

Genome Wide Sequencing Compared to Candidate Gene Association Studies for Predisposition to Substance Abuse a Subset of Reward Deficiency Syndrome (RDS): Are we throwing the Baby Out with the Bathwater?

Kenneth Blum, Eric R. Braverman, Florian Kreuk, Kristina Dushaj, Mona Li, Debmaya Barh, and Marlene Oscar-Berman

'HSDUWPHQW RI 3V\FKLDWU\ OF.QLJKW %UDLQ ,QVWLWXWH 8QLYHUVLW\ RI)ORULGD &ROOHJH RI OHGLF
'HSDUWPHQW RI &OLQLFDO 1HXURORJ\ 3\$7+)RXQGDWLRQ 1HZ <RUN 1< 86\$
,QVWLWXWH RI ,QWHJUDWLYH 2PLFV DQG \$\$\$OLHG %LRWHFKQRORJ\ 1RQDNXUL 3XUED OHGLQLSXU :HVV
'HSDUWPHQW RI +ROLVWLF OHGLFLQH 1DWLRQDO ,QVWLWXWH IRU +ROLVW \$GGLFWLRQ 6WXGLHV 1RUW
+XPDQ ,QWHJUDWHG 6HUFLFHV 8QLW 8QLYHUVLW\ RI 9HUPRQW &HQWHU IRU &OLQLFDO 7UDQVODWLRQD
'RPLQLRQ 'LDJQRVWLFV //& 1RUWK .LQJVWRZQ 5, 86\$
'HSDUWPHQWRI \$GGLFWLRQ 5HVHDFK 7KHUHS\ ODOLX %HDFK 5HFHYHU\ &HQWHU ODOLX %HDFK &\$
,*(1(//& \$XVWLQ 7H[DV 86\$
5'6ROXWLRQV //& /D -ROOD &DOLIRUQLD 86\$
'HSDUWPHQWV RI 3V\FKLDWU\ 1HXURORJ\ DQG \$QDWRP\ 1HXURELORJ\ %RVWRQ 8QLYHUVLW\ 6FKRR
86\$

Corresponding author: .HQQHWK %OXP 'HSDUWPHQW RI 3V\FKLDWU\ OF.QLJKW %UDLQ ,QVWLWXWH 8
[@P@L@H@Q@H#@J@P@D@L@O@F@R@P](#)

Received date: ODUFK Accepted date: Published date: \$\$ULO

Copyright: %OXP . HW DO 7KLV LV DQ RSHQ DFFHVV DUWLFOH GLVWULEXWHG XQGHU WKH W
XVH GLVWULEXWLRQ DQG UHSURGXFWLRQ LQ DQ\ PHGLXP SURYLGHG WKH RULJLQDO DXWKRU D

Abstract

,Q %OXP 1REOH DQG DVVRFLDWHV XWLOL]HG D FDQGLGDWH DSSURDFK
DVVRFLDWLRQ ZLWK VHYHUH DFRKROLVP WKDW ZDV SXEOLVKHG LQ -\$O\$ 7
UHSDUG FLUFXLWU\ SURSRVHG DV WKH †EUDLQ 5HZDUG &DVFDGH. ,PSDLUP
VHHNLQJ EHKDYLRU 2YHU WKH ODVW ILYH \HUV QHZHU DQG PRUH VRSKLVV
ZKROH JHORPH VHTXHQFLQJ DV ZHOO DV H[RPH VHTXHQFLQJ :KLOH WKHU
DSSURSULDWH DSSURDFKHV WR GLVVHFWLQJ D YHU\ FRPSOH[GLVRUGHU NQF

VXSSRUWV HDUOLHU QRQ JHQHWLF FRQFHSWV RI DGGLFWLRQ LQ SV\FKLDWULF PHGLFLQH > @

:H DUH FRJQLJDQW WKDW WKHUH LV FRQWURYHUV\ UHODWHG WR WKH LVVXH RI LPSRUWDQFH RI ERWK *:\$6 DQG :(6 DQDO\WLFDO DSSURDFKHV UHODWLYH WR FDQGLGDWH DVVFLDWLRQ DQG OLQNDJH VWXGLHV WR XQUDYHO FRQWULEXWLRQ VSHFLILF JHQHV DQG DVVFLDWHG SRO\PRUSKLVV WR DGGLFWLRQ OLDELWLW\ 2XU ODERUDWRU\ LQ WKH ODWH dV UHDOLJLQJ WKH FRPSOH[LW\ RI WKH SUREOHP RI ERWK YXOQHUDELOLW\ DQG UHVLOLHQFH IRU ULVN RI GUXJ DEXVH DQ RWKHU EHKDYLRUDO DGGLFWLRQV GHFLGHG WR DQDO\JH FDQGLGDWH JHQHV EDV RQ D WKHRUHWLFDO PRGHO ZH GHYHORSHG DQG VXEVHTXHQWO\ SXEOLVKHG DQG LGHQWLILHG DV WKH f%UDLQ 5HZDUG &DVFDGHg > @ 2XU LQLWLDO DSSURDFK XWLOLJLQJ WKLV fEOXH SULQW RI UHZDUGg LQYROYHG DVVFLDWLRQ UDWKHU W OLQNDJH DQDO\VLV EHFDXVH /DQGHU HW DO > @ DUJXHG DJDLQVW OLQNDJH DQDO\VLV IRU FRPSOH[GLVRUGHUV OLNH GUXJ DGGLFWLRQ LQVWHDG RI OLQNDJH DQDO\VLV DV SUHYLRXVO\ DFFRPSOLVKHG ZLWK RQH JHQH a RQH GLVHDVH 2*2'

,PSRUWDQW DGYDQFHV KDYH EHHQ PDGH RYHU WKH ODVW WZR GHFDGHV FRQFHUQLQJ f3V\FKDWULF *HQHWLFV g &HUWDLQO\ VXEVWDQWLDO JHQHWLF FRQWULEXWLRQV WR DGGLFWLRQ OLDELWLW\ DUH QRZ VXSSRUWHG E\ HDUOLHU VWXGLHV DQG PRUH UHFHQWO\ OLQNDJH FDQGLGDWH DVVFLDWLRQ DQG *:\$6 VWXGLHV \$QLPDO VWXGLHV LQLWLDOO\ IRFXVHG XSRQ JHQHV WKDW WDUJHW PDMRU GUXJV RI DEXVH PHFKDQLV RI DFWRQ 0DQ\ RI WKHVH VWXGLHV ZHUH VXFHVVIXO LQ WKH LGHQWLILFDWLRQ RI TXDQWLWDWLYH WUDLW ORFL LQFOX DVVFLDWLRQ RI FKURPRVPO '5' JHQH DQG HWKDQRO EHKDYLRUDO UHVSQRVHV > @ DV ZHOO DV RWKHU UHZDUG JHQHV LQFOXGLQJ VHURWRQLQ RSLRLGV DQG *\$%\$ > @ 0RVW RI WKHVH DQG PDQ\ RWKHU VWXGLHV KDYH LGHQWLILHG JHQH SURWHLQV WKDW DIIHFU UHVSQRVHV WR GUXJV RI DEXVH > 3DUDOOHO WR WKHVH DQLPDO VWXGLHV KXPdq JHQHWLF UHVHDFK H[SORGHG R WKH ODVW ILYH \HDUV WR LQH[SHQVLYHO\ GHWHFW JHQHWLF YDULDWLRQ LQ KXPdq JHQRP 7KH HUD RI JHQRP VHTXHQLQJ EHJDQ ZLWK WKH LGHQWLILFDWLRQ RI VLQJOH QXFOHRWLGH SRO\PRUSKLVV 613V XWLOLJLQJ JHQH FKLSV 9HU\ UHFHQWO\ ZH DUH DOVR XWLOLJLQJ :(6 ZKLFK XWLOLJHV KLJK WKURXJKSXW VHTXHQLQJ WR LGHQWL\ WKH PROHFODU DUUDQJHPHQW RI '1\$ EDVH SDLUV VSHFLILQJ WKH FRGLQJ UHJLRQV RI D SHUVRQdV JHQRP DOVR UHIHUHG WR DV WKH H[RPH :KLOH WKLV LV H[FLWLQJ LW PD\ QRW KDYH FOLQLFDO XWLOLW\ EHFDXVH WKH H[RPH RQO\ FRPSULVHV DERXW RI WKH HQWLUH JHQRP > @ +RZHYHU ZKLOH WKH H[RPH UHSUHVHQWV a RI WKH JHQRP RI FXUUHQWO\ GHVFULEHG GLVHDVH DOWHUDWLRQV DUH ORFDW ZLWKLQ WKH FRGLQJ UHJLRQV WKLV 7KH SUXGHQW DUJXPHQW KHUH LV WKDW SV\FKLDWULF GLVHDVH PD\ RYHU UHSUHVHQWHG ZLWKLQ WKH a RI DOWHUDWLRQV RXWVLGH RI WKH FRGLQJ UHJLRQ UHJXODWRU\ HOHPHQWV HSLJHQHWLF IDFWRUV ZKLFK DUH PRUH RIWHQ DVVFLDWHG ZLWK PXOWL IDFWRUV GLVHDVHV

&RPSDUHG WR DQ HQRUPRXV OLWHUDWXUH RQ FDQGLGDWH JHQH DQDO\VLV VWXGLHV WKHUH LV FXUUHQWO\ D SDXFLW\ RI *:\$6 :(6 VWXGLHV UHOHYDQW WR DGGLFWLRQ OLDELWLW\ VWXGLHV \$ FRPPHQWU\ E\ +DOO HW DO > @ IURP 1,'\$ DQG RWKHUV KDYH DUJXHG WKDW FDQGLGDWH JHQH DQDO\VLV PD\ EH ZURQJ +RZHYHU WKH\ GR VXJJHVW WKDW IURP PDQ\

VLJQLILFDQWO\ DVVRFLDWHG ZLWK WKH YDULDQFH 7KH\ VXJJHVWHG WKDW L
RQO\ 613V RI JHQHV ZLWK WKHRUHWLFDQ LPSRUWDQFH DUH LQYHVWLJDWHG WKI
UHSOLFDEOH HIIHFWV DUH PRUH OLNHO\ WR EH LGHQWLILHG IXUWKHUPRUH I
VFRULQJ DSSURDFK HYDOXDWLQJ WKH DJJUHJDWH RI WKH KLJKHVW DVVRFLDWH
613V LV XWLOL]HG WKDQ PRUH UHSOLFDEOH HIIHFWV FDQ EH LGHQWLILHG WKD
ZRXOG EH UHYHDOHG LQ LQGLYLGXDO 613 OHYHO VWXGLHV \$ORQJ ZLWK WKHVH
SUHFDXWLRQV ZH DOVR SURSRVH WKH XWLOL]DWLRQ RI fVXSHU FRQWUROVg W
HOLPLQDWH FURVV FRQWDPLQDWLRQ RI KDYLQJ D FRQWURO SKHQRW\SH WKDW DQ
FDUULHV WKH DVVRFLDWHG GLVRUGHU HVSHFLDOO\ ZKHQ FRQVLGHULQJ WKH
FRPSOH[QDWXUH RI 5'6 ,Q RQH VWXG\ ZH IRXQG WKDW ZKLOH WKH ULVN
DOOHOH RI WKH '5' 7DT \$ LQ RYHU QRQ VFUHHQHGH SRSXODWLRQ
FRQWUROV ZDV VXSHU FRQWUROV VFUHHQHGH IRU DOO 5'6 EHKDYLRUV LQ

