A Comparison of Head Circumference Growth Trajectories in the Context of the CHD8 Regulatory Network

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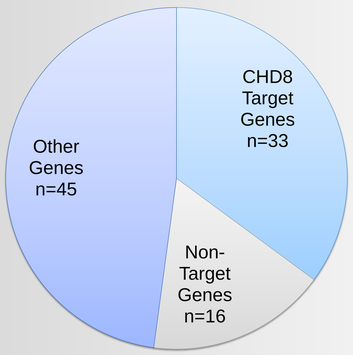
INTRODUCTION

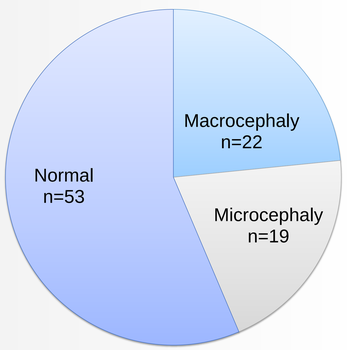
Research has examined converging regulatory networks and shared deficiencies in neural growth pathways, including genes targeted by *CHD8*, a gene strongly associated with ASD (Cotney et al., 2015). One of the most prominent phenotypes in *CHD8* is macrocephaly (Bernier et al., 2014; Barnard, Pomaville, & O'Roak, 2015). Despite the relevance of head size to brain development, growth trajectories have not been examined across functional gene classifications.

METHOD

Head circumference (HC) measurements derived from medical records & medical examination at the research visit were evaluated for 94 participants (female *n=39*, male *n*=55) with a disruptive mutation to an ASD-associated gene. Participants were characterized as Macrocephalic or Microcephalic if they met criteria at any time point (i.e. +/- 2 population-based z-scores).

Head Circumference Categorization





Gene Categorization Criteria
(Cotney et al., 2015; Sugathan 2014)

	CHD8 Target Gene	Other Gene		Non-Target Gene
CHD8 binding site	✓	Mixed evidence		X
CHD8 co-expression	✓			X
Expressed in human brain	✓			X
Specific genes	CHD8 ARID1B CTNNB1 PTEN SETBP1 TBL1X41 TRIP12	ADNP ASH1L CHD1 CHD2 DYRK1A FOXP1 KDM6B LZTR1 MED13L	MYH10 NCKAP1 POGZ SCN2A SETD2 SUB420H1 SYNCRIP WDFY3 WDR33	ANK2 CAPN8 DSCAM GRIN2B LARP4B STXBP1 TBR1

Functional gene classifications of ***CHD8*** and its target variants in the **CHD8 regulatory network** relative to **non-targets** and to other non-associated genes **did not reveal** consistent and non-overlapping **growth trajectories**.

Head circumference growth patterns among individuals with **ASD-associated** disruptive gene events differ significantly between discrete **macrocephalic** and **microcephalic** groups.

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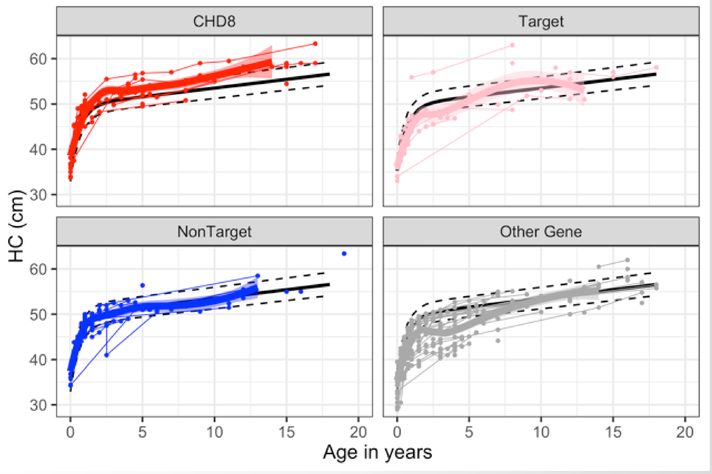
RESULTS

Best fitting random effect linear models (via MPLUS) indicated that HC increased linearly with a quadratic deceleration with age, β = -.11, SE = .02, p < .001.
There was no main effect of CHD8 regulatory group, indicating that all groups exhibited similar growth trajectories.

	Quadratic		
Effect/Group	**β**	**SE**	**p**
Age	-0.11	0.02	<.001
CHD8 Target	-1.51	0.21	<.001
Non-Target	-1.24	0.65	0.058
Other	-1.2	0.12	<.001
Microcephaly	-0.98	0.19	<.001
Macrocephaly	-1.28	0.21	<.001
Normal HC	-1.29	0.12	<.001



DISCUSSION

Analyses of functional gene classifications in the context of the CHD8 regulatory network did not reveal significant differences in head circumference growth trajectories.
This functional gene classification may not have sufficient specificity to predict head growth at this time. Other limitations may include the study being underpowered; miscategorization of genes, which could include unknown causal mechanisms in the Other Gene category; and/or that a real effect may be occurring but it is too small to be captured by the current analyses.
Grey matter overgrowth in the first years of life (Courchesne, Campbell, & Solso, 2011) and atypical levels of cerebral fluids (Shen et al., 2013) are common in ASD and may contribute to macro- and microcephalic phenotypes. Further exploration of HC phenotypes and their possible associations with genomic subtypes of ASD may provide clues to the neurobiological and developmental etiology of neurodevelopmental disorders.

References:
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