Genotype-Phenotype Correlations

Subjects: Genetics & Heredity

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Coffin-Siris syndrome (CSS, MIM 135900) is a multi-system intellectual disability syndrome characterized by classic dysmorphic features, developmental delays, and organ system anomalies. Genes in the BRG1(BRM)-associated factors (BAF, Brahma associated factor) complex have been shown to be causative, including ARID1A, ARID1B, ARID2, DPF2, SMARCA4, SMARCB1, SMARCC2, SMARCE1, SOX11, and SOX4.

Coffin-Siris syndrome genotype-phenotype BAF complex

1. Introduction

Genes in the BAF (Brahma/BRG1-associated factor) complex are essential in chromatin remodeling. Pathogenic variants in this complex have been associated with a number of conditions, including Coffin-Siris syndrome (CSS, MIM 135900, ORPHA:1465), Nicolaides-Baraitser syndrome (NCBRS, MIM 601358) and other CSS-like conditions (*SOX4*) [1][2]. A range of learning and developmental differences, organ-related anomalies, and variable physical and facial features typically characterize BAFopathies, a term that has been proposed in its description. The most well-known among these syndromes is CSS. CSS is a well-described intellectual disability disorder characterized classically by facial features and organ-system anomalies. Historically, CSS was classified upon recognition of typical phenotype changes, hypoplasia of the distal phalanx, hypertrichosis, and sparse scalp hair. Genes in the BAF complex have been shown to be causative, including *ARID1A*, *ARID1B*, *ARID2*, *DPF2*, *SMARCA4*, *SMARCB1*, *SMARCC2*, *SMARCE1*, *SOX11*, and *SOX4*. Individuals display significant variability in terms of learning and developmental differences, as well as cardiac, renal, brain, and skeletal malformations [3]. Some more common physical manifestations include agenesis of the corpus callosum, variable cardiac defects, feeding difficulties, hypotonia, and vision and hearing anomalies.

A number of genotype-phenotype correlations have been conducted in individuals with molecularly confirmed CSS. Work in this field has incorporated genotype-phenotype associations for individuals with pathogenic variants in *ARID1A*, *ARID1B*, *SMARCA4*, *SMARCB1*, *SMARCE1*, and *SOX11* [3][4][5][6][7][8][9]. Current hypotheses suggest that genes in the BAF complex associate with transcription factors that play a role in neurodevelopment [2][8][10]. In general, more significant developmental delays and fewer anatomic anomalies have been described in individuals with *ARID*-related variants, compared to individuals with *SMARC*-related variants in whom developmental delays are thought to be milder, and more severe organ-related complications are seen. *SOX11* has been associated with more neurodevelopmental complications [8]. The exact etiology behind these genotype-phenotype correlations remains unknown.

2. Cohort Description

We identified 208 individuals in our cohort with molecularly confirmed pathogenic variants along the BAF complex and with sufficient phenotypic information for inclusion in our study. Pathogenic variants within ARID1B (*n* = 130, 63%) and SMARCA4 (*n* = 32, 15%) were found to be the most common within our cohort. The remaining 22% of our CSS patients were found to have variants in the following genes (Table 1): ARID1A (*n* = 15, 7%), SMARCB1 (*n* = 14, 7%), ARID2 (*n* = 8, 4%), SOX11 (*n* = 5, 2%), and SMARCE1 (*n* = 4, 2%). Males account for 60% (*n* = 125) of individuals in our sample population, females account for the additional 40% (*n* = 83). Across our entire CSS cohort, the four most common phenotypes are as follows: hypertrichosis (109/208, 52%), sparse scalp hair (98/208, 47%), hypotonia (89/208, 43%), and hypoplasia of the distal phalanx (85/208, 41%).

3. Phenotype Generalizations

To determine the frequency of CSS phenotypes within patients affected by pathogenic variants in different BAF complex components, we analyzed 28 classic CSS phenotypes in patients with pathogenic variants in each of the seven BAF complex genes represented in our cohort. The results of these analyses are shown in Table 2. Sparse scalp hair (8/15, 53%), hypoplasia of the distal phalanx (8/15, 53%), and strabismus (8/15, 53%) were the most common phenotypes reported in individuals with variants in ARID1A. In the ARID1B population, hypertrichosis (81/130, 62%) was the only phenotype reported in the majority of individuals. Sparse scalp hair (5/8, 63%) and global developmental delay (4/8, 50%) were seen in a majority of ARID2 patients. Hypoplasia of the distal phalanx was seen in the majority of SMARCA4 patients (20/32, 63%). Cryptorchidism, sparse scalp hair, and hypertrichosis were all seen in 50% of SMARCB1 patients (7/14, 3/6 males for cryptorchidism). The SMARCE1 and SOX11 groups each had five or fewer patients, making it difficult to make any general statements about phenotype frequency in these populations.

4. Phenotype Frequency

To assess for differences in phenotype frequency across different CSS patient groups, the frequency of each phenotype across all genotype groups was compared (Figure 1A). Altogether, five phenotypes were identified with nominally statistically significant differences across CSS genotype groups: fifth digit hypoplasia ($p = 3.185 \times 10^{-3}$), hypertrichosis ($p = 1.381 \times 10^{-2}$), kidney malformations ($p = 1.294 \times 10^{-6}$), microcephaly ($p = 2.694 \times 10^{-3}$), and macrocephaly ($p = 3.852 \times 10^{-2}$). It should be noted that some of our genotype groups (notably SOX11 and SMARCE1) are composed of very few patients, making the interpretation of some of these statistical results more difficult for these groups in particular. For kidney malformations, these significant differences were primarily driven by the relative overabundance of kidney malformations in individuals with ARID1A (normalized Pearson residual of Chi-square analysis = 2.19), SMARCE1 (residual = 3.44), and SMARCB1 (residual = 3.1) variants, and an underabundance of kidney malformations in individuals with ARID1B (residual = −2.18) variants. The significant differences in microcephaly were chiefly driven by the overabundance of this phenotype in the SMARCA4 patients (residual = 3.3), and the significant differences in macrocephaly were driven by the corresponding underabundance

of this phenotype in the SMARCA4 (relative residual = −2.08) group. For fifth digit hypoplasia, there is a trend towards the enrichment of the phenotype in SMARCA4 (residual = 1.91) and SMARCE1 (residual = 1.85) patients, and a trend towards underrepresentation of this phenotype in ARID1B (residual = −1.39) and ARID2 (residual = −1.26) patients. For the hypertrichosis phenotype, there is a trend towards the enrichment of this phenotype in ARID1B patients (residual = 1.48) compared to all other patient groups.

5. Developmental Differences

Individuals with CSS are known to have a wide range of global developmental differences. To identify patient genotypes with the most significant delays, we ran a BAF complex by-gene analysis of five developmental milestones—walk, sit, first word, roll, and crawl acquisition. We compared the average age, in months, that each genotype met these milestones to the average age demonstrated by the DDST-II. The percent delays were then calculated for each genotype. While all genotypes were delayed in walking, individuals with variants in *ARID1A* were the most significantly delayed (64%). Individuals with variants in *SMARCB1* were most delayed in acquiring their first word (78%), rolling (57%), and sitting (55%). While all genotypes were delayed in crawling, *ARID1A* individuals (44%) were the most significantly delayed. Oddly enough, individuals with variants in *SOX11* were early (50%) in meeting their roll milestone. Individuals with variants in *SOX11* also met their first word (44%), sit (10%), and crawl (10%), milestones earlier than other genotypes.

6. Quantitative Traits

To more rigorously assess differences in quantitative traits across genotype groups, we compared mean values in age at developmental milestone acquisition and birth length/weight (Figure 1B–D). For roll acquisition, there was a general trend towards patients with SMARCB1 variants having delayed acquisition of this developmental milestone compared to all other gene groups, with significant differences specifically seen between patients with ARID1B variants and those with SMARCB1 variants ($p = 4.0 \times 10^{-2}$). Similarly, there was a general trend towards patients with SMARCB1 variants having delayed sit acquisition compared to all other genotype groups, with significant differences seen between SMARCB1 patients and ARID1B patients ($p = 6.0 \times 10^{-4}$), and ARID1A patients ($p = 3.0 \times 10^{-2}$) and SMARCA4 patients ($p = 5.0 \times 10^{-2}$). Lastly, patients with ARID2 pathogenic variants were found to have significantly shorter birth lengths compared to almost all other genotype groups (ARID2 vs. ARID1B $p = 4.8 \times 10^{-9}$, ARID2 vs. SMARCA4 $p = 1.9 \times 10^{-8}$, ARID2 vs. ARID1A $p = 4.3 \times 10^{-7}$, ARID2 vs. SMARCB1 $p = 5.1 \times 10^{-7}$, ARID2 vs. SOX11 $p = 1.5 \times 10^{-3}$).

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