

## Supplementary note - *de novo* mutation validation

We classified the inheritance status per variant as *de novo*, inherited, false positive or unclear, using a maximum likelihood approach. The probability of the variant being *de novo* in the proband was computed as:

$$\log(P(DNM)) = \log\left(P(Alt_{proband} | Het_{proband})\right) + \log\left(P(Alt_{mat} | Ref_{mat})\right) + \log\left(P(Alt_{pat} | Ref_{pat})\right)$$

$$P(Alt_{proband} | Het_{proband}) \sim Binom(\theta = 0.5)$$

$$P(Alt_{mat} | Ref_{mat}) \sim Poiss(\lambda_\epsilon)$$

$$P(Alt_{pat} | Ref_{pat}) \sim Poiss(\lambda_\epsilon)$$

With  $Alt_{proband}$ ,  $Alt_{mat}$ ,  $Alt_{pat}$  being the count of alternative alleles in the proband and parental samples and  $\lambda_\epsilon$  being an estimate of the sequencing error rate (0.003).

The probability of the variant being inherited was computed as:

$$\log(P(INH)) = \log\left(P(Alt_{proband} | Het_{proband})\right) + \log\left(P(Alt_{mat} | Het_{mat})\right) + \log\left(P(Alt_{pat} | Ref_{pat})\right)$$

or

$$\log(P(INH)) = \log\left(P(Alt_{proband} | Het_{proband})\right) + \log\left(P(Alt_{mat} | Ref_{mat})\right) + \log\left(P(Alt_{pat} | Het_{pat})\right)$$

or

$$\log(P(INH)) = \log\left(P(Alt_{proband} | Het_{proband})\right) + \log\left(P(Alt_{mat} | Het_{mat})\right) + \log\left(P(Alt_{pat} | Het_{pat})\right)$$

$$P(Alt_{mat} | Het_{mat}) \sim Binom(\theta = 0.5)$$

$$P(Alt_{pat} | Het_{pat}) \sim Binom(\theta = 0.5)$$

And finally the probability of the variant site being a false positive call was computed as:

$$\log(P(FP)) = \log\left(P(Alt_{proband} | Ref_{proband})\right) + \log\left(P(Alt_{mat} | Ref_{mat})\right) + \log\left(P(Alt_{pat} | Ref_{pat})\right)$$

$$P(Alt_{proband} | Ref_{proband}) \sim Poiss(\lambda_\epsilon)$$

The allelic depths used to compute these probabilities were rescaled to represent the expected number of input template DNA molecules present in the PCR amplification.

## PhenIcons

The pages below display PhenIcons for the 94 genes exceeding genome-wide significance. Each page has up to three parts. The left hand half of each page provides visual representations of the gene name, the number of individuals with de novo mutations in that gene, sex ratio, gestation (in weeks), anthropometric data (z scores for birth weight, height, weight and occipital-frontal head circumference (ofc)) and developmental milestones (in months for attainment of social smile, sitting unaided, walking unaided and first clear words) from individuals with DNMs in the gene. The scaled cartoon figure shows the height weight and OFC with the colour of the head, trunk and height graded with grey representing a z score of 0 and red increasing negative and green increasing positive scores. For each metric a scatter plot is given above the indicator bar representing the measurement for each individual. Where more than four values are available two density plots are given below the bar the grey representing the data for all individuals in the 94-gene set and coloured the density plot for the gene in question. For the z score data mean values are provided and for the developmental data median values are given above the bar. The top panel on the left hand side of the page summarises the key Human Phenotype Ontology (HPO) terms for each gene. The HPO terms in the individuals were selected, including the ancestral terms. Terms that are rarer in the 4,293 individuals rank higher, adjusted by the number of individuals with DNMs who had the term. The heatmaps are shaded by the number of individuals with each term. The heatmaps exclude terms that rank lower than a descendant term (excluding more general terms if a more specific term occurred first), and terms where fewer than 25% of individuals had the term, or in genes with less than 8 individuals, terms with fewer than two individuals. The bottom panel on the right hand half of the page summarises the facial photographs from individuals with DNMs in each gene (see Methods). The averaged face images are only available for selected genes, based on the availability of sufficient high-quality facial photographs of individuals for each gene.

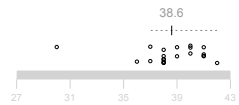
# ADNP

n = 21

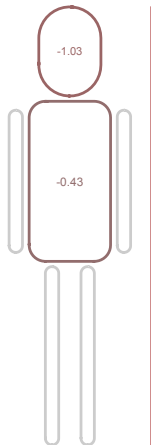
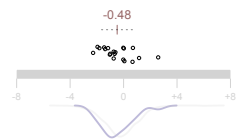
sex ratio



gestation (w)



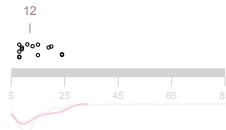
birth weight (z)



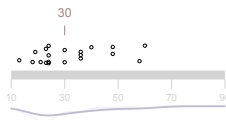
social smile (m)



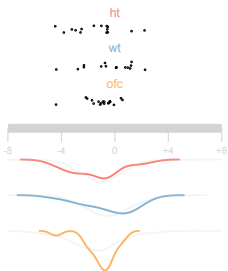
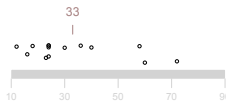
sat unaided (m)



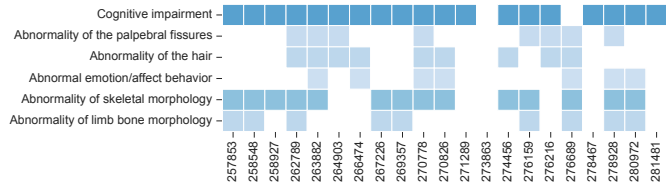
walked unaided (m)



first words (m)



## recurrent HPO terms used in ADNP cases



aggregate face  
from 12  
photographs



WWW.NATURE.COM/NATURE 3

# AHDC1

n = 8

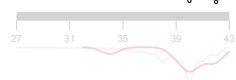
sex ratio

0.62



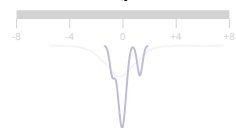
gestation (w)

39.8

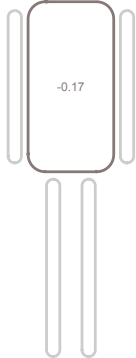


birth weight (z)

0.04



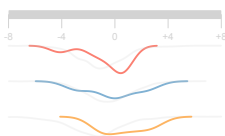
0.68



ht

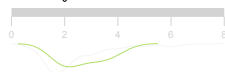
wt

ofc



social smile (m)

2.5



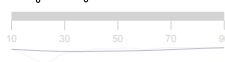
sat unaided (m)

15



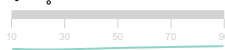
walked unaided (m)

44.5

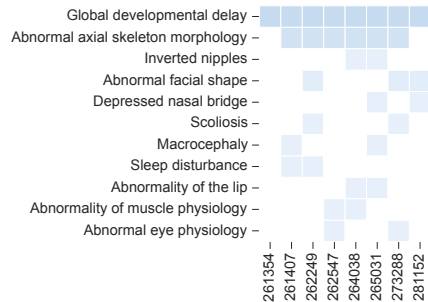


first words (m)

30



recurrent HPO terms used in AHDC1 cases



# ALG13

n = 2

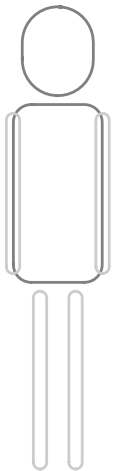
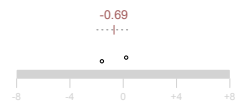
sex ratio



gestation (w)



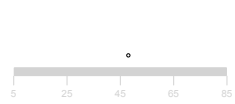
birth weight (z)



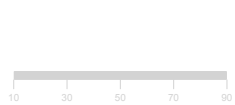
social smile (m)



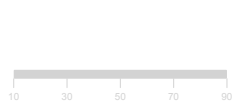
sat unaided (m)



walked unaided (m)



first words (m)



Abnormality of body height		
Seizures		
Cognitive impairment		
	258986	263083

# ANKRD11

n = 34

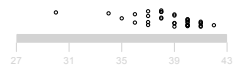
sex ratio

0.53



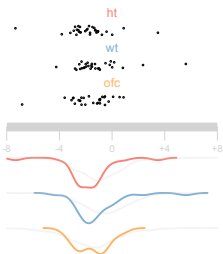
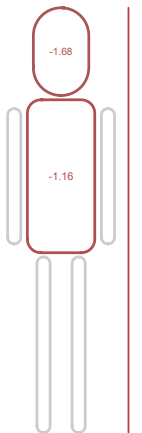
gestation (w)

38.6

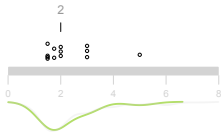


birth weight (z)

-0.38



social smile (m)



sat unaided (m)

12



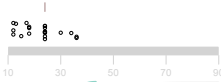
walked unaided (m)

22

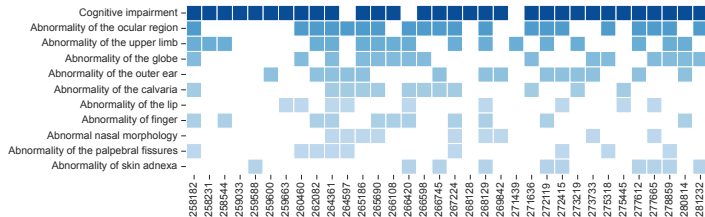


first words (m)

24



recurrent HPO terms used in ANKRD11 cases



aggregate face  
from 19  
photographs



WWW.NATURE.COM/NATURE 6

# ARID1B

n = 32

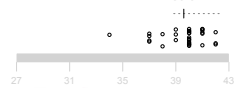
sex ratio

0.47



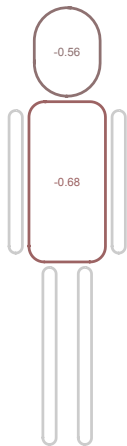
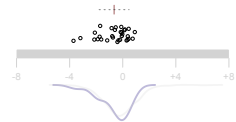
gestation (w)

39.6



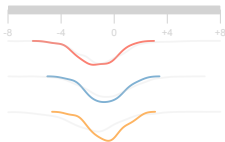
birth weight (z)

-0.65



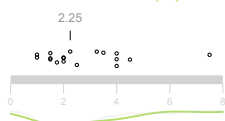
-1.33

ht  
wt  
ofc



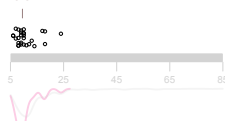
social smile (m)

2.25



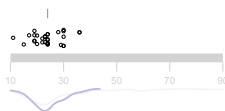
sat unaided (m)

9.5



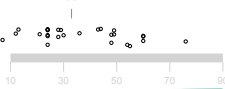
walked unaided (m)

24

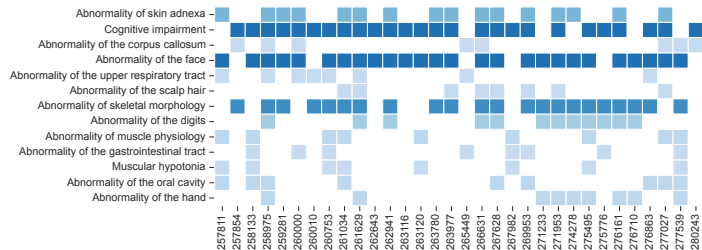


first words (m)

33



recurrent HPO terms used in ARID1B cases



aggregate face  
from 21  
photographs



WWW.NATURE.COM/NATURE7

# ASXL1

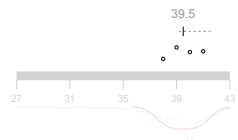
recurrent HPO terms used in ASXL1 cases

n = 4

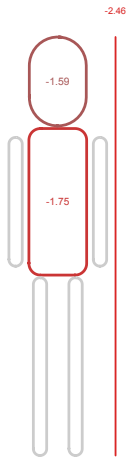
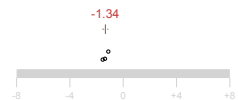
sex ratio



gestation (w)



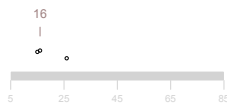
birth weight (z)



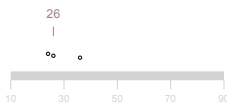
social smile (m)



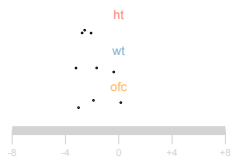
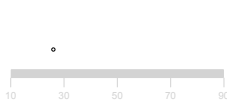
sat unaided (m)



walked unaided (m)



first words (m)



	267713	271396	272742	279573
Proptosis				
Abnormality of the oral cavity				
Abnormality of the skin				
Severe global developmental delay				
Abnormality of finger				



# ASXL3

n = 14

sex ratio

0.5



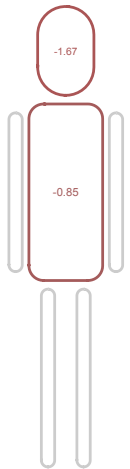
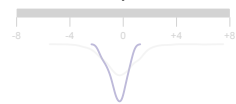
gestation (w)

39.9



birth weight (z)

-0.43

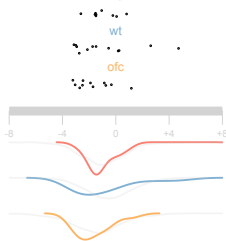


-0.1

ht

wt

ofc



social smile (m)

2.25



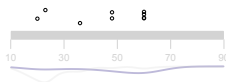
sat unaided (m)

13



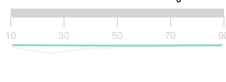
walked unaided (m)

60

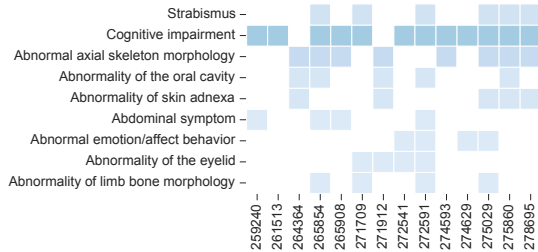


first words (m)

73



recurrent HPO terms used in ASXL3 cases



# AUTS2

n = 5

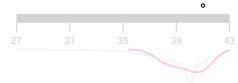
sex ratio

0.6



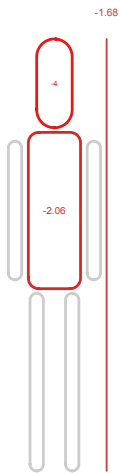
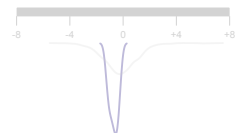
gestation (w)

39.8



birth weight (z)

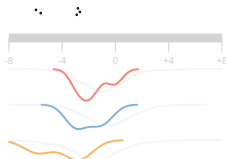
-0.7



ht

wt

ofc



social smile (m)

6.5



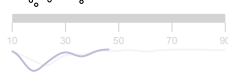
sat unaided (m)

11



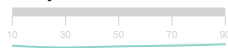
walked unaided (m)

19

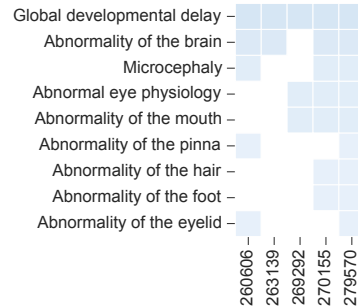


first words (m)

36.5



recurrent HPO terms used in AUTS2 cases



# BCL11A

n = 6

sex ratio

0.83

all male = all female

gestation (w)

38.7

27 31 35 39 43

birth weight (z)

0.8

-8 -4 0 +4 +8

-2.39

-1.22

-1.33

social smile (m)

2

0 2 4 6 8

sat unaided (m)

10

5 25 45 65 85

walked unaided (m)

22

10 30 50 70 90

first words (m)

24

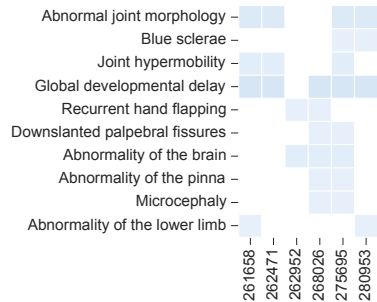
10 30 50 70 90

ht

wt

ofc

-8 -4 0 +4 +8



# BRAF

n = 6

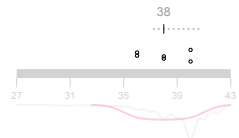
sex ratio

0.33



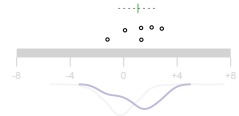
gestation (w)

38

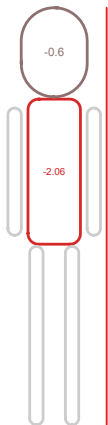


birth weight (z)

1.07



-2.62



social smile (m)

3



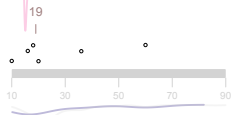
sat unaided (m)

10



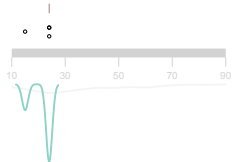
walked unaided (m)

19



first words (m)

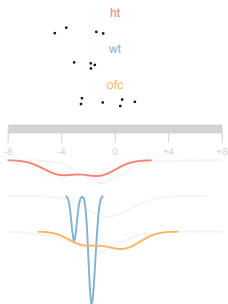
24



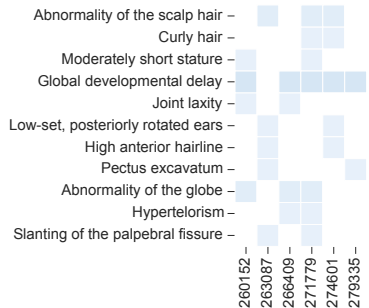
ht

wt

ofc



recurrent HPO terms used in BRAF cases



# CASK

n = 9

sex ratio

0.78

all male = all female

gestation (w)

40.2

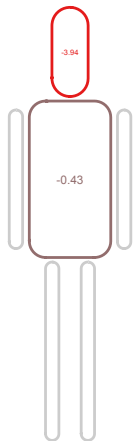
27 31 35 39 43

birth weight (z)

0.4

-8 -4 0 +4 +8

-1.72



social smile (m)



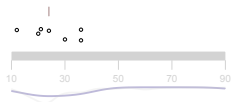
sat unaided (m)

12



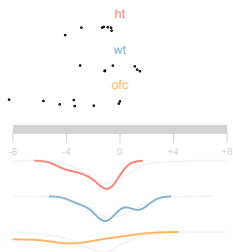
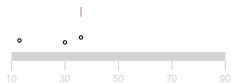
walked unaided (m)

24

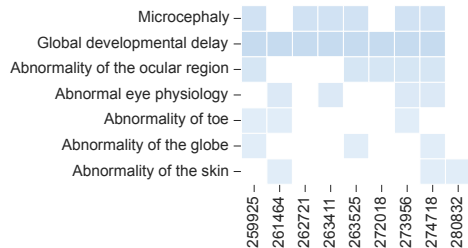


first words (m)

36



recurrent HPO terms used in CASK cases



# CDK13

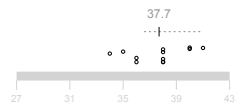
recurrent HPO terms used in CDK13 cases

n = 12

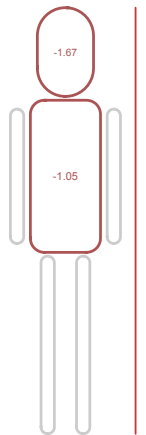
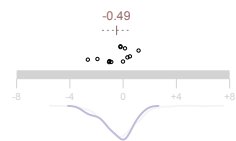
sex ratio



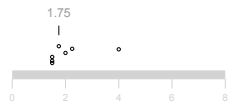
gestation (w)



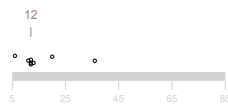
birth weight (z)



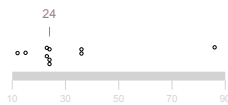
social smile (m)



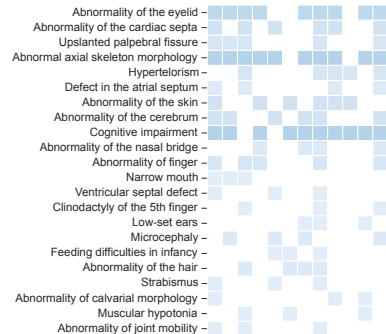
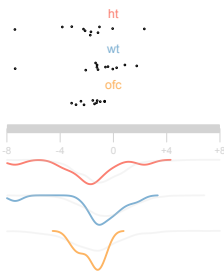
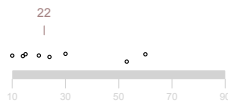
sat unaided (m)



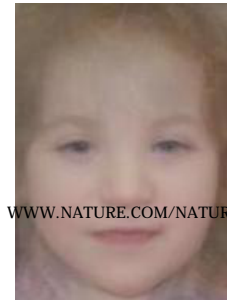
walked unaided (m)



first words (m)



aggregate face  
from 11  
photographs



WWW.NATURE.COM/NATURE 14

# CDKL5

n = 6

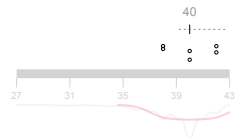
sex ratio

0.67



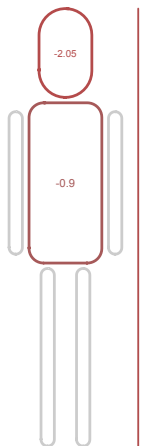
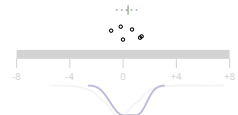
gestation (w)

40



birth weight (z)

0.37



social smile (m)

2.12



sat unaided (m)

26



walked unaided (m)

34



first words (m)

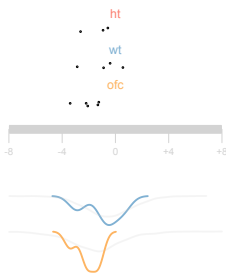
45



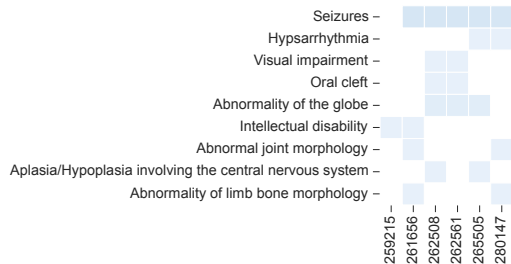
ht

wt

ofc



recurrent HPO terms used in CDKL5 cases



# CHAMP1

recurrent HPO terms used in CHAMP1 cases

n = 5

sex ratio

0.4



gestation (w)

39.8



birth weight (z)

0.41



social smile (m)

1.75



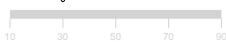
sat unaided (m)

11



walked unaided (m)

24



first words (m)

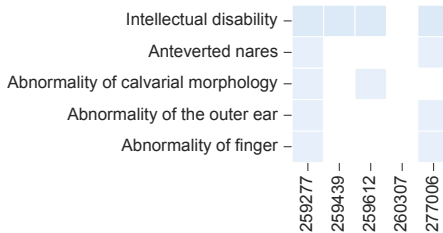
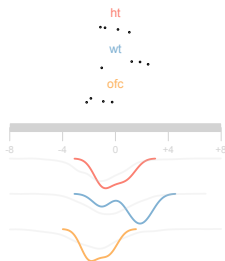
53.5



ht

wt

ofc





# CHD2

n = 9

sex ratio

0.44



gestation (w)

39.6



birth weight (z)

-0.38



ht  
wt  
ofc



social smile (m)

2



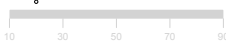
sat unaided (m)

8.5



walked unaided (m)

21

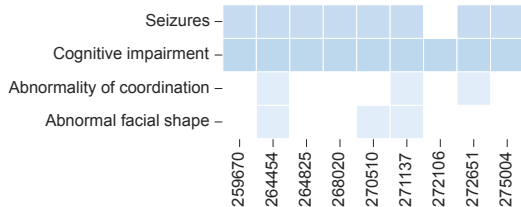


first words (m)

41.5



recurrent HPO terms used in CHD2 cases



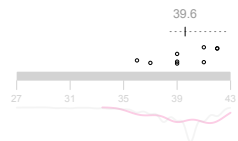
# CHD4

n = 9

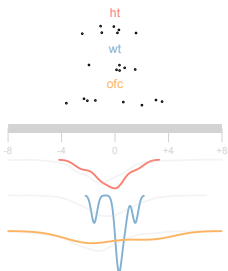
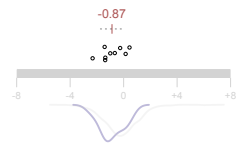
sex ratio



gestation (w)



birth weight (z)

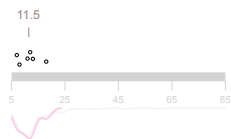


-0.37

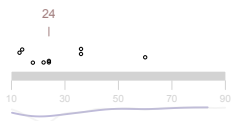
social smile (m)



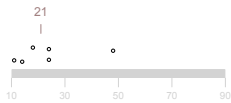
sat unaided (m)



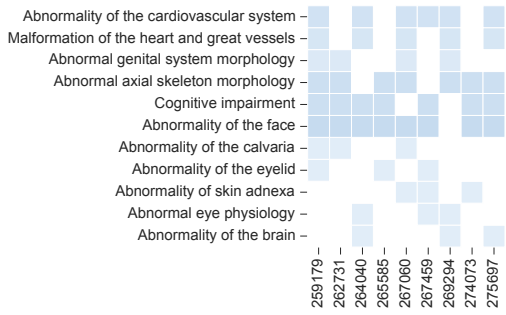
walked unaided (m)



first words (m)



recurrent HPO terms used in CHD4 cases



# CHD8

n = 3

sex ratio

0.33

all male = all female

gestation (w)

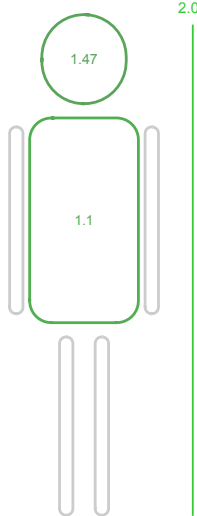
39

27 31 35 39 43

birth weight (z)

0.7

-8 -4 0 +4 +8



ht

wt

ofc

social smile (m)



sat unaided (m)

22



walked unaided (m)

24



first words (m)

31



recurrent HPO terms used in CHD8 cases

Abnormal shape of the frontal region -

Downslanted palpebral fissures -

Global developmental delay -



# CNKSR2

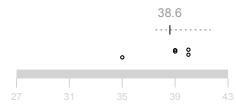
recurrent HPO terms used in *CNKSR2* cases

n = 5

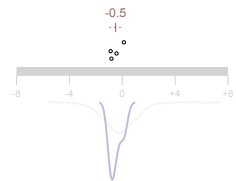
sex ratio



gestation (w)



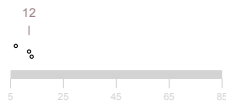
birth weight (z)



social smile (m)



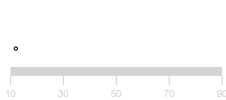
sat unaided (m)



walked unaided (m)



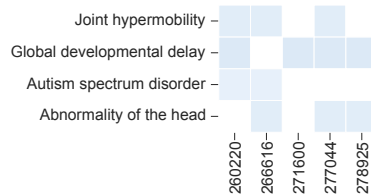
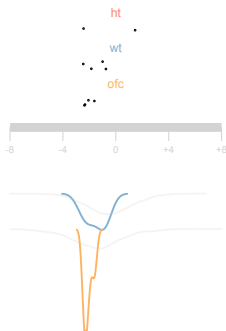
first words (m)



ht

wt

ofc



# CNOT3

n = 7

sex ratio

0.57



gestation (w)

39.3

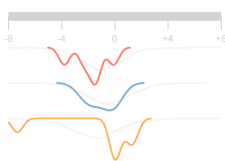
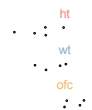
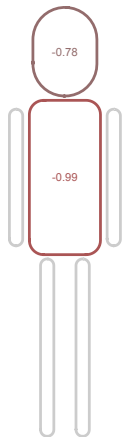


birth weight (z)

-0.34



-1.82



social smile (m)

1.88



sat unaided (m)

11.5



walked unaided (m)

23.5

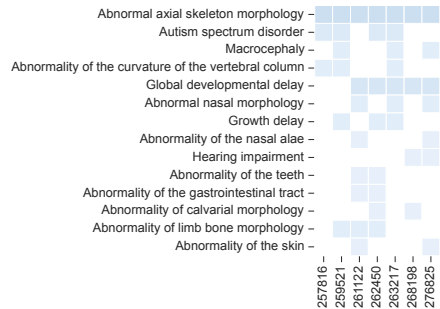


first words (m)

45



recurrent HPO terms used in CNOT3 cases



# COL4A3BP

n = 4

sex ratio

0.25

all male = all female

gestation (w)

39.2

27 31 35 39 43

birth weight (z)

-0.78

-8 -4 0 +4 +8

-3.08

0.64

ht

wt

ofc

-0.8

social smile (m)

1.75

0 2 4 6 8

sat unaided (m)

22

5 25 45 65 85

walked unaided (m)

47

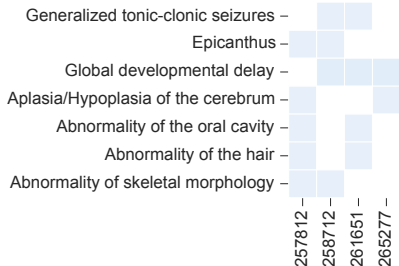
10 30 50 70 90

first words (m)

10 30 50 70 90

101

recurrent HPO terms used in COL4A3BP cases



# CREBBP

n = 12

sex ratio

0.67



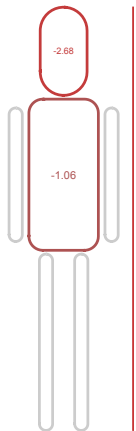
gestation (w)

38.9



birth weight (z)

-1.18



ht

wt

ofc



social smile (m)

1.75



sat unaided (m)



walked unaided (m)

20

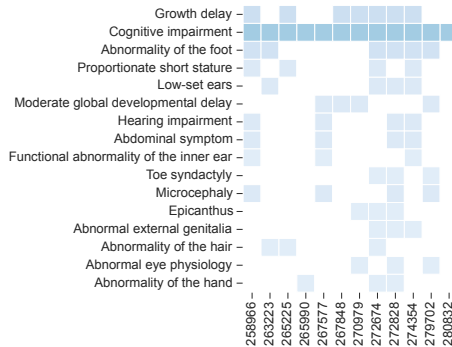


first words (m)

33

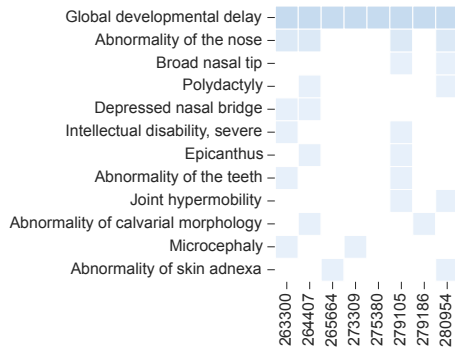
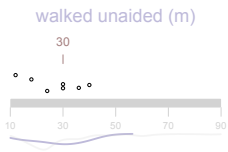
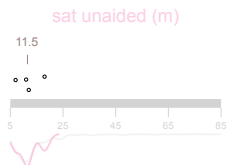
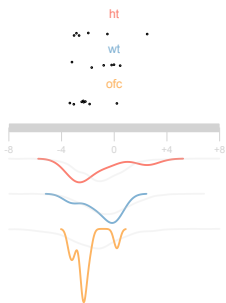
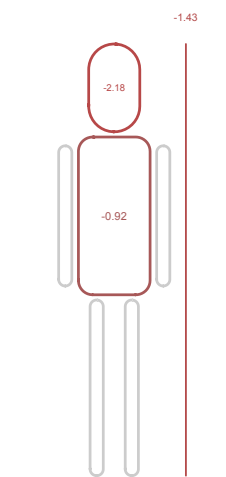
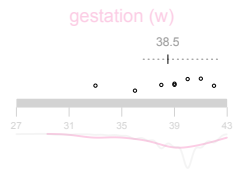


recurrent HPO terms used in CREBBP cases



# CSNK2A1

recurrent HPO terms used in CSNK2A1 cases





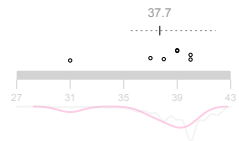
# CTCF

n = 7

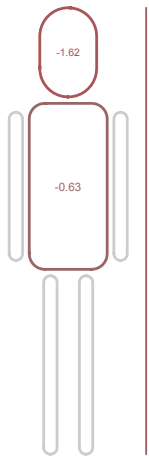
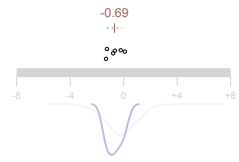
sex ratio



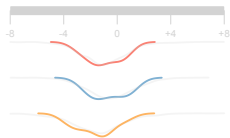
gestation (w)



birth weight (z)



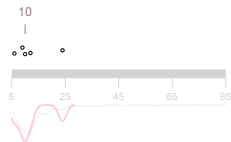
ht  
wt



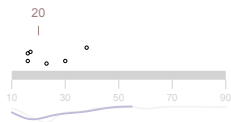
social smile (m)



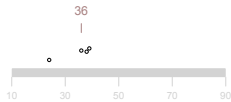
sat unaided (m)



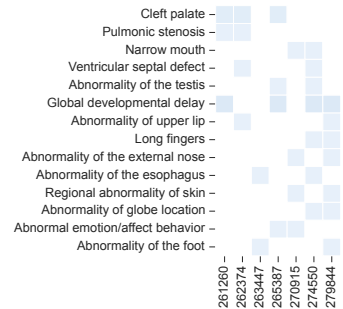
walked unaided (m)



first words (m)



recurrent HPO terms used in CTCF cases



# CTNNB1

n = 11

sex ratio

0.64



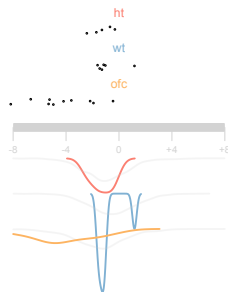
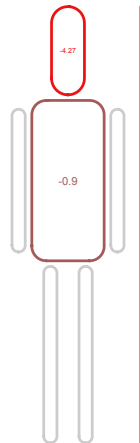
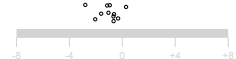
gestation (w)

40.1



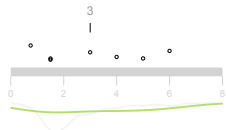
birth weight (z)

-1.05



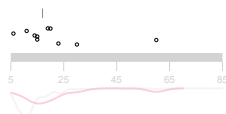
social smile (m)

3



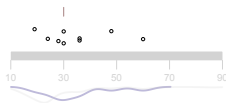
sat unaided (m)

17



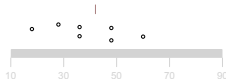
walked unaided (m)

30

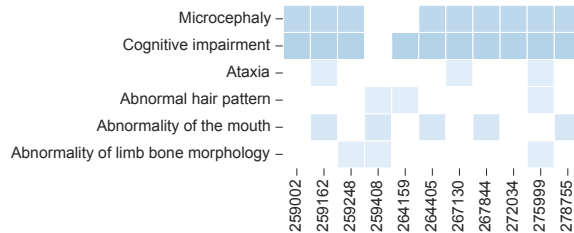


first words (m)

42



recurrent HPO terms used in CTNNB1 cases



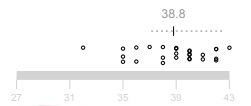
# DDX3X

n = 28

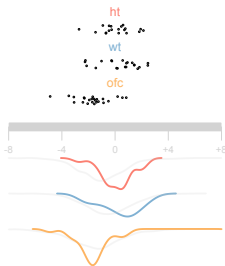
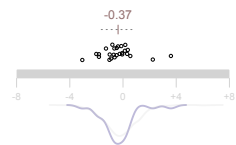
sex ratio



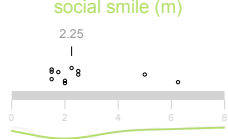
gestation (w)



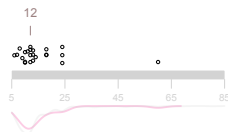
birth weight (z)



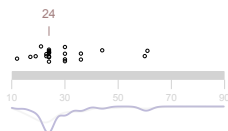
social smile (m)



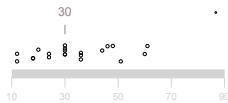
sat unaided (m)



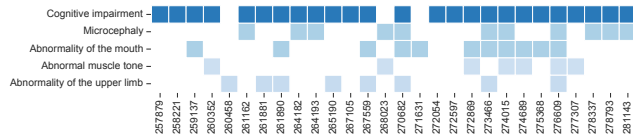
walked unaided (m)



first words (m)



recurrent HPO terms used in DDX3X cases



aggregate face  
from 18  
photographs



WWW.NATURE.COM/NATURE 27

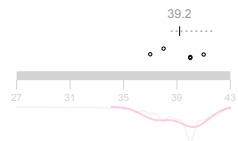
# DNM1

n = 5

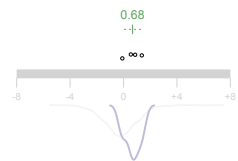
sex ratio



gestation (w)



birth weight (z)



-0.98

0.53

ht

wt

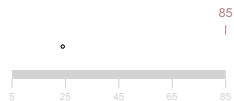
ofc

1.63

social smile (m)



sat unaided (m)



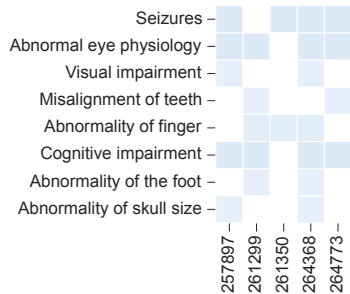
walked unaided (m)



first words (m)



recurrent HPO terms used in *DNM1* cases



118

146

# DYNC1H1

n = 12

sex ratio

0.67

all male = all female

gestation (w)

38.6

27 31 35 39 43

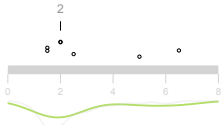
birth weight (z)

0.01

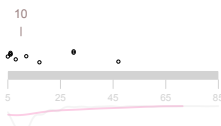
-8 -4 0 +4 +8



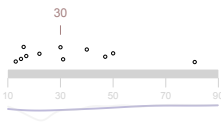
social smile (m)



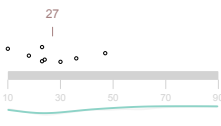
sat unaided (m)



walked unaided (m)



first words (m)



ht

wt

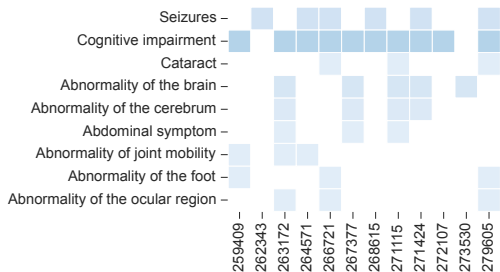
ofc

-8 -4 0 +4 +8

-8 -4 0 +4 +8

-8 -4 0 +4 +8

recurrent HPO terms used in DYNC1H1 cases



# DYRK1A

n = 18

sex ratio

0.33



gestation (w)

39.2



birth weight (z)

-1.82



social smile (m)

2.5



sat unaided (m)

10.5



walked unaided (m)

24



first words (m)

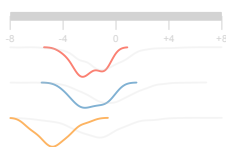
36



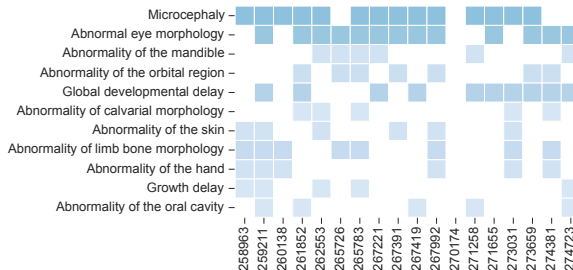
ht

wt

ofc



recurrent HPO terms used in *DYRK1A* cases



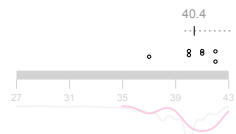
# EEF1A2

n = 7

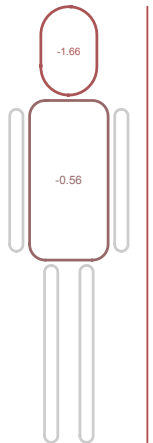
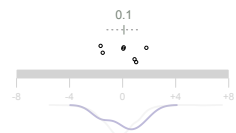
sex ratio



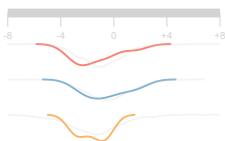
gestation (w)



birth weight (z)



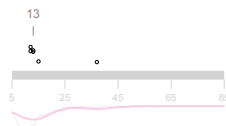
ht  
wt  
ofc



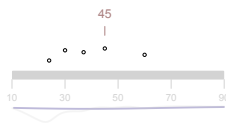
social smile (m)



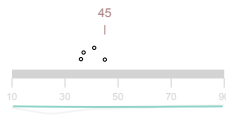
sat unaided (m)



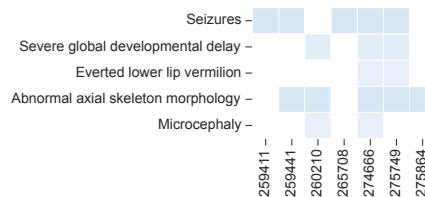
walked unaided (m)



first words (m)



recurrent HPO terms used in *EEF1A2* cases



# EHMT1

n = 10

sex ratio

0.5



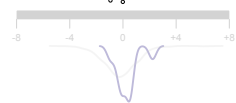
gestation (w)

37.5



birth weight (z)

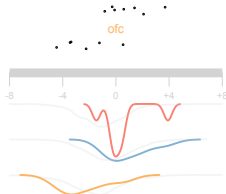
0.28



ht

wt

ofc



0.41

social smile (m)

2.25



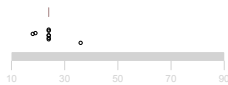
sat unaided (m)

12



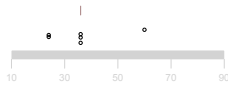
walked unaided (m)

24

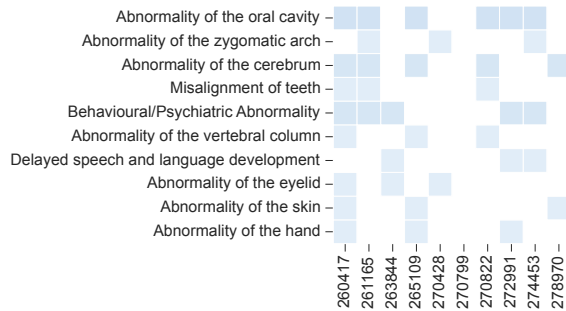


first words (m)

36



recurrent HPO terms used in EHMT1 cases





# EP300

n = 17

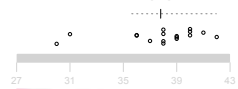
sex ratio

0.53



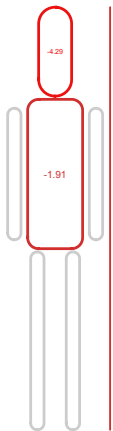
gestation (w)

37.8



birth weight (z)

-1.09



social smile (m)

2.12



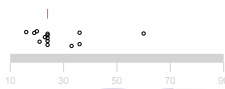
sat unaided (m)

12



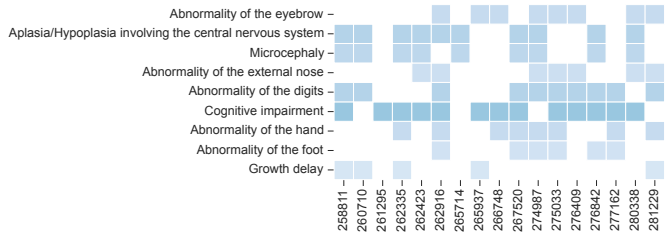
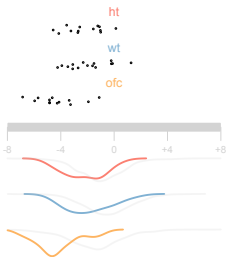
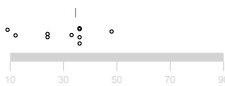
walked unaided (m)

24



first words (m)

34.5



aggregate face  
from 11  
photographs



# FOXP1

n = 7

sex ratio

0.43

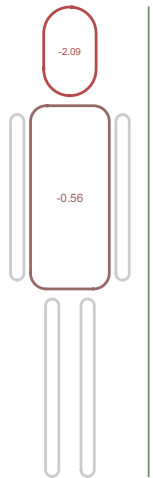
all male = all female

gestation (w)

40.4

birth weight (z)

1.3



social smile (m)

2.75



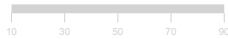
sat unaided (m)

16



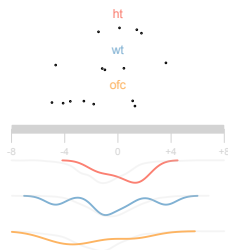
walked unaided (m)

35.5

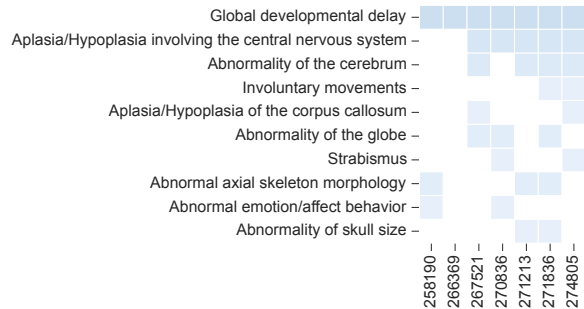


first words (m)

50.5



recurrent HPO terms used in FOXP1 cases



# FOXP1

n = 12

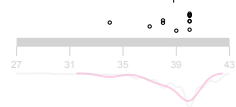
sex ratio

0.33



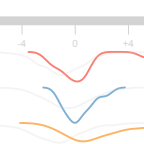
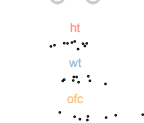
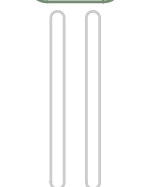
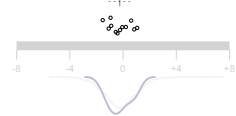
gestation (w)

38.8



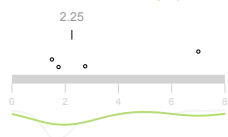
birth weight (z)

-0.25



social smile (m)

2.25



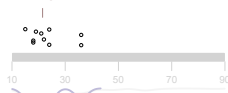
sat unaided (m)

12



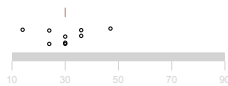
walked unaided (m)

21.5

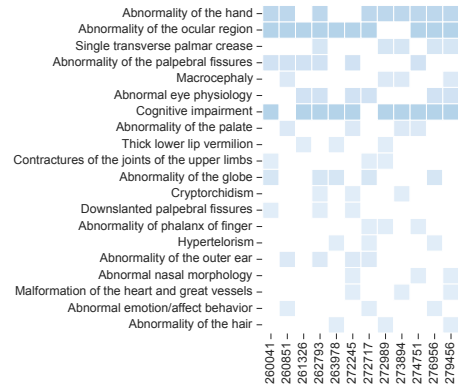


first words (m)

30



recurrent HPO terms used in FOXP1 cases



aggregate face  
from 10  
photographs



WWW.NATURE.COM/NATURE 35

# GABRB3

recurrent HPO terms used in GABRB3 cases

n = 3

sex ratio

0.33

all male = all female

gestation (w)

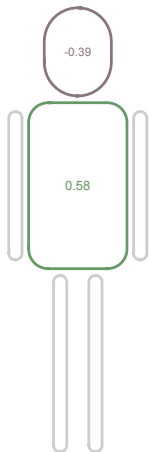
40.3

27 31 35 39 43

birth weight (z)

0.37

-8 -4 0 +4 +8



social smile (m)

2



sat unaided (m)

10



walked unaided (m)

24



first words (m)

30



ht

wt

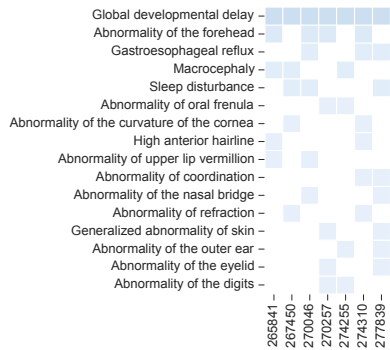
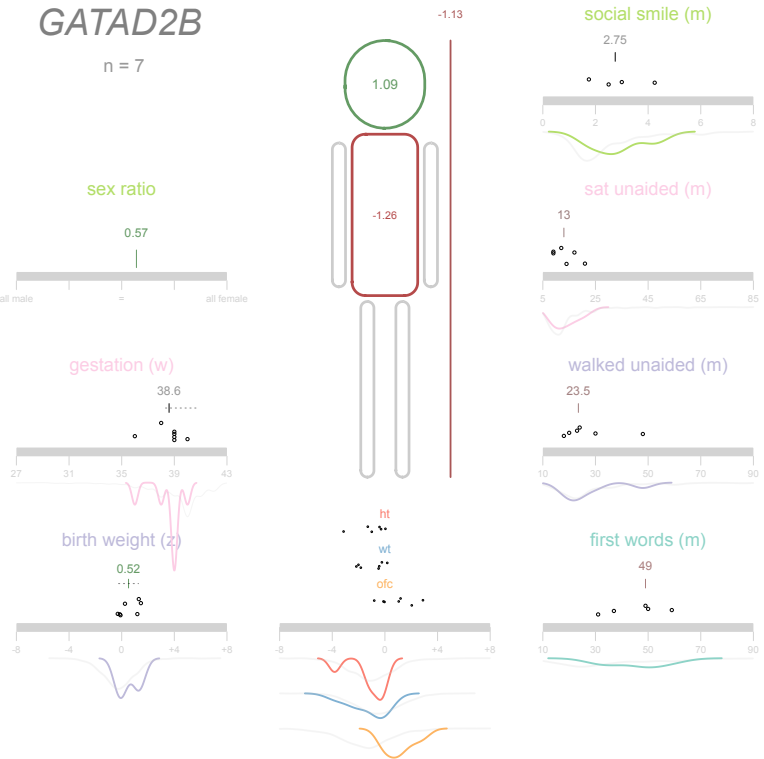
ofc



Global developmental delay -



# GATAD2B



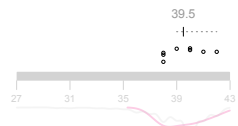
# GNAI1

n = 8

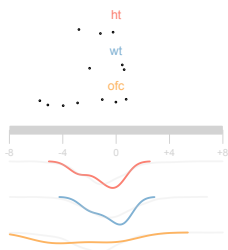
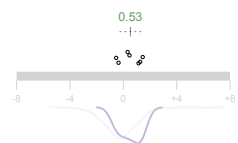
sex ratio



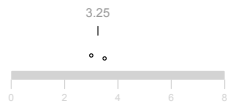
gestation (w)



birth weight (z)



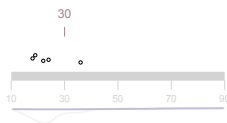
social smile (m)



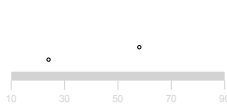
sat unaided (m)



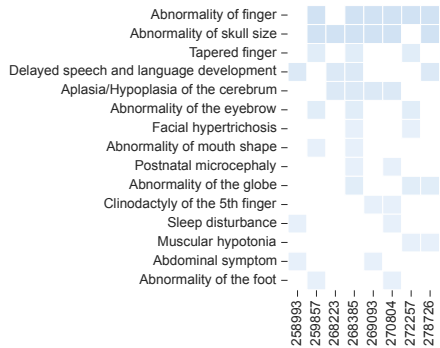
walked unaided (m)



first words (m)



recurrent HPO terms used in GNAI1 cases



# GNAO1

n = 8

sex ratio

0.62



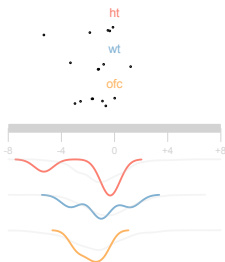
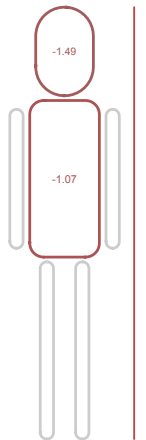
gestation (w)

39.9



birth weight (z)

-0.41



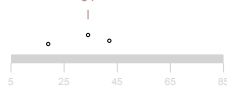
social smile (m)

1.25



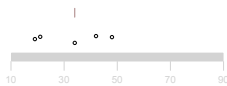
sat unaided (m)

34



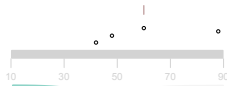
walked unaided (m)

34

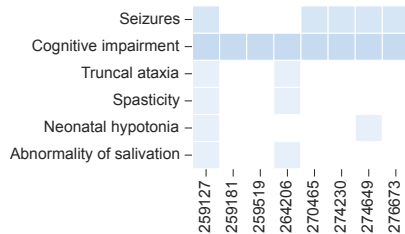


first words (m)

60



recurrent HPO terms used in GNAO1 cases



# GRIN2B

n = 7

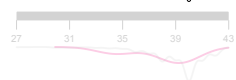
sex ratio

0.29



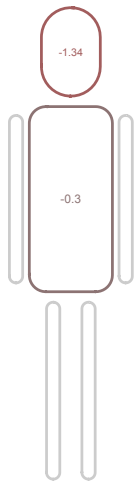
gestation (w)

37.9



birth weight (z)

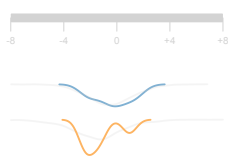
-0.14



ht

wt

ofc



social smile (m)

4.5



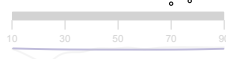
sat unaided (m)

27



walked unaided (m)

70



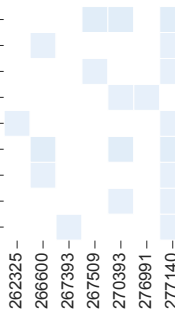
first words (m)

73.5



## recurrent HPO terms used in GRIN2B cases

- Severe global developmental delay –
- Abnormality of the esophagus –
- Abnormality of the teeth –
- Generalized seizures –
- Muscular hypotonia –
- Abnormal axial skeleton morphology –
- Abnormality of skull size –
- Abnormal eye physiology –
- Abnormality of the brain –





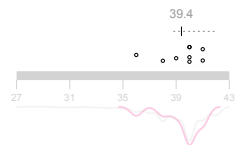
# HDAC8

n = 9

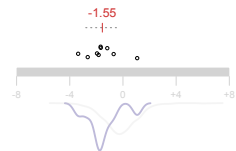
sex ratio



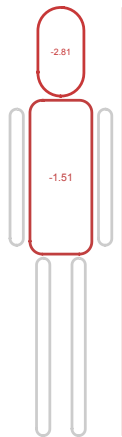
gestation (w)



birth weight (z)



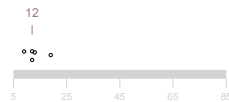
-1.86



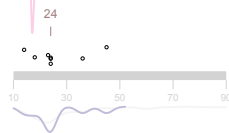
social smile (m)



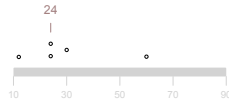
sat unaided (m)



walked unaided (m)



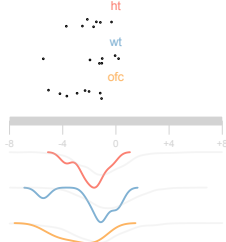
first words (m)



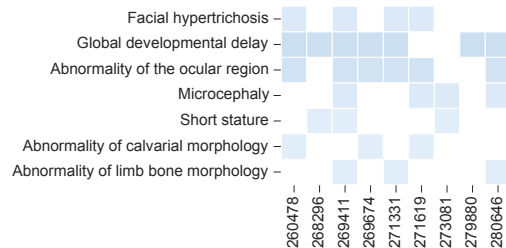
ht

wt

ofc



recurrent HPO terms used in HDAC8 cases



# HNRNPU

recurrent HPO terms used in HNRNPU cases

n = 8

sex ratio

0.5



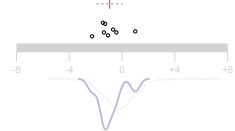
gestation (w)

38.5



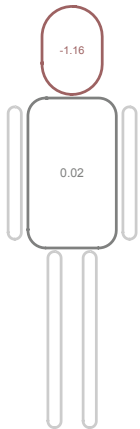
birth weight (z)

-0.94



-1.16

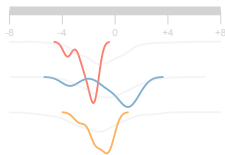
0.02



ht

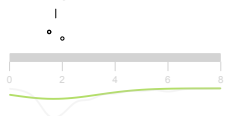
wt

ofc



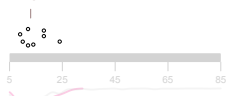
social smile (m)

1.75



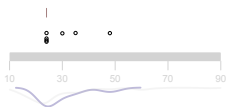
sat unaided (m)

13



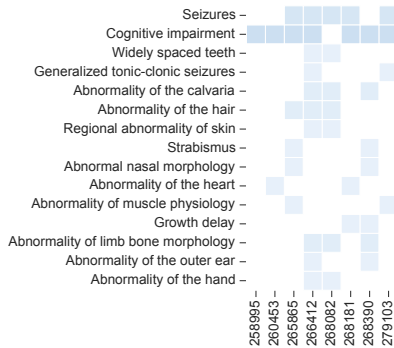
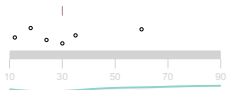
walked unaided (m)

24



first words (m)

30



# IQSEC2

n = 7

sex ratio

0.43

all male = all female

gestation (w)

40

27 31 35 39 43

birth weight (z)

-0.03

-8 -4 0 +4 +8

-1.16

-0.04

-0.51

ht

wt

ofc

-8 -4 0 +4 +8

social smile (m)

5

0 2 4 6 8

sat unaided (m)

21

5 25 45 65 85

walked unaided (m)

36

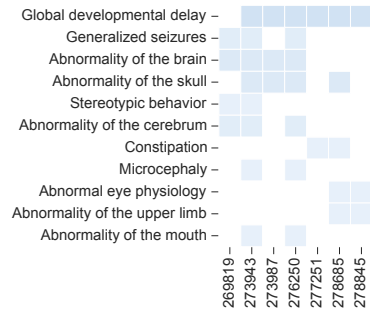
10 30 50 70 90

first words (m)

69

10 30 50 70 90

recurrent HPO terms used in IQSEC2 cases



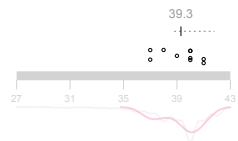
# ITPR1

n = 10

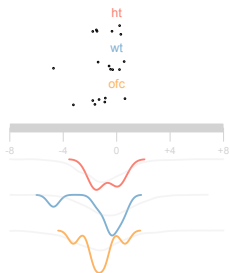
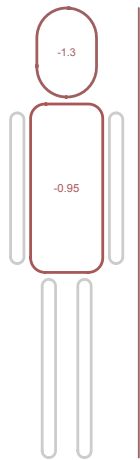
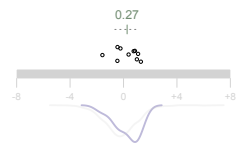
sex ratio



gestation (w)



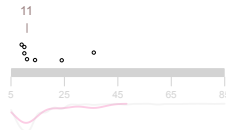
birth weight (z)



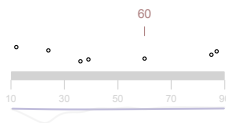
social smile (m)



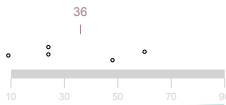
sat unaided (m)



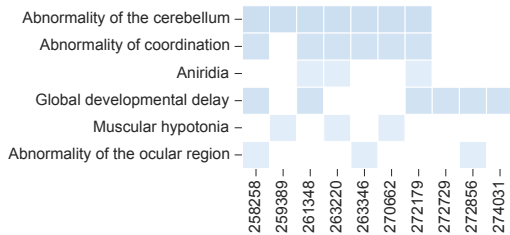
walked unaided (m)



first words (m)



recurrent HPO terms used in ITPR1 cases



# KANSL1

n = 8

sex ratio

0.5



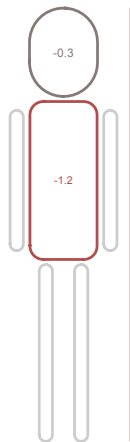
gestation (w)

39.2



birth weight (z)

-1.55



social smile (m)

3



sat unaided (m)

10.5



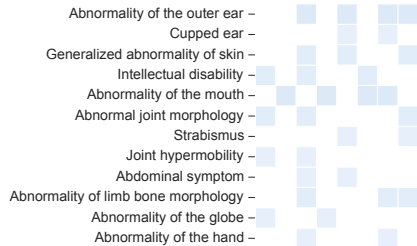
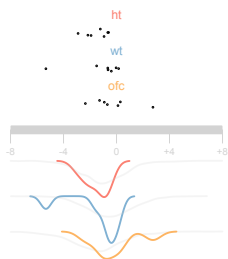
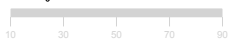
walked unaided (m)

18.5



first words (m)

27



259666  
260423  
262684  
263820  
264382  
273323  
274624  
279853

# KAT6A

n = 11

sex ratio

0.36



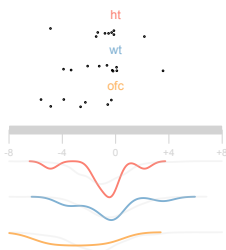
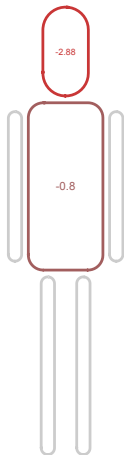
gestation (w)

39.3



birth weight (z)

0.23



social smile (m)

2.25



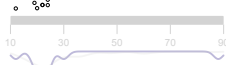
sat unaided (m)

12



walked unaided (m)

22

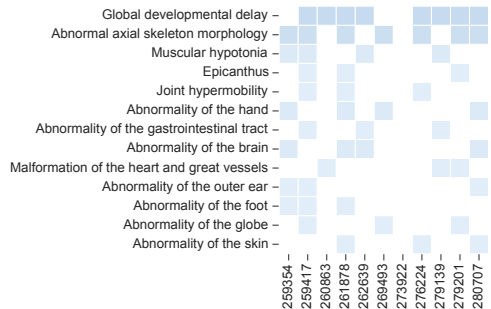


first words (m)

36



recurrent HPO terms used in KAT6A cases



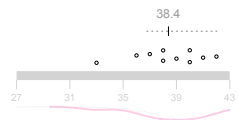
# KAT6B

n = 10

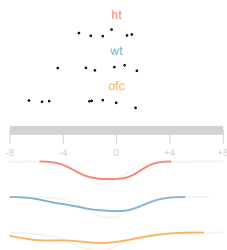
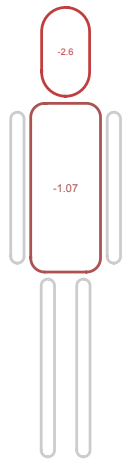
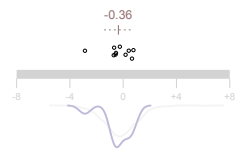
sex ratio



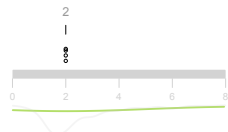
gestation (w)



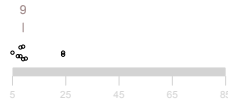
birth weight (z)



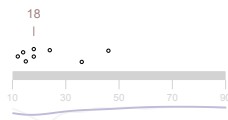
social smile (m)



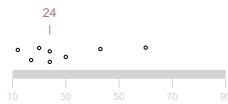
sat unaided (m)



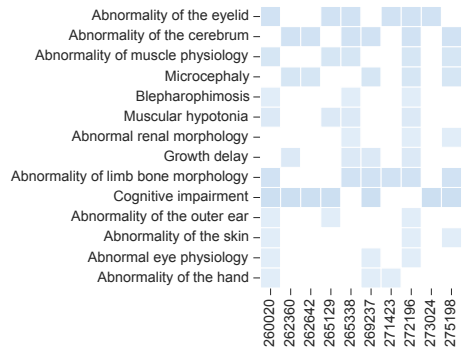
walked unaided (m)



first words (m)



recurrent HPO terms used in KAT6B cases



# KCNH1

n = 5

sex ratio

0.4

all male = all female

gestation (w)

40

27 31 35 39 43

birth weight (z)

0.11

-8 -4 0 +4 +8

-1.42

-0.19

ht

wt

ofc

-8 -4 0 +4 +8

social smile (m)

1.62

0 2 4 6 8

sat unaided (m)

17

5 25 45 65 85

walked unaided (m)

60

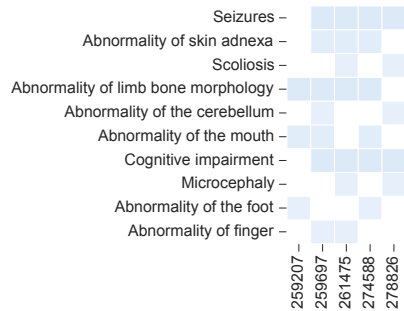
10 30 50 70 90

first words (m)

10 30 50 70 90

113

recurrent HPO terms used in *KCNH1* cases





# KCNQ2

n = 16

sex ratio

0.56

all male = all female

gestation (w)

40.2

27 31 35 39 43

birth weight (z)

0.71

-8 -4 0 +4 +8



ht  
wt  
ofc

-8 -4 0 +4 +8

-8 -4 0 +4 +8

social smile (m)

2.12



sat unaided (m)

36



walked unaided (m)

60

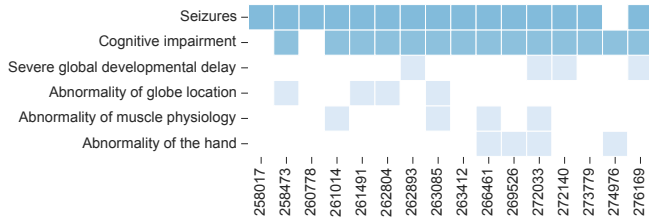
10 30 50 70 90

first words (m)

60

10 30 50 70 90

recurrent HPO terms used in KCNQ2 cases



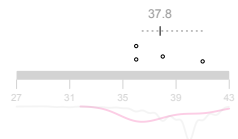
# KCNQ3

n = 4

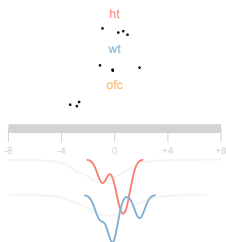
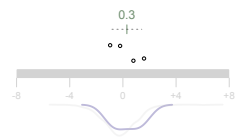
sex ratio



gestation (w)



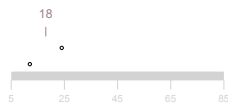
birth weight (z)



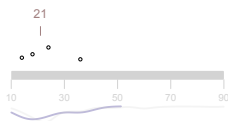
social smile (m)



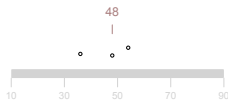
sat unaided (m)



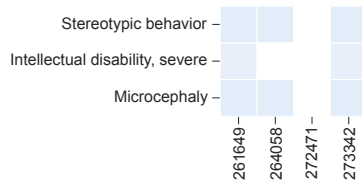
walked unaided (m)



first words (m)



recurrent HPO terms used in KCNQ3 cases



# KDM5B

n = 3

sex ratio

0.33



gestation (w)

37.7



birth weight (z)

-0.24



social smile (m)



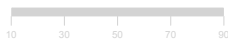
sat unaided (m)

12



walked unaided (m)

20



first words (m)



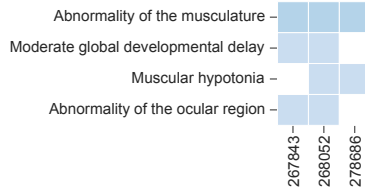
ht

wt

ofc



recurrent HPO terms used in KDM5B cases



# KIF1A

n = 8

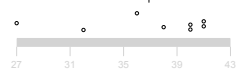
sex ratio

0.62



gestation (w)

36.9

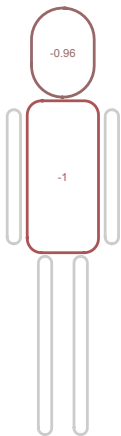


birth weight (z)

-0.23



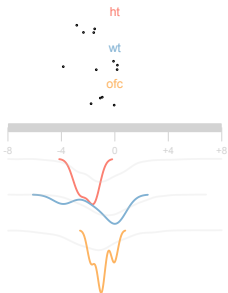
-2.07



ht

wt

ofc



social smile (m)

1.5



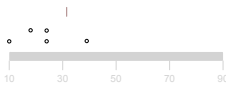
sat unaided (m)

53



walked unaided (m)

31.5

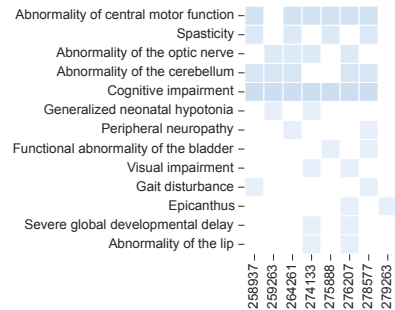


first words (m)

39



recurrent HPO terms used in KIF1A cases



# KMT2A

n = 29

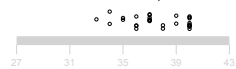
sex ratio

0.41



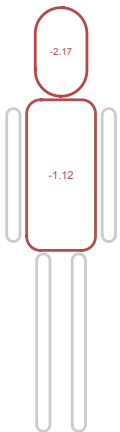
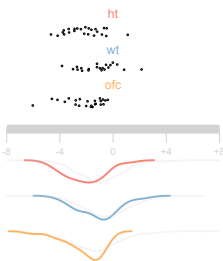
gestation (w)

37.7

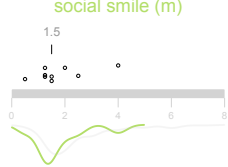


birth weight (z)

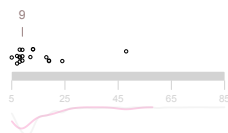
-0.43



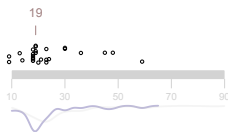
social smile (m)



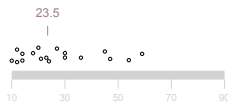
sat unaided (m)



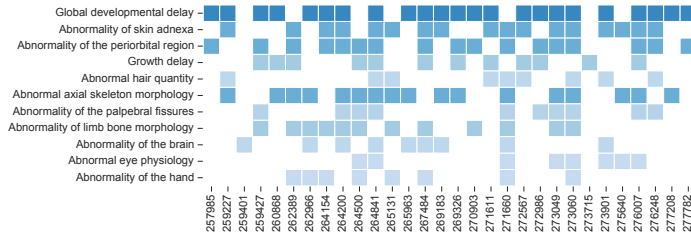
walked unaided (m)



first words (m)



recurrent HPO terms used in KMT2A cases



aggregate face  
from 19  
photographs



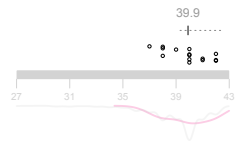
# MECP2

n = 15

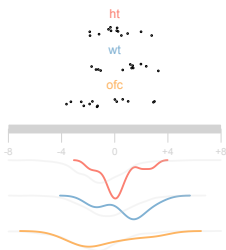
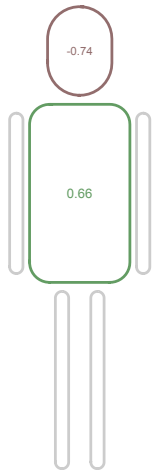
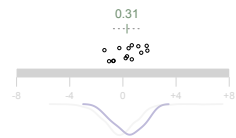
sex ratio



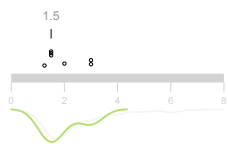
gestation (w)



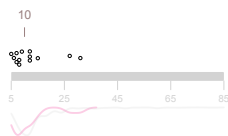
birth weight (z)



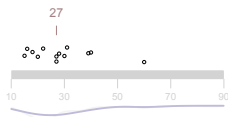
social smile (m)



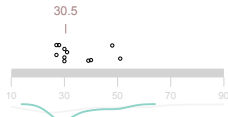
sat unaided (m)



walked unaided (m)

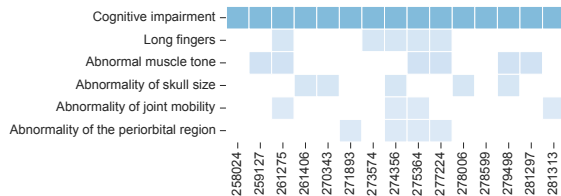


first words (m)



0.06

recurrent HPO terms used in MECP2 cases



# MED13L

n = 19

sex ratio

0.42



gestation (w)

39.4



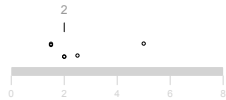
birth weight (z)

-0.87



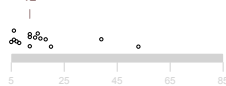
-0.72

social smile (m)



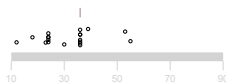
sat unaided (m)

12



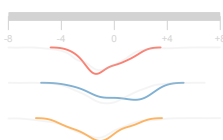
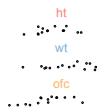
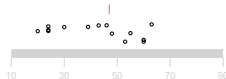
walked unaided (m)

36

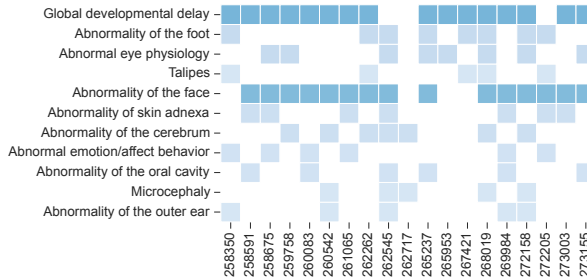


first words (m)

47



recurrent HPO terms used in MED13L cases



aggregate face  
from 14  
photographs



WWW.NATURE.COM/NATURE 55

# MEF2C

n = 8

sex ratio

0.38



gestation (w)

-0.79



ht

wt

ofc

birth weight (z)

0.09



-1.02

0.44



social smile (m)

2.25



sat unaided (m)

16.5



walked unaided (m)

36

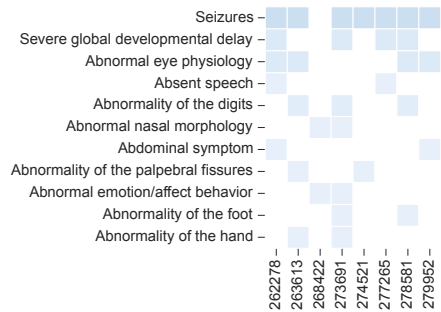


first words (m)

118.5



recurrent HPO terms used in MEF2C cases





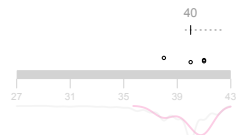
# MSL3

n = 4

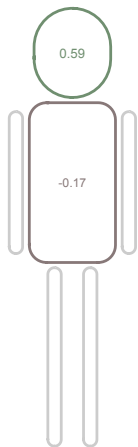
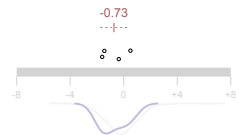
sex ratio



gestation (w)



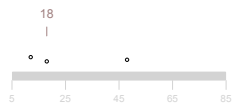
birth weight (z)



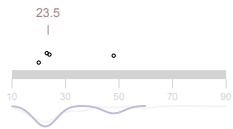
social smile (m)



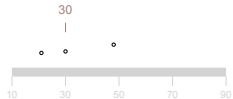
sat unaided (m)



walked unaided (m)



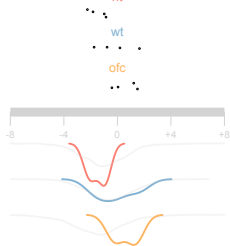
first words (m)



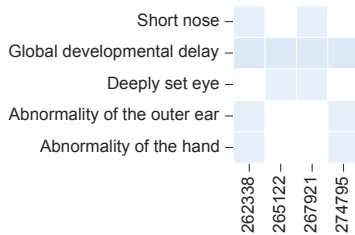
ht

wt

ofc



recurrent HPO terms used in MSL3 cases



# MYT1L

n = 4

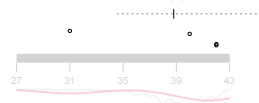
sex ratio

0.5



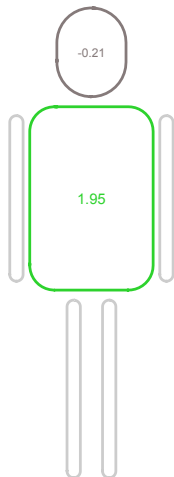
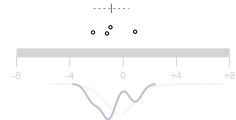
gestation (w)

38.8



birth weight (z)

-0.88



ht

wt

ofc



0.45

social smile (m)

0.75



sat unaided (m)

18



walked unaided (m)

60

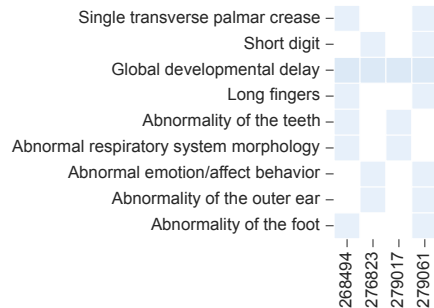


first words (m)

36



recurrent HPO terms used in MYT1L cases



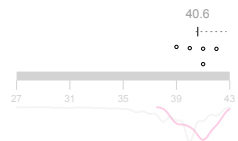
# NAA10

n = 5

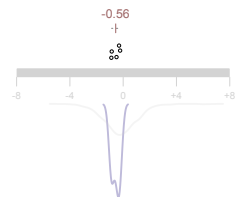
sex ratio



gestation (w)



birth weight (z)



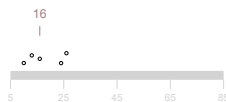
-1.78



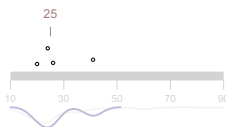
social smile (m)



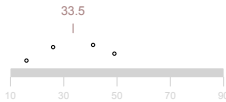
sat unaided (m)



walked unaided (m)



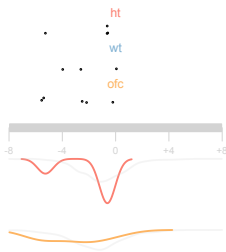
first words (m)



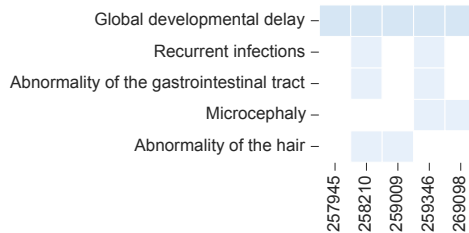
ht

wt

ofc



recurrent HPO terms used in NAA10 cases



# NFIX

n = 6

sex ratio

0.5

all male = all female

gestation (w)

39.7

27 31 35 39 43

birth weight (z)

-0.55

-8 -4 0 +4 +8

0.89

-0.5

-0.83

ht

wt

ofc

social smile (m)

3.5

0 2 4 6 8

sat unaided (m)

11

5 25 45 65 85

walked unaided (m)

33

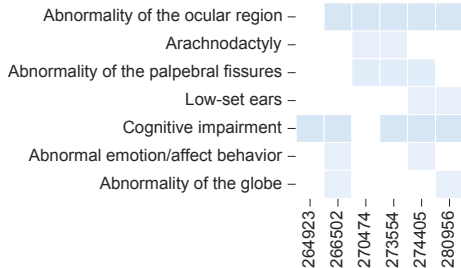
10 30 50 70 90

first words (m)

54

10 30 50 70 90

recurrent HPO terms used in NFIX cases



# NSD1

n = 10

sex ratio

0.3



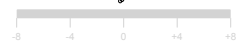
gestation (w)

36.1



birth weight (z)

0.67



1.37

1.2



ht

wt

ofc



social smile (m)

3



sat unaided (m)

10



walked unaided (m)

24

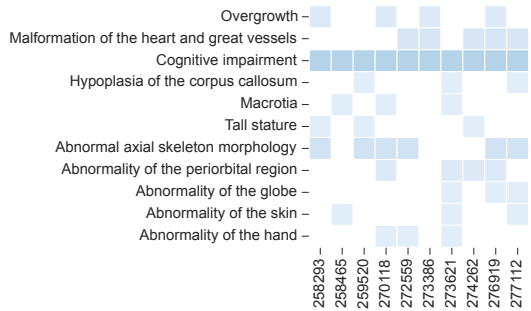


first words (m)

30



recurrent HPO terms used in NSD1 cases



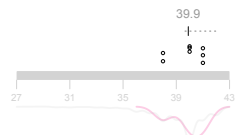
# PACS1

n = 8

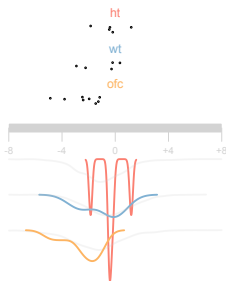
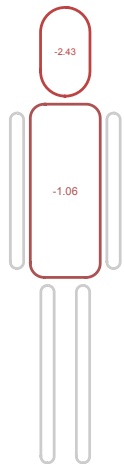
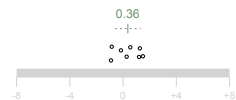
sex ratio



gestation (w)



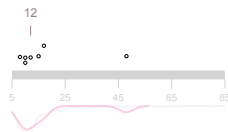
birth weight (z)



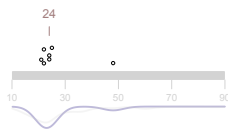
social smile (m)



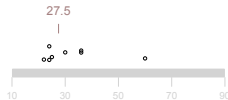
sat unaided (m)



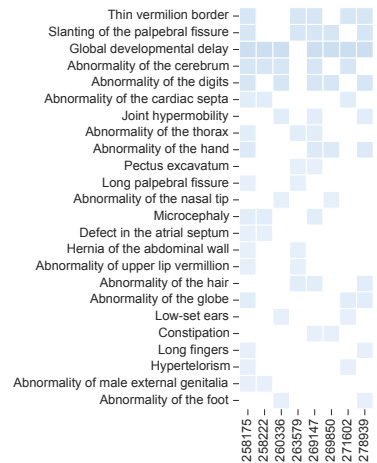
walked unaided (m)



first words (m)



recurrent HPO terms used in PACS1 cases



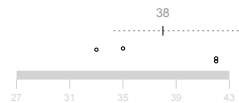
# PDHA1

n = 4

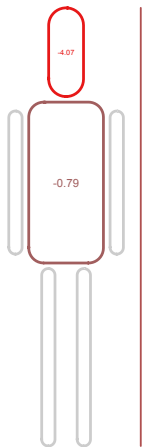
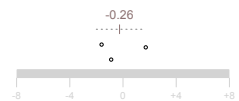
sex ratio



gestation (w)



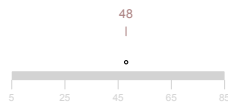
birth weight (z)



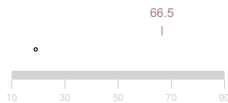
social smile (m)



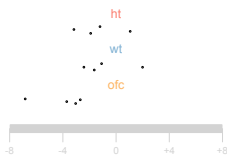
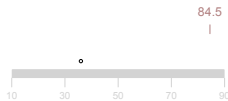
sat unaided (m)



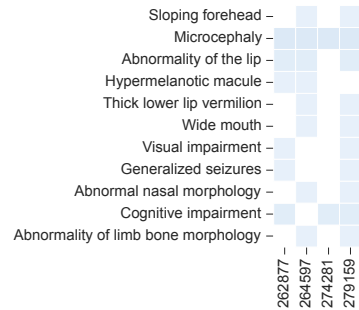
walked unaided (m)



first words (m)



recurrent HPO terms used in PDHA1 cases



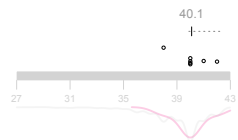
# POGZ

n = 7

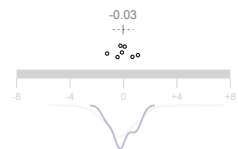
sex ratio



gestation (w)



birth weight (z)

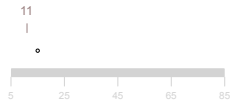


-0.45

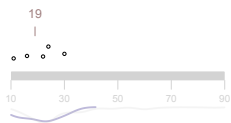
social smile (m)



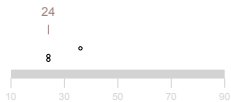
sat unaided (m)



walked unaided (m)



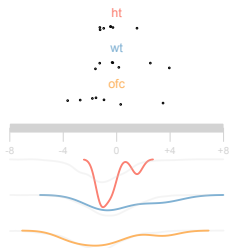
first words (m)



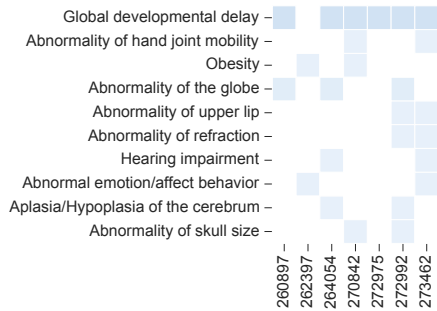
ht

wt

ofc



recurrent HPO terms used in POGZ cases





# PPM1D

n = 5

sex ratio

0.4



gestation (w)

39

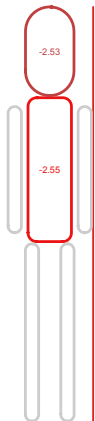


birth weight (z)

-1.37



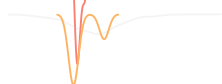
-2.64



ht

wt

ofc



social smile (m)

3.25



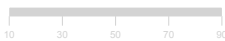
sat unaided (m)

12



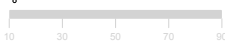
walked unaided (m)

24

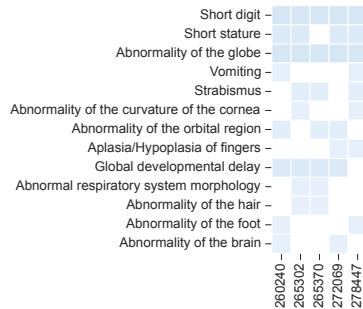


first words (m)

22



recurrent HPO terms used in PPM1D cases



# PPP2R1A

recurrent HPO terms used in PPP2R1A cases

n = 4

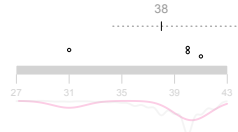
sex ratio

0.5



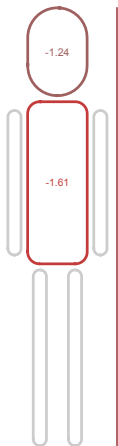
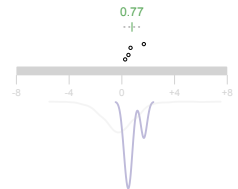
gestation (w)

38



birth weight (z)

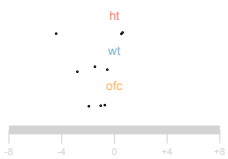
0.77



ht

wt

ofc



social smile (m)

2



sat unaided (m)

16



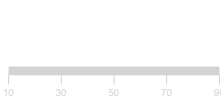
walked unaided (m)

21



first words (m)

106



Aplasia/Hypoplasia of the corpus callosum

Abnormality of the calvaria

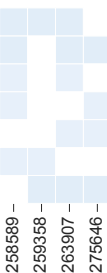
Plagiocephaly

Abnormality of skin adnexa

Abnormal eye physiology

Abnormality of the digits

Cognitive impairment



# PPP2R5D

n = 12

sex ratio

0.5

all male = all female

gestation (w)

39.2

27 31 35 39 43

birth weight (z)

1.2

-8 -4 0 +4 +8

2.08

-0.26

-0.68

ht

wt

ofc

social smile (m)

3.38

0 2 4 6 8

sat unaided (m)

19

5 25 45 65 85

walked unaided (m)

48

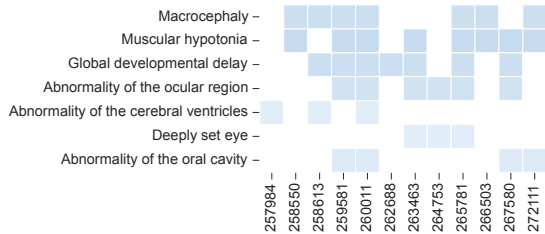
10 30 50 70 90

first words (m)

60

10 30 50 70 90

recurrent HPO terms used in PPP2R5D cases



# PTEN

n = 3

sex ratio

0.67



gestation (w)

40.3



birth weight (z)

0.86

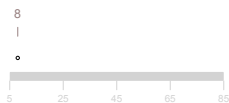


social smile (m)

3.25



sat unaided (m)



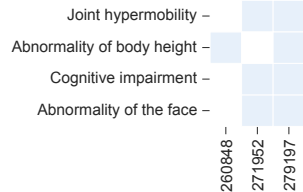
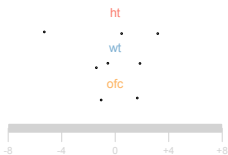
walked unaided (m)

17.5



first words (m)

15



# PTPN11

n = 6

sex ratio

0.33



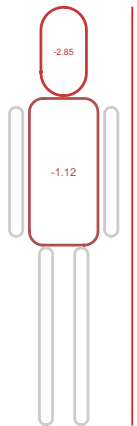
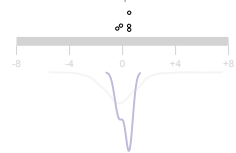
gestation (w)

38.3



birth weight (z)

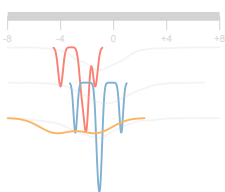
0.19



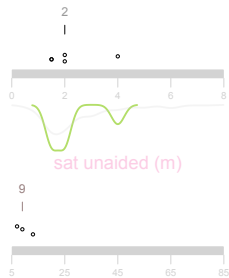
ht

wt

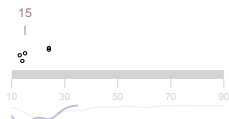
ofc



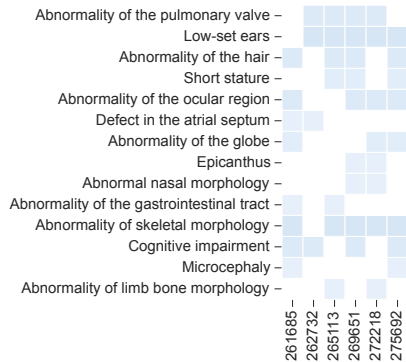
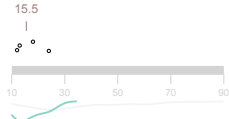
social smile (m)



walked unaided (m)



first words (m)



# PUF60

recurrent HPO terms used in PUF60 cases

n = 7

sex ratio

0.57



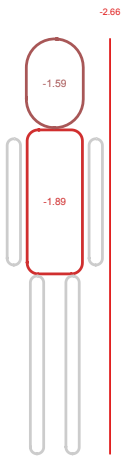
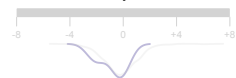
gestation (w)

38.1



birth weight (z)

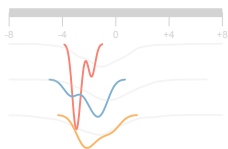
-0.82



ht

wt

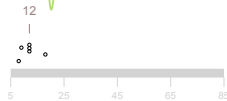
ofc



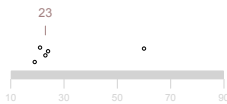
social smile (m)



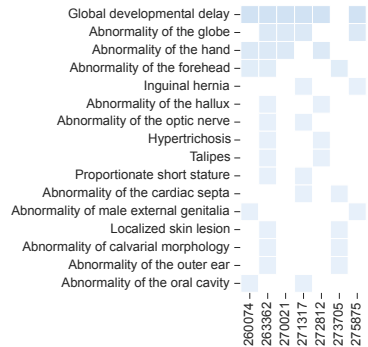
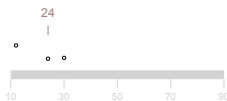
sat unaided (m)



walked unaided (m)



first words (m)



# PURA

n= 12

sex ratio

0.58



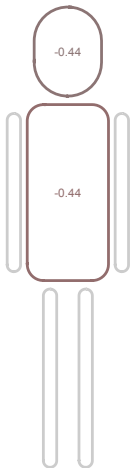
gestation (w)

40.1



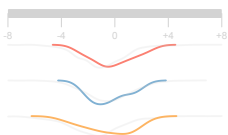
birth weight (z)

0.84



-0.18

ht  
wt  
ofc



social smile (m)

3.25



sat unaided (m)

14



walked unaided (m)

32.5

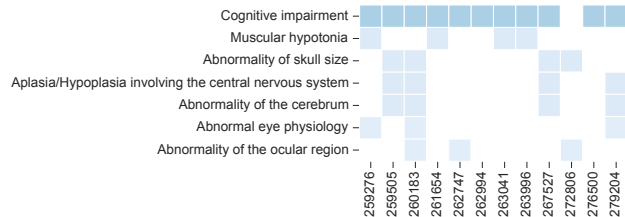


first words (m)

36



# recurrent HPO terms used in PURA cases



# QRICH1

recurrent HPO terms used in QRICH1 cases

n = 3

sex ratio

0.67



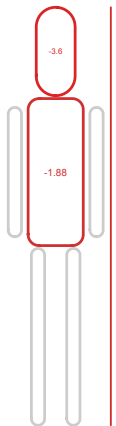
gestation (w)

39.3



birth weight (z)

-0.73

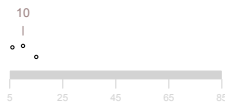


social smile (m)

2.5



sat unaided (m)



walked unaided (m)

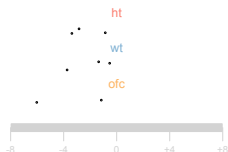
22



ht

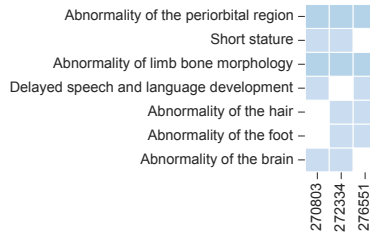
wt

ofc



first words (m)

24





# SATB2

n = 14

sex ratio

0.21

all male = all female

gestation (w)

39.6

birth weight (z)

0.34

-0.8

-0.43

-0.43

ht

wt

ofc

social smile (m)

1.5

sat unaided (m)

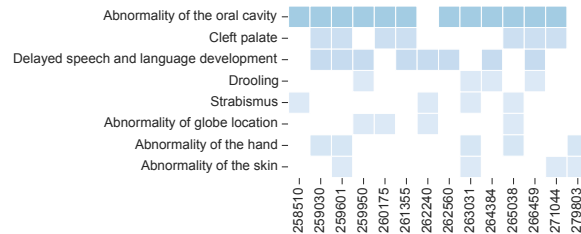
walked unaided (m)

24

first words (m)

74

recurrent HPO terms used in SATB2 cases



aggregate face  
from 10  
photographs



WWW.NATURE.COM/NATURE 73

# SCN1A

n = 2

sex ratio

0.5



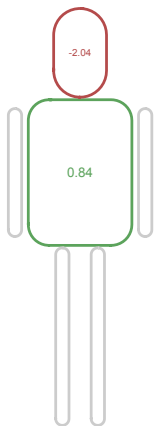
gestation (w)

37.5



birth weight (z)

-1.26



ht

wt

ofc



social smile (m)

2.5



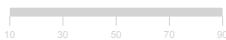
sat unaided (m)

80



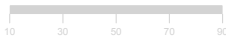
walked unaided (m)

48.5



first words (m)

80



Abnormality of movement		
Abnormality of the calvaria		
Seizures		
Global developmental delay		
	264245	273250

# SCN2A

n = 17

sex ratio

0.59



gestation (w)

38.5



birth weight (z)

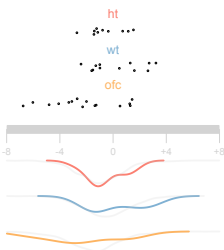
-0.04



-2.22

0.26

-0.57



social smile (m)

6



sat unaided (m)

12



walked unaided (m)

30

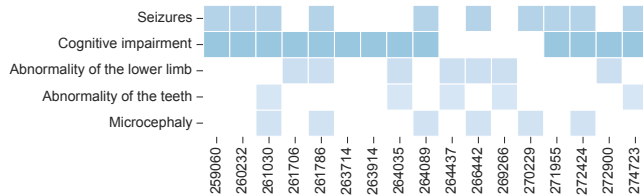


first words (m)

36.5



recurrent HPO terms used in SCN2A cases



# SCN8A

n = 7

sex ratio

0.57



gestation (w)

39.7



birth weight (z)

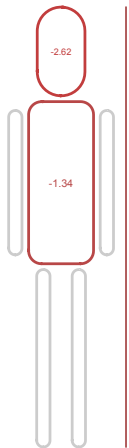
-0.32



-2.62

-1.34

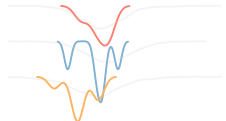
-1.21



ht

wt

ofc



social smile (m)

1.62



sat unaided (m)

64



walked unaided (m)

85.5

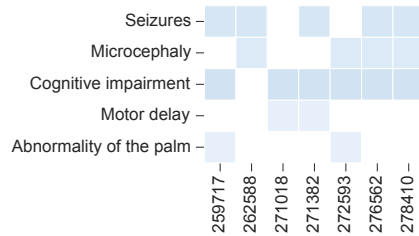


first words (m)

64



recurrent HPO terms used in SCN8A cases



# SETD5

n = 17

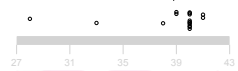
sex ratio

0.59



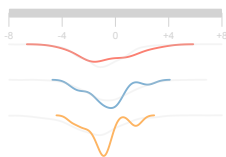
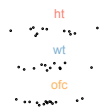
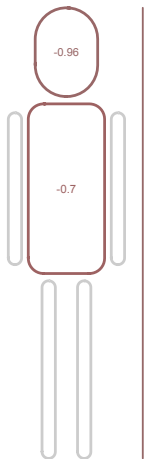
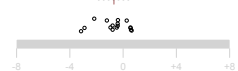
gestation (w)

38.8



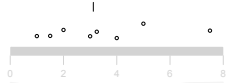
birth weight (z)

-0.69



social smile (m)

3.12



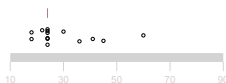
sat unaided (m)

12



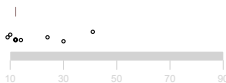
walked unaided (m)

24

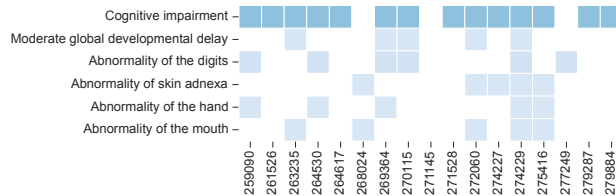


first words (m)

12



recurrent HPO terms used in SETD5 cases



# SET

n = 3

sex ratio

0.33



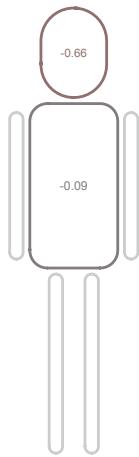
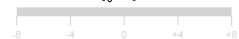
gestation (w)

41



birth weight (z)

-0.62



ht  
wt  
ofc



social smile (m)

3



sat unaided (m)

11.5



walked unaided (m)

27

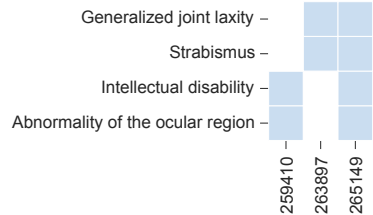


first words (m)

36



recurrent HPO terms used in SET cases



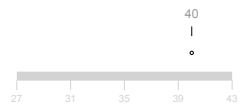
# SLC35A2

n = 1

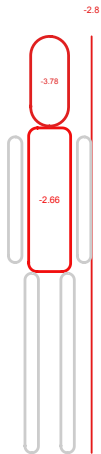
sex ratio



gestation (w)



birth weight (z)



ht

wt

ofc



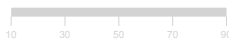
social smile (m)



sat unaided (m)



walked unaided (m)



first words (m)



101

101

101

# SLC6A1

n = 8

sex ratio

0.5

all male = all female

gestation (w)

39.6

27 31 35 39 43

birth weight (z)

0.59

-8 -4 0 +4 +8



social smile (m)

1.5

8

0 2 4 6 8

sat unaided (m)

9.5

5 25 45 65 85

walked unaided (m)

22

10 30 50 70 90

first words (m)

24

10 30 50 70 90

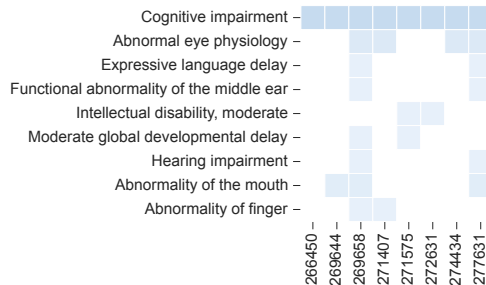
ht  
wt  
ofc

-8 -4 0 +4 +8

-8 -4 0 +4 +8

-8 -4 0 +4 +8

recurrent HPO terms used in SLC6A1 cases





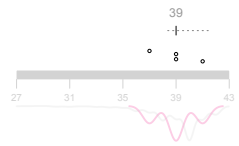
# SMAD4

n = 4

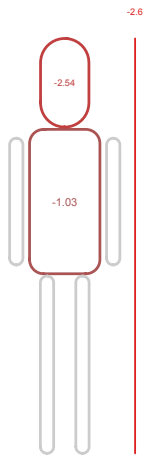
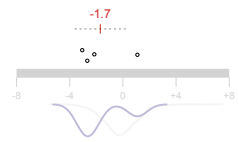
sex ratio



gestation (w)



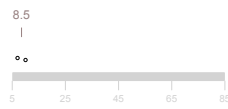
birth weight (z)



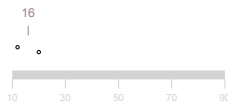
social smile (m)



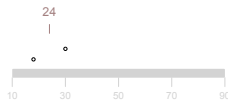
sat unaided (m)



walked unaided (m)



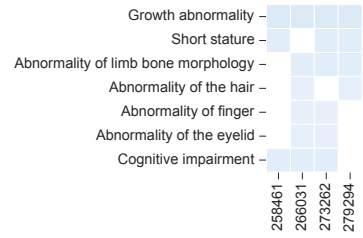
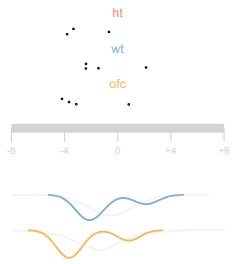
first words (m)



ht

wt

ofc



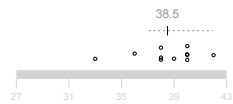
# SMARCA2

n = 11

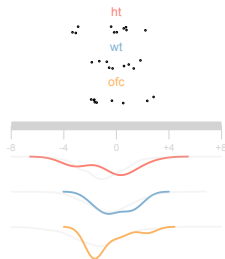
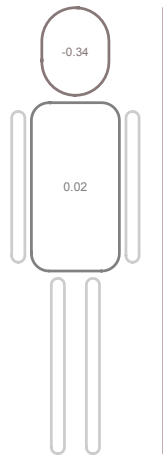
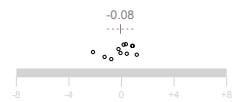
sex ratio



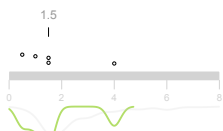
gestation (w)



birth weight (z)



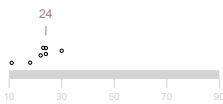
social smile (m)



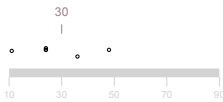
sat unaided (m)



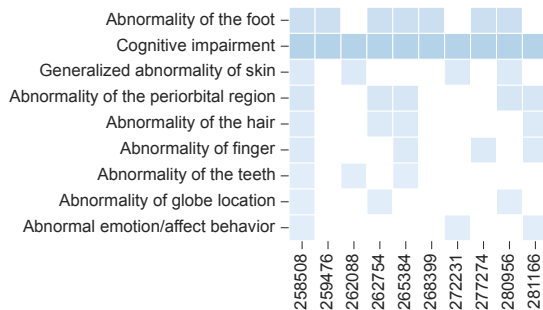
walked unaided (m)



first words (m)



recurrent HPO terms used in SMARCA2 cases



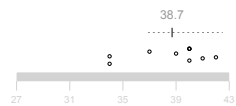
# SMC1A

n = 10

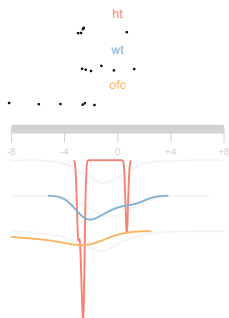
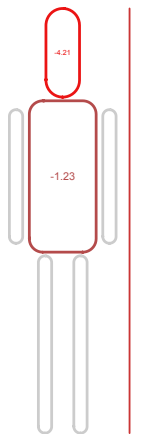
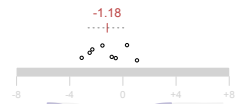
sex ratio



gestation (w)



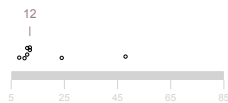
birth weight (z)



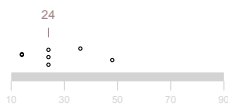
social smile (m)



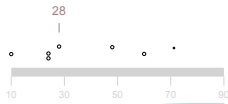
sat unaided (m)



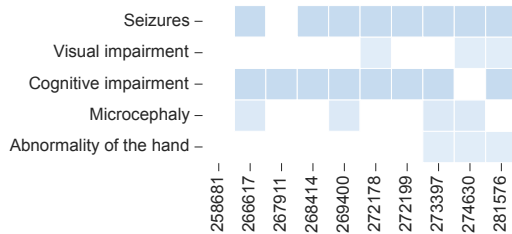
walked unaided (m)



first words (m)



recurrent HPO terms used in SMC1A cases



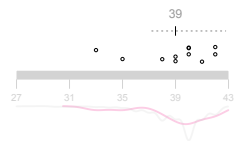
# STXBP1

n = 11

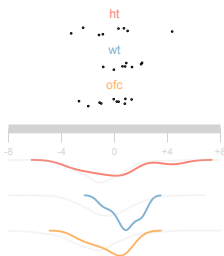
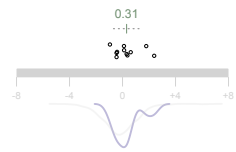
sex ratio



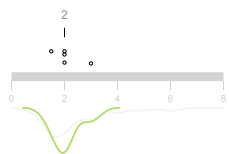
gestation (w)



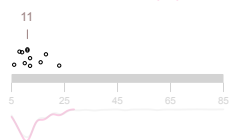
birth weight (z)



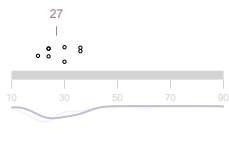
social smile (m)



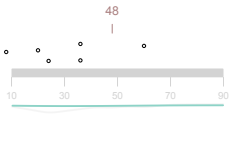
sat unaided (m)



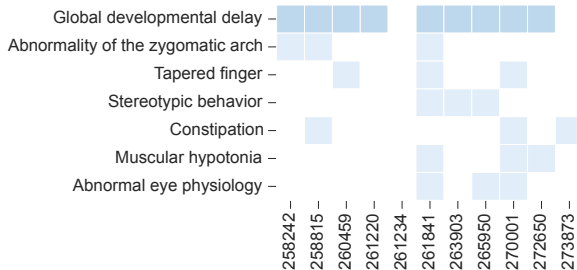
walked unaided (m)



first words (m)



recurrent HPO terms used in STXBP1 cases



# SUV420H1

n = 2

sex ratio

0.5

all male = all female

gestation (w)

40.5

27 31 35 39 43

birth weight (z)

0.98

-8 -4 0 +4 +8



ht

wt

ofc

social smile (m)

1.75



sat unaided (m)

10



walked unaided (m)

19

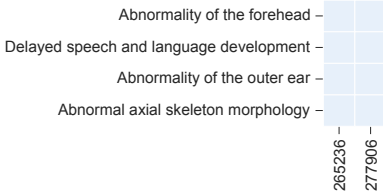


first words (m)

18



recurrent HPO terms used in SUV420H1 cases



# SYNGAP1

recurrent HPO terms used in SYNGAP1 cases

n = 15

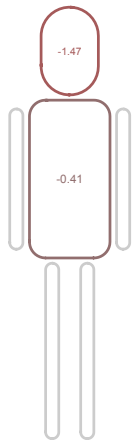
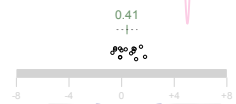
sex ratio



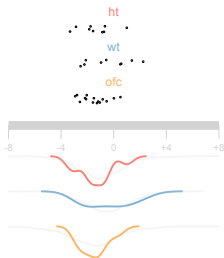
gestation (w)



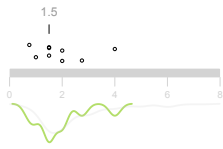
birth weight (z)



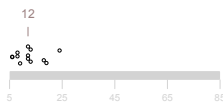
-1.41



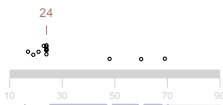
social smile (m)



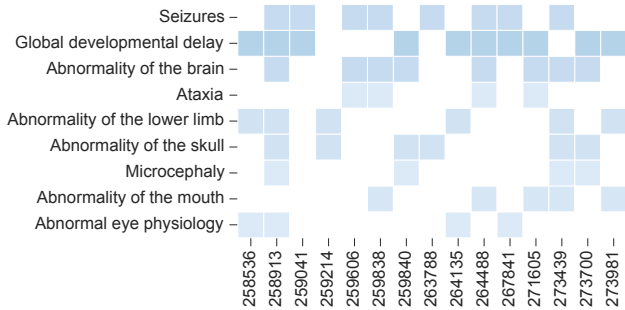
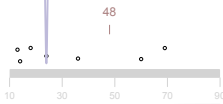
sat unaided (m)



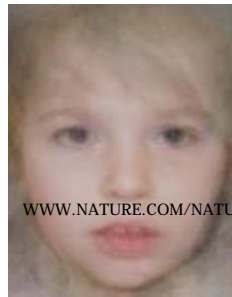
walked unaided (m)



first words (m)



aggregate face  
from 10  
photographs



WWW.NATURE.COM/NATURE 86

# TBL1XR1

n = 10

sex ratio

0.3

all male = all female

gestation (w)

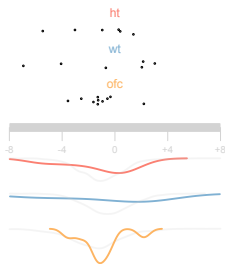
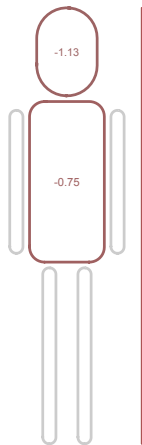
37.1

27 31 35 38 43

birth weight (z)

-0.3

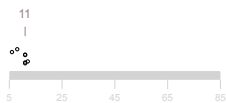
-8 -4 0 +4 +8



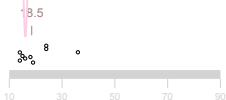
social smile (m)



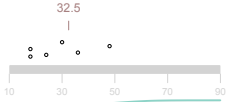
sat unaided (m)



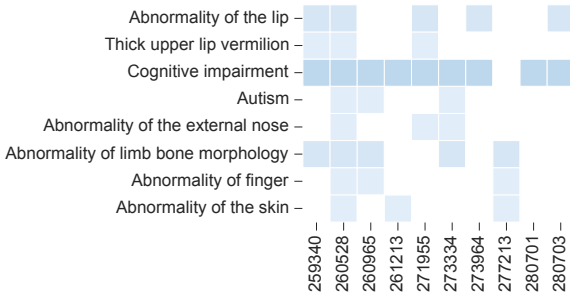
walked unaided (m)



first words (m)



recurrent HPO terms used in TBL1XR1 cases



# TCF20

n = 7

sex ratio

0.43



gestation (w)

39.7



birth weight (z)

0.07



-0.33

1.06

ht

wt

ofc



0.87

social smile (m)

2.75



sat unaided (m)

8



walked unaided (m)

19

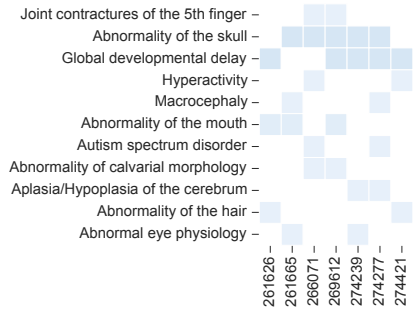


first words (m)

30



recurrent HPO terms used in TCF20 cases





# TCF4

n = 13

sex ratio

0.54



gestation (w)

38.5



birth weight (z)

0.24



ht

wt

ofc



-0.91

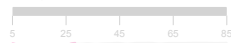
social smile (m)

2.75



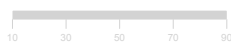
sat unaided (m)

15



walked unaided (m)

35

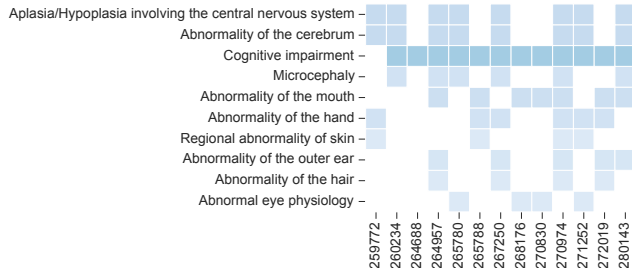


first words (m)

84.5



## recurrent HPO terms used in TCF4 cases



aggregate face  
from 10  
photographs



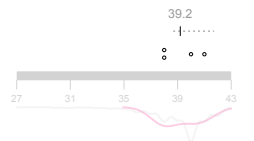
# TRIO

n = 4

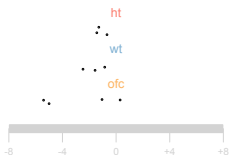
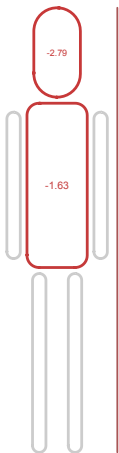
sex ratio



gestation (w)



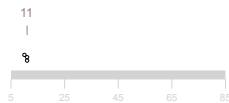
birth weight (z)



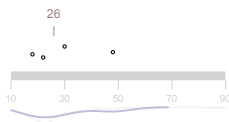
social smile (m)



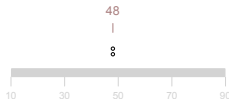
sat unaided (m)



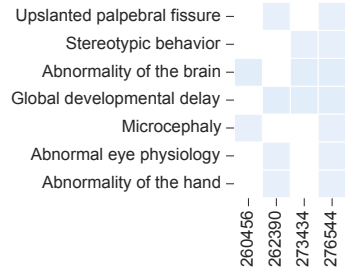
walked unaided (m)



first words (m)



recurrent HPO terms used in TRIO cases



# USP9X

n = 9

sex ratio

0.78



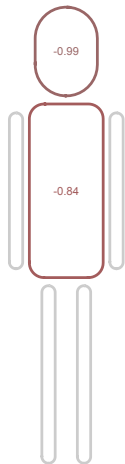
gestation (w)

38.8



birth weight (z)

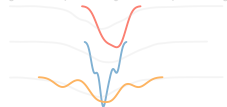
-0.64



ht

wt

ofc



social smile (m)

5.75



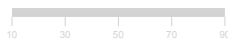
sat unaided (m)

11



walked unaided (m)

24

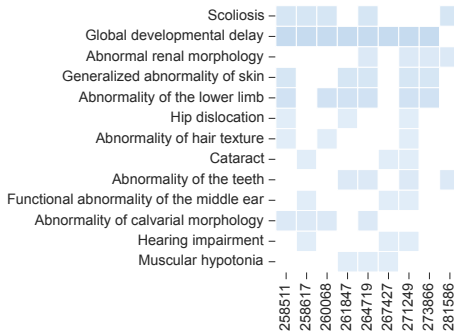


first words (m)

30



recurrent HPO terms used in USP9X cases



# WAC

n = 4

sex ratio

0.5



gestation (w)

39



birth weight (z)

-0.59



-0.52



ht

wt

ofc



social smile (m)

1.5



sat unaided (m)

11



walked unaided (m)

24

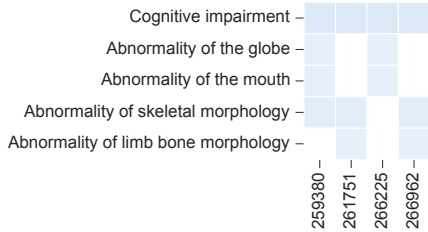


first words (m)

25.5



recurrent HPO terms used in WAC cases



# WDR45

n = 9

sex ratio

0.89



gestation (w)

38.7



birth weight (z)

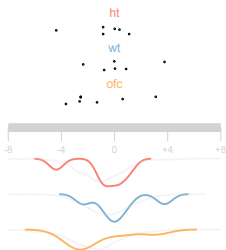
1.74



-1.29

0.25

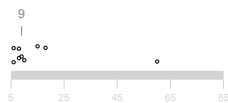
-0.77



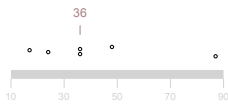
social smile (m)



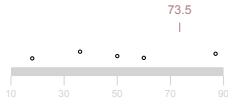
sat unaided (m)



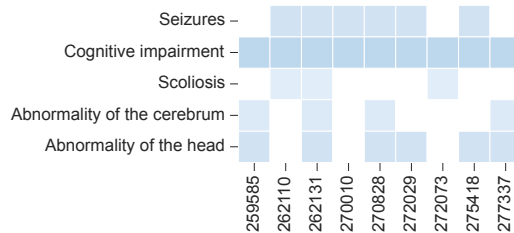
walked unaided (m)



first words (m)



recurrent HPO terms used in WDR45 cases



# ZBTB18

n = 5

sex ratio

0.4

all male = all female

gestation (w)

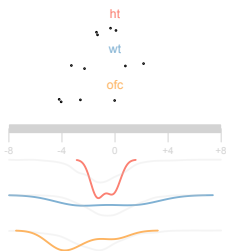
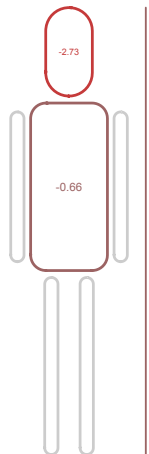
38.2

27 31 35 39 43

birth weight (z)

0.75

-8 -4 0 +4 +8



social smile (m)

7.75



sat unaided (m)

10.5

5 25 45 65 85



walked unaided (m)

23

10 30 50 70 90



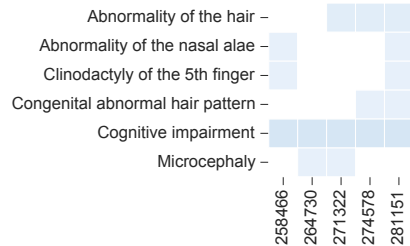
first words (m)

30

10 30 50 70 90



recurrent HPO terms used in ZBTB18 cases



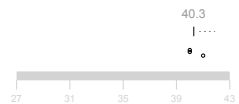
# ZC4H2

n = 3

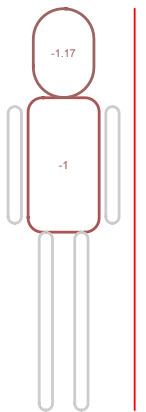
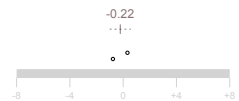
sex ratio



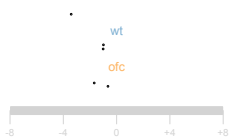
gestation (w)



birth weight (z)



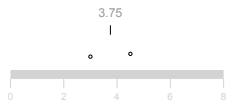
ht



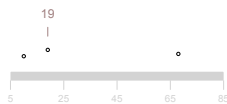
wt

ofc

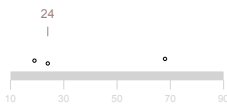
social smile (m)



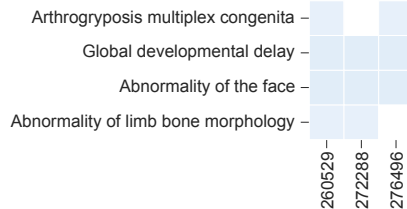
sat unaided (m)



walked unaided (m)



first words (m)



# ZMYND11

n = 5

sex ratio

0.4

all male = all female

gestation (w)

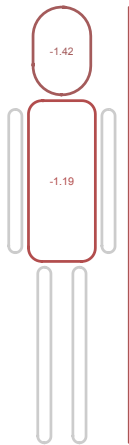
40

27 31 35 39 43

birth weight (z)

-0.64

-8 -4 0 +4 +8



social smile (m)

1.5

0 2 4 6 8

sat unaided (m)

9

5 25 45 65 85

walked unaided (m)

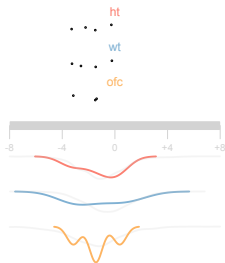
15

10 30 50 70 90

first words (m)

24

10 30 50 70 90



recurrent HPO terms used in ZMYND11 cases

