The American Journal of Human Genetics

Supplemental Data

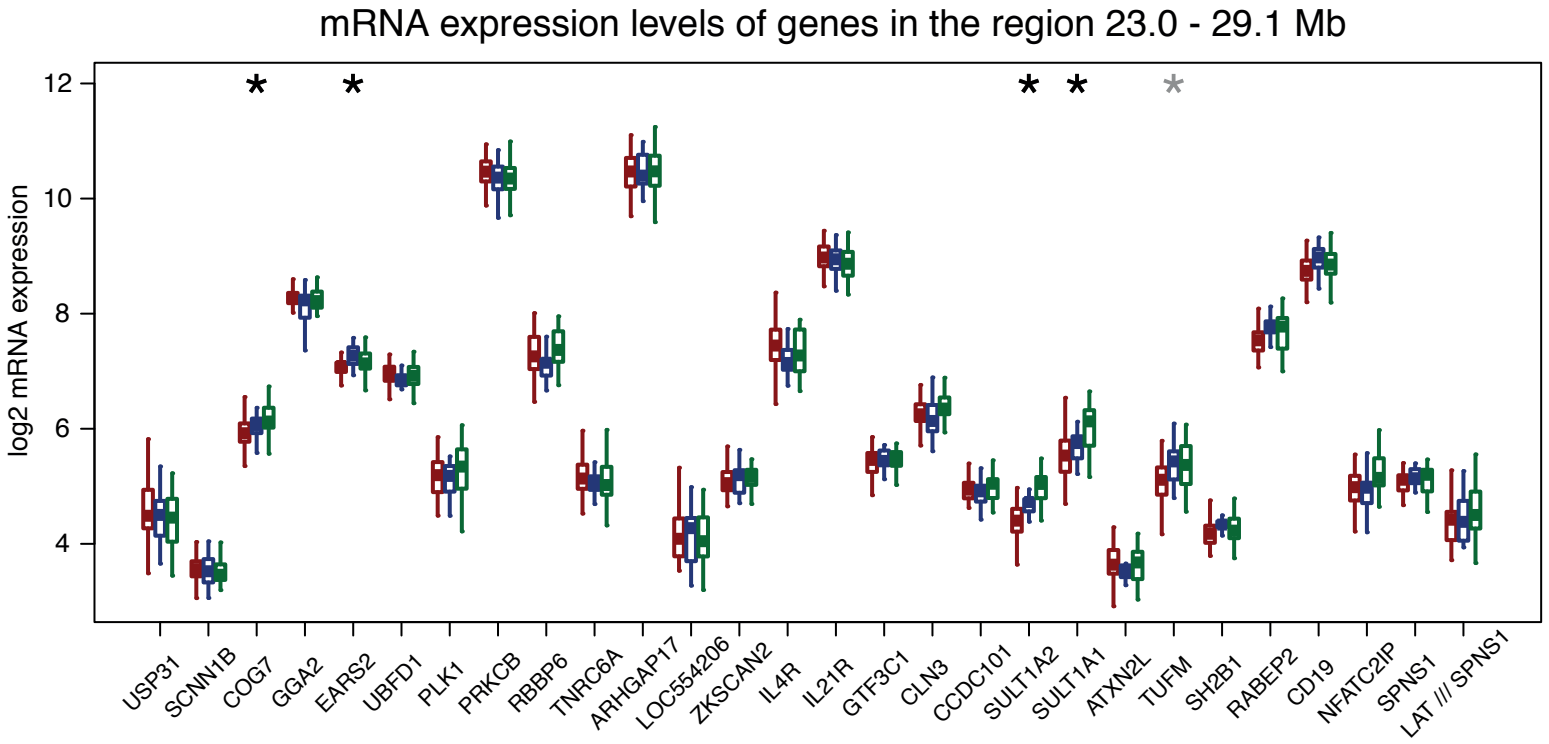
A Potential Contributory Role for Ciliary Dysfunction in the 16p11.2 600 kb BP4-BP5 Pathology

Eugenia Migliavacca, Christelle Golzio, Katrin Männik, Ian Blumenthal, Edwin C. Oh, Louise Harewood, Jack Kosmicki, Maria Nicla Loviglio, Giuliana Giannuzzi, Loyse Hippolyte, Anne M. Maillard, Ali Abdullah Alfaiz, 16p11.2 European Consortium, Mieke M. van Haelst, Joris Andrieux, James F. Gusella, Mark J. Daly, Jacques S. Beckmann, Sébastien Jacquemont, Michael E. Talkowski, Nicholas Katsanis, and Alexandre Reymond

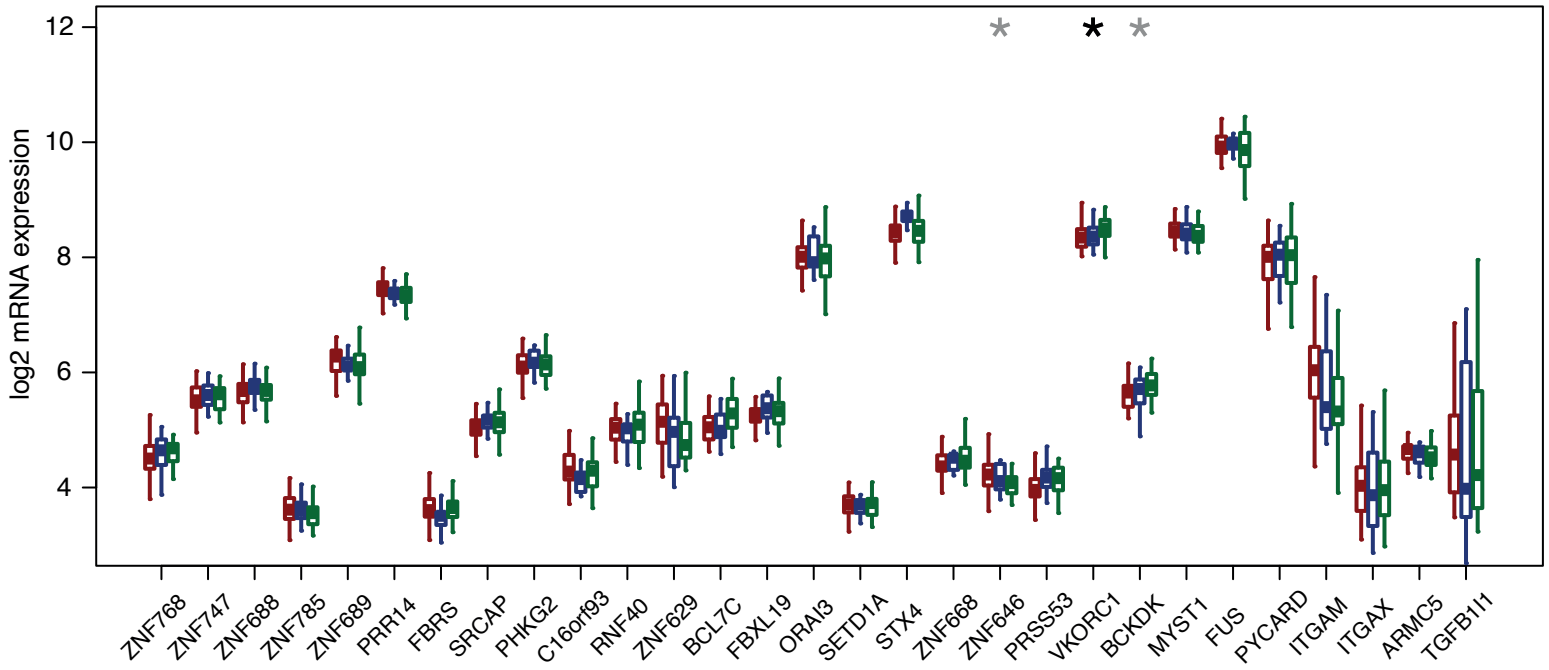
Supplementary Figure S1: Influence of the CNV on expression levels of neighboring genes.

Relative expression levels measured by microarrays in deletion (n=50) and duplication (n=31) carriers (red and green, respectively), and control LCLs (n = 17, blue) of genes distal **(A)** and proximal **(B)** to the 16p11.2 BP4-BP5 interval. A similar number of genes are shown for both regions but the telomeric interval is 5.3-fold larger than the centromeric one. Black and grey asterisks mark genes associated with the 16p11.2 CNV using a dosage effect model and moderated t-statistics at FDR≤1% and between <1% and ≤5%, respectively.

A

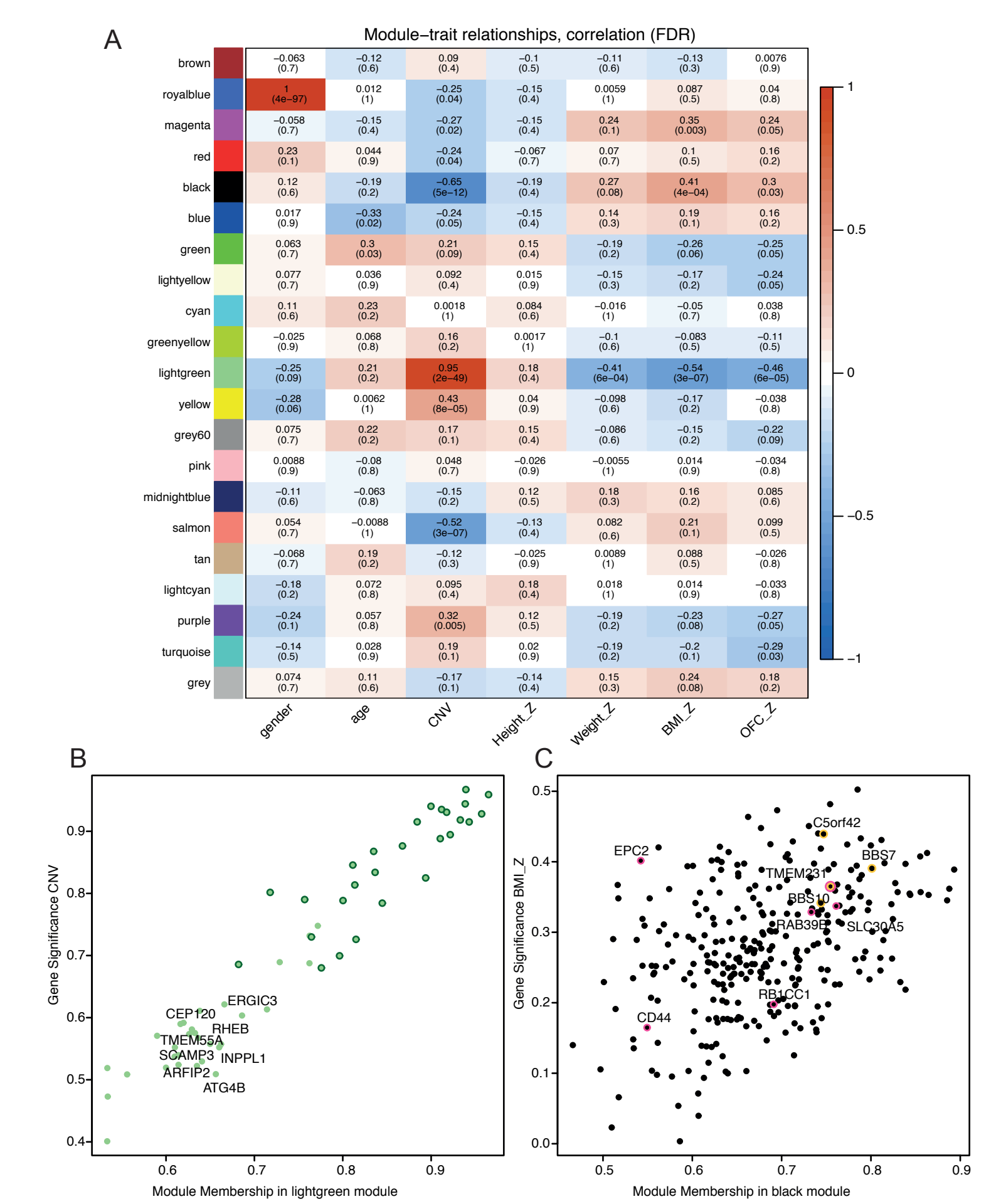

mRNA expression levels of genes in the region 23.0 - 29.1 Mb
log2 mRNA expression
12
10
8
6
4
USP31
SCNN1B
COG7
GGA2
EARS2
UBFD1
PLK1
PRKCB
RBBP6
TNRC6A
ARHGAP17
LOC554206
ZKSCAN2
IL4R
IL21R
GTF3C1
CLN3
CCDC101
SULT1A2
SULT1A1
ATXN2L
TUFM
SH2B1
RABEP2
CD19
NFATC2IP
SPNS1
LAT /// SPNS1

B


mRNA expression levels of genes in the region 30.35 - 31.5 Mb
log2 mRNA expression
12
10
8
6
4
ZNF768
ZNF747
ZNF688
ZNF785
ZNF689
PRR14
FBRS
SRCAP
PHKG2
C16orf93
RNF40
ZNF629
BCL7C
FBXL19
ORAI3
SETD1A
STX4
ZNF668
ZNF646
PRSS53
VKORC1
BCKDK
MYST1
FUS
PYCARD
ITGAM
ITGAX
ARMC5
TGFB1I1

Supplementary Figure S2: 16p11.2 transcriptome expression modules and traits.

Relationships between weighted gene co-expression module (each color coded line) and gender, age, number of copies of the 16p11.2 CNV (CNV) and Z scores for height, weight, BMI and HC (OFC). Both the Pearson correlation coefficient (top) and FDR (bottom in bracket) estimated as Benjamini-Hochberg adjusted p-value are indicated. The "light-green module" (51 genes) is anticorrelated with weight, BMI and HC and includes all 22 imbalanced 16p11.2 genes expressed in LCLs. The "black" module (264) groups genes involved in RNA biosynthesis/regulation, gene expression/transcription and cilium morphogenesis. The "purple" and "salmon" modules are enriched in genes regulating RNA splicing (191 and 131 genes), while gene expression regulation by chromatin modification/organization characterizes the "yellow module" (444 genes including *CEP290*). Among these, the purple module is also anticorrelated with HC. **(B)** "Light-green" module membership (defined as $k_{E,i}^{(q)} = cor(x_i, E^{(q)})$ where x_i is the expression level for gene i and $E^{(q)}$ is the eigengene for the module q light green) and CNV-correlation gene significance $GS.CNV_i=|cor(x_i,CNV)|$ (Pearson=0.96; *P*=4.4e-32). Each gene is represented by a light-green disk. Disks denoting genes mapping within the 16p11.2 BP4-BP5 interval are circled by a dark green ring, while genes important for vesicle trafficking, Golgi-apparatus, centrosome regulation, and phosphoinositide metabolism are annotated. **(C)** "Black" module membership and BMI gene significance (Pearson = 0.4; *P*=5.0e-13). Each gene is represented by a black disk. Known ASD and BBS/JBTS genes are labeled and circled by yellow and magenta rings, respectively.


A
Module−trait relationships, correlation (FDR)
brown −0.063 (0.7) −0.12 (0.6) 0.09 (0.4) −0.1 (0.5) −0.11 (0.6) −0.13 (0.3) 0.0076 (0.9)
royalblue 1 (4e−97) 0.012 (1) −0.25 (0.04) −0.15 (0.4) 0.0059 (1) 0.087 (0.5) 0.04 (0.8)
magenta −0.058 (0.7) −0.15 (0.4) −0.27 (0.02) −0.15 (0.4) 0.24 (0.1) 0.35 (0.003) 0.24 (0.05)
red 0.23 (0.1) 0.044 (0.9) −0.24 (0.04) −0.067 (0.7) 0.07 (0.7) 0.1 (0.5) 0.16 (0.2)
black 0.12 (0.6) −0.19 (0.2) −0.65 (5e−12) −0.19 (0.4) 0.27 (0.08) 0.41 (4e−04) 0.3 (0.03)
blue 0.017 (0.9) −0.33 (0.02) −0.24 (0.05) −0.15 (0.4) 0.14 (0.3) 0.19 (0.1) 0.16 (0.2)
green 0.063 (0.7) 0.3 (0.03) 0.21 (0.09) 0.15 (0.4) −0.19 (0.2) −0.26 (0.06) −0.25 (0.05)
lightyellow 0.077 (0.7) 0.036 (0.9) 0.092 (0.4) 0.015 (0.9) −0.15 (0.3) −0.17 (0.2) −0.24 (0.05)
cyan 0.11 (0.6) 0.23 (0.2) 0.0018 (1) 0.084 (0.6) −0.016 (1) −0.05 (0.7) 0.038 (0.8)
greenyellow −0.025 (0.9) 0.068 (0.8) 0.16 (0.2) 0.0017 (1) −0.1 (0.6) −0.083 (0.5) −0.11 (0.5)
lightgreen −0.25 (0.09) 0.21 (0.2) 0.95 (2e−49) 0.18 (0.4) −0.41 (6e−04) −0.54 (3e−07) −0.46 (6e−05)
yellow −0.28 (0.06) 0.0062 (1) 0.43 (8e−05) 0.04 (0.9) −0.098 (0.6) −0.17 (0.2) −0.038 (0.8)
grey60 0.075 (0.7) 0.22 (0.2) 0.17 (0.1) 0.15 (0.4) −0.086 (0.6) −0.15 (0.2) −0.22 (0.09)
pink 0.0088 (0.9) −0.08 (0.8) 0.048 (0.7) −0.026 (0.9) −0.0055 (1) 0.014 (0.9) −0.034 (0.8)
midnightblue −0.11 (0.6) −0.063 (0.8) −0.15 (0.2) 0.12 (0.5) 0.18 (0.3) 0.16 (0.2) 0.085 (0.6)
salmon 0.054 (0.7) −0.0088 (1) −0.52 (3e−07) −0.13 (0.4) 0.082 (0.6) 0.21 (0.1) 0.099 (0.5)
tan −0.068 (0.7) 0.19 (0.2) −0.12 (0.3) −0.025 (0.9) 0.0089 (1) 0.088 (0.5) −0.026 (0.8)
lightcyan −0.18 (0.2) 0.072 (0.8) 0.095 (0.4) 0.18 (0.4) 0.018 (1) 0.014 (0.9) −0.033 (0.8)
purple −0.24 (0.1) 0.057 (0.8) 0.32 (0.005) 0.12 (0.5) −0.19 (0.2) −0.23 (0.08) −0.27 (0.05)
turquoise −0.14 (0.5) 0.028 (0.9) 0.19 (0.1) 0.02 (0.9) −0.19 (0.2) −0.2 (0.1) −0.29 (0.03)
grey 0.074 (0.7) 0.11 (0.6) −0.17 (0.1) −0.14 (0.4) 0.15 (0.3) 0.24 (0.08) 0.18 (0.2)
gender
age
CNV
Height_Z
Weight_Z
BMI_Z
OFC_Z
1
0.5
0
−0.5
−1
B
Gene Significance CNV
Module Membership in lightgreen module
ERGIC3
CEP120
RHEB
TMEM55A
SCAMP3
INPPL1
ARFIP2
ATG4B
C
Gene Significance BMI_Z
Module Membership in black module
C5orf42
EPC2
BBS7
TMEM231
BBS10
RAB39B
SLC30A5
RBICC1
CD44