSS(full)}{df(full)} \quad (1)$$

A A/B C (K, 2003), = 0.62% ± 0.08% (E) (1). A ,

(COMT, SLC6A, *DDC* MAOB; *Gene-behavior association results*). , , . C (COMT: P = 0.028, SLC6A4: P = 0.038, *DDC*: P = 0.070 , MAOB: P = 0.029), .

Permutation tests

C (H *et al.*, 2011 ; *et al.*, 2014). (B , 2001; K , 2004; C *et al.*, 2008; G - *et al.*, 2014), (. P). (C , 2001).

Empirical tests

P -F
G A
(et al., 2014). E p A
( )
( )
. A
2).

Protein–protein interactions

K ’
H I G 10 (
I G /
(://
K K et al., 2015)
–
( )
( )
, -
, -
, .
’
(H et al.,
1999; G K , 2003). I K
(B et al., 2004). ,
-
K
. C ’ -
I G 10, CL
(=4),
(://
H , 2006),
(F 1).

SNP–SNP interactions

CA
. F
CA
90%
(3).

Results

Behavioral results

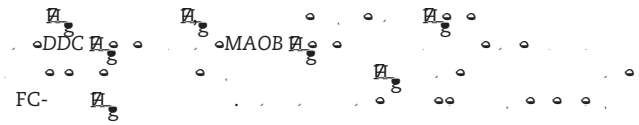
C (D et al., 2006;
et al., 2009; et al., 2013; G et al., 2016),
K K

: 59.75%±0.47% (E) vs 45.23% ± 0.46%
$t_{(1316)} = 42.08$, $P < 0.0001$. K
(. K
, . I
(F , 1990; H
2010), 2 (: F vs)×2 (vs
) (A A) -
$F_{(1, 1315)} = 15.587$, $P < 0.001$, $F_{(1, 1314)} = 14.701$, $P < 0.001$,
. I ,
, -
$\beta = -0.052$, $t = -1.903$, $P = 0.057$. (, 2009;
et al., 2011).
.

Gene-behavior association results

C
COMT (G
et al., 2016), -
COMT 0.9%
, R^2
= 0.009, -F = 2.648, P = 0.015. ,
et al. (2009) 5-H L -
, ,
SLC6A4 0.4%
R^2 = 0.004, -F = 2.795, P = 0.039. I ,
DDC
, -
R^2 = 0.006, -F = 2.329, P = 0.031, -
0.6%
K (1).
, -
. A C
10 000
(,
(1), COMT: P = 0.014,
SLC6A4: P = 0.038, DDC: P = 0.031.
G
B (FD)
(D).
K
G A
. D
(1), ,
(1), COMT: P = 0.027, SLC6A4:
P = 0.037, DDC: P = 0.038.
B MAOA/B -

MAOB -
2.8%
R^2 =0.028,
-F = 2.499, P = 0.031.
(P = 0.038) (P = 0.043).
MAOA
CA - , - ,
- H ,
DDC
SLC6A4 ,
COMT MAOB
(3).
I G
(*COMT*, *SLC6A4*, *DDC* *MAOB*) -
(F 1).
G CA -
(H , 1975),
F 2
( ). F COMT 4680
, LD


DDC
MAOB
FC-

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K A., K , K., H , J., *et al.* (2007). A A -A . *Neuropsychobiology*, **56**(56), 191 6.

K -K B. ., G , J., . . (2007). - C , H 1B, , . *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*

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