These codes cluster under four clinically meaningful FASD diagnoses: fetal alcohol syndrome (FAS) (4-Digit Code Diagnostic Categories A, B): Partial FAS (PFAS) (Diagnostic Category C); Static Encephalopathy/Alcohol-Exposed (SE/AE) (Diagnostic Categories E, F); and Neurobehavioral Disorder/Alcohol-Exposed (ND/AE) (Diagnostic Categories G, H) (Figure 1D). Individuals that did not meet criteria for one of these FASD diagnostic classifications were identified in this study as Not FASD/Alcohol-Exposed (Diagnostic Categories I, J).

Study groups

The sibling pairs were partitioned into four study groups: 1. monozygotic twins, 2. dizygotic twins, 3. full-siblings, and 4. half-siblings sharing a common birth mother. Monozygotic twin pairs share virtually 100% of their genome. Dizygotic twin pairs and full-sibling pairs share, on average, 50% of their genome. Half-sibling pairs with a common birth mother share, on average, 25% of their genome [8,9].

Data from all twin and sibling pairs that met the following inclusion criteria were used in this study:

- Sibling pairs were monozygotic twins, dizygotic twins, full-siblings, or half-siblings sharing the same birth mother.
- Both siblings received an FASD diagnostic evaluation at an FASDPN clinic by the same interdisciplinary team using the 2004 FASD 4-Digit Diagnostic Code.
- Siblings did not present with another genetic syndrome.
- Age at diagnosis could range from newborn to adult. Effort was made to select pairs that both fit into one of three age ranges at the time of diagnosis (0-3 years, 4-8 years, 9 or more years). This minimized the chance that FASD diagnostic contrasts between pairs may be due to one sibling being too young to fully assess or comparably assess brain function.
- All siblings had confirmed PAE. Twin pairs, by definition, had virtually identical PAE. Full sibling pairs and half-sibling pairs had to have concordant Alcohol Ranks (e.g., both siblings had to have Rank 3 alcohol exposure or both had to Rank 4 alcohol exposure).
- Effort was made to select siblings raised together who experienced identical or similar other prenatal and postnatal risk factors.
- Siblings could be of any gender or race.

Data set

All data collected during an FASD diagnostic evaluation at the FASDPN are entered into the FASDPN database with patient consent and University of Washington Human Subjects Division approval. Approximately 3,000 patients have been evaluated in the clinic to date. The data document patient demographics, PAE, all other reported prenatal and postnatal adverse exposures and events and measures of growth, facial features, and structural and/or functional brain abnormalities used to derive the FASD 4-Digit Code. These data are recorded on three standardized diagnostic forms: the New Patient Information Form, FASD Diagnostic Form, and FAS Facial Photographic Analysis Report posted on the FASDPN website www.FASDPN.org [2,8].

Key data used in this study included the patient's FASD 4-Digit Code, FASD diagnostic category (FAS, PFAS, SE/AE, ND/AE and Not FASD/AE), and their Growth, Face, CNS and Alcohol Ranks (Figure 1). The CNS Rank in the 4-Digit Code serves two purposes: 1) Ranks 1 through 4 document the probability of underlying CNS structural abnormality (Rank 1: unlikely; Rank 2: possible; Rank 3: probable; and Rank 4: definite). 2) Ranks 1 through 3 also document the magnitude of CNS dysfunction as measured using standardized neuropsychological tools (Rank 1: no dysfunction; Rank 2: moderate dysfunction; and Rank 3 severe dysfunction). The CNS functional Ranks 1-3 introduced by the 4-Digit Code were case-defined to predict increasing likelihood of structural CNS abnormality—a predictive correlation that was subsequently confirmed through magnetic resonance imaging [7]. To distinguish these two CNS measures in the current study, they are labeled CNS1-4 and CNS1-3. PAE is ranked by the 4-Digit Code on a 4-point Likert scale (Figure 1A). Only subjects with Rank 3 or Rank 4 PAE were enrolled in this study. An Alcohol Rank 4 is assigned when PAE is confirmed and reported to be high risk (generally high peak blood alcohol concentrations

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