Chromatin Remodeler CHD8

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Chromodomain Helicase DNA-binding 8 (CHD8) is a high confidence risk factor for autism spectrum disorders (ASDs) and the genetic cause of a distinct neurodevelopmental syndrome with the core symptoms of autism, macrocephaly, and facial dysmorphism. The role of CHD8 is well-characterized at the structural, biochemical, and transcriptional level. By contrast, much less is understood regarding how mutations in *CHD8* underpin altered brain function and mental disease. Studies on various model organisms have been proven critical to tackle this challenge.

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1. Introduction

The nuclear DNA of eukaryotic cells is tightly packaged with the help of histone proteins to form the so-called chromatin. This structure can adopt an open (transcriptionally active) or closed (transcriptionally inactive) configuration that critically controls the access of transcription factors (TFs) to their binding sites. Epigenetic factors control these chromatin states by imposing posttranslational modifications of free histone tails and by chromatin remodeling (reviewed in [1]). Chromatin states additionally depend on epigenetic factors imposing DNA modifications (e.g., DNA methylation) (reviewed in [2]). Both processes, modification of chromatin and of DNA, closely interact with each other and play an important role in the precise temporal and spatial control of gene expression during development and beyond. Consistent with this scenario, epigenetic factors have been increasingly recognized for their role in the initiation and progression of mental diseases (reviewed in [3][4]).

Mutations in genes that encode for chromatin remodelers (CRs) have been originally identified as the genetic cause of distinct neurodevelopmental syndromes (reviewed in [5][6]). In addition, genome-wide association studies (GWAS) on neurodevelopmental disorders, including intellectual disability (ID) and ASD, have reported genetic variation in CRs to be significantly associated with disease. These findings have spurred research on the biochemical, structural, and biological properties of CRs.

2. Mutations in CHD8 Associate with Autism and Macrocephaly

ASD comprises a group of neurodevelopmental disorders that share to varying degree clinical symptoms and genetic risk factors (reviewed in [7]). ASD affects about one in 100 people worldwide and is more prevalent in boys than in girls. Early dysfunction in communication and social interaction frequently concurs with restricted, repetitive behavior. Concurrently, ASD associates with ID (35%), language delay (50%), or epilepsy (5–15%) [8]. All of these impairments persist lifelong and greatly reduce the quality of life.

Heritability for ASD in monozygotic twins is high (0.62–0.94), and siblings of affected individuals show a high risk for relative recurrence risk (10.1%) [7]. The genetic architecture of ASD is complex, with risk being conferred by many independent loci containing common and rare variants as well as by de novo mutations with genetic variation ranging from single nucleotide polymorphism (SNP) to chromosomal deletion/duplication or other rearrangements. All of these genetic factors can combine in small or large number in ASD. Thereby, their relative contribution is likely different in specific syndromes and subpopulations; e.g., a single sporadic presentation in an individual with no previous family history is likely to differ from multiple affected individuals in a family.

CHD8 is one of the most frequently mutated and most penetrant genes in ASD [7]. Large scale analysis of parent-child trios/quads through whole exome sequencing (WES) [9][10][11][12] and targeted resequencing [11][13][14][15][16][17][18] established heterozygote de novo mutations in *CHD8* as high confidence risk factor in ASD. These mutations included frameshift, nonsense, missense, translocation, single nucleic acid deletion, and splice site variant mutations and are predicted to lead to a loss of function.

Interestingly, patients with de novo mutation in *CHD8* frequently exhibited an unusual large head circumference [11][13]. This phenotype was also observed in patients carrying a balanced translocation disrupting *CHD8* [19]. Additional facial dysmorphisms consisted of prominent forehead and eyes, and posteriorly rotated ears. In support of these early observations, integrated analysis of 15 patients with disruptive *CHD8* mutation (13 de novo, one inherited, and one of unknown origin) revealed that autism was the most common diagnosis (N =13) closely followed by macrocephaly (N = 12) [14]. Orbital overgrowth developed already within the first 2 months postnatally, pointing to a neurodevelopmental origin, and associated with increased head growth throughout early childhood. Besides these core symptoms, patients with de novo *CHD8* mutation developed to a lesser degree recurrent obstipation and sleep disturbances.

These landmark studies are supported by recent findings that strengthen the hypothesis that de novo mutations in *CHD8* underpin a distinct subtype in ASD. Another patient with a de novo balancing translocation disrupting *CHD8* presented with autistic features, developmental delay, and language disability at 2 years age [20]. Collated clinical data from individuals with deleterious *CHD8* mutations (N = 51) corroborated further the existence of a distinct ASD subtype in which children manifest developmental delay, ID, and/or ASD in addition to characteristic facies (see Figure 3 of [20]).

Recent studies also sought to reassess the overgrowth phenotype in individuals with de novo *CHD8* mutations. Ostrowski et al. [21] identified 27 unrelated patients with pathogenic or likely pathogenic *CHD8* mutation (25 null variants, 2 missense variants). All of them showed ID with 85% in the mild or moderate range, and 85% had a height and/or head circumference ≥ 2 standard deviations above the mean. Behavioral symptoms were common (78%) with over half (56%) either diagnosed with ASD or autistic traits (see Table 1 of [21]). Similarly, An et al. [22] reported the identification of 4 new de novo *CHD8* mutations (including 2 nonsense variants, 1 splice variant, and 1 missense variant) in Chinese individuals with ASD. Comprehensive phenotyping revealed that these individuals shared prenatal onset macrocephaly, facial dysmorphism, overgrowth during puberty, ID, and sleep disorders (see Table 1 of [22]).

In a recent phenotype-to-genotype approach, Wu et al. [23] carried out WES on 67 families with ASD and abnormal head circumference. Pathogenic or likely pathogenic mutations were identified in 15% of the affected individuals with *CHD8* and *PTEN* (phosphatase and tensin homolog) top ranked among disrupted candidate genes.

Moving beyond genetics, Beighley et al. [24] focused on biological pathways shared by multiple ASD-associated risk genes. Thereby, the researchers investigated clinical and behavioral features of individuals with ASD (see Table 1 of [24]) carrying disruptive mutations (i) in *CHD8* (N = 15), (ii) in genes regulated by CHD8 (N = 22) or (iii) in genes unrelated to *CHD8* (N = 106). Subgroup (i) and (ii) shared less severe adaptive deficits in communication skills, similar functional language, more social motivation challenges in those with ASD, macrocephaly, higher weight, and lower seizure prevalence when compared to subgroup (iii). This suggests that neurodevelopmental subtypes defined by gene–gene interactions can improve stratification of patients relative to mutations alone.

In summary, compelling genetic and clinical evidence supports a role of de novo mutations in *CHD8* as genetic cause of a distinct subtype in ASD that includes the core symptoms of autism, macrocephaly, and facial dysmorphism.

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