18q- Brain Development with Age and the Effect of Deletion Size

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Introduction: 18q deletion (18q-) is a chromosomal disorder that affects about 1 out of 40,000 people when a part of the long arm of chromosome 18 is missing. People with 18q- are typically mental retarded and developmental delayed[1], however, few studies have investigated the brain, the hub of the nervous system that let human beings communicate with each other and outside, of 18q-. The goal of this study was to investigate i) the brain volume development from 0 to 25 years old ii) and the effect of chromosomal deletion size on the brain development on distal 18q- subjects, whose deletions on chromosome 18 are terminal deletions.

Methods: Total 103 T1 weighted high-resolution MRI brain images were acquired from 18q- subjects aged 0.5—24.7 years, among which 32 were from males and 71 females. Total 67 T1 weighted high-resolution MRI brain images were acquired from typically developed control participants (39 males and 28 females, aged 1.4—20.1 years old). BET and FAST from FSL were used to extract brain and segment grey matter (GM) and white matter (WM). Whole brain, GM and WM volumes were calculated and were then regressed with age by exponential growth equations in Matlab (Mathworks, Inc.). The deletion sizes were evaluated to determine a linear effect on those brain volumes.

Whole brain, GM and WM volumes were regressed separately with age by the eq. 1, and the best fitting curves were plotted in Figure 1 in blue for 18q- and in green for controls.

$$Volumes = a \times (1 - e^{-b \times Age}) + c$$

(eq. 1)

Then, corresponding 18q- volumes were regressed with age and deletion size (DS) of the chromosome by equation 2.

$$Volumes = a \times (1 - e^{-b \times Age}) + c + d \times DS$$

(eq. 2)

Results and Discussion:

Pink dashed curves plotted eq. 1 using the regression coefficients results of eq. 2, and are considered as fitting curve after corrected for DS effect (Figure 1).

i) From observing coefficient b, we found that 18q- brain, GM, WM volumes grow quicker to get to the equilibrium volumes, except for male brain volume. Addition of coefficients a and c gave us the equilibrium volume. 18q- equilibrium volumes are smaller than controls (by 9%, 13%, 9% in males and 20%, 13% and 15% in females for brain, GM and WM volumes)., and 18q- male equilibrium volumes are similar to control females'.

ii)For 18q- subjects, all the regressions with eq. 2 have better goodness of fit than regressions with eq. 1, and the coefficients d are all negative. After corrected for DS effect, the equilibrium volumes of 18q- all get bigger and comparable with controls. These all proved that deletion size has a negatively linear effect on the whole brain, GM and WM volumes.

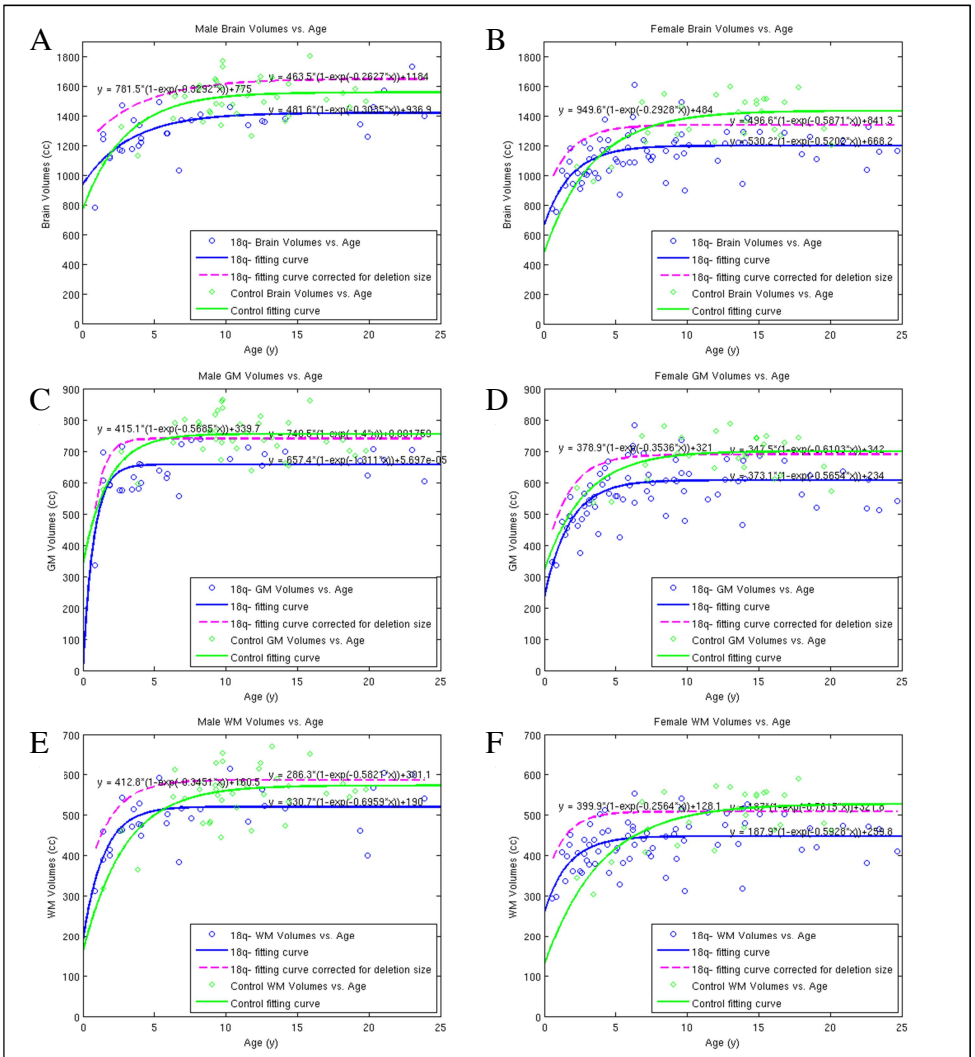

Figure 1 A-F. Left column (A, C, E) shows all male volumes plots, and right column females. Upper two (A and B) are brain volumes plots, middle two (C and D) grey matter volumes plots and lower two (E and F) white matter plots. In each plot, corresponding 18q- volumes vs. age is plotted in blue circles, and blue curve is best fit of the data with eq. 1. Pink dashed curves are fitting curve corrected for deletion size effect after regressing by eq. 2. Green diamond marks and curves are volumes and best fitting curves of control subjects.

Conclusion: This study demonstrated that i) whole brain, GM and WM volumes of 18q- grow quicker than those of controls (except for male brain volumes), and the equilibrium volumes in 18q- are more than 9% smaller than those corresponding volumes in controls, and that ii) deletion size on chromosome 18 have a negatively linear effect on the brain, GM and WM volumes, and after corrected for deletion size effect in our model, those equilibrium volumes are comparable with controls'.

Reference: Gay, C.T., et al. American Journal of Medical Genetics, 1997. **74**(4): p. 422-431