Supplemental Table 1. Frequency of eligible defects among the 4,750 cases classified as having multiple defects with only one eligible defect in the National Birth Defects Prevention Study (NBDPS).

|  |  |
| --- | --- |
| Birth Defects | Cases classified as multiple but excluded as they only had one NBDPS-eligible defect |
|
| Congenital heart defect  | 2003 |
| Oral clefts | 490 |
| Anorectal atresia/stenosis | 365 |
| Esophageal atresia | 213 |
| Hypospadias | 197 |
| Neural tube defects† | 191 |
| Limb deficiency | 165 |
| Diaphragmatic hernia | 140 |
| Intestinal atresia/stenosis | 128 |
| Gastroschisis | 128 |
| Anotia/Microtia | 123 |
| Craniosynostosis | 114 |
| Omphalocele | 99 |
| Eye defects‡ | 71 |
| Hydrocephaly | 64 |
| Dandy-Walker malformation or cerebellar hypoplasia  | 42 |
| Amniotic band syndrome and limb-body wall complex  | 37 |
| Choanal atresia | 36 |
| Holoprosencephaly | 34 |
| Biliary atresia | 29 |
| Sacral agenesis | 25 |
| Cloacal exstrophy | 22 |
| Renal agenesis/hypoplasia | 21 |
| Bladder exstrophy | 13 |

†This group includes all neural tube defects eligible for the NBDPS (spina bifida, encephalocele, anencephaly and craniorachischisis).

‡ This group includes all eye defects eligible for the NBDPS (anophthalmia/microphthalmia, glaucoma and anterior chamber defects, and infantile cataracts).

Supplemental Table 2. Additional MCAs with at least 5 affected cases observed in the National Birth Defects Prevention Study, in descending order of observed-to-expected ratio.

|  |  |  |
| --- | --- | --- |
| **Combination of MCAs** | **Observed** | **Adjusted O:E ratio** |
| CHD + Oral cleft + DWM/Cerebellar hypoplasia | 10 | 12.6 |
| Anotia/microtia + Choanal atresia  | 9 | 12.1 |
| CHD + Limb deficiency + Renal agenesis/hypoplasia | 7 | 11.8 |
| Oral cleft + Limb deficiency + Anotia/microtia | 11 | 11.8 |
| CHD + Limb deficiency + Choanal atresia | 5 | 11.4 |
| Anorectal atresia/stenosis + Esophageal atresia  | 122 | 10.8 |
| Anotia/microtia + Sacral agenesis  | 7 | 9.9 |
| Anorectal atresia/stenosis + Esophageal atresia + Intestinal atresia/stenosis  | 8 | 9.8 |
| CHD + Esophageal atresia + Limb deficiency | 22 | 9.5 |
| CHD + Anorectal atresia/stenosis + Limb deficiency | 32 | 9.3 |
| CHD + Oral cleft + Anotia/microtia | 22 | 9.1 |
| CHD + Limb deficiency + Anotia/microtia | 15 | 8.7 |
| CHD + Anorectal atresia/stenosis + Renal agenesis/hypoplasia | 7 | 8.2 |
| CHD + Anotia/microtia + Eye defect | 7 | 7.8 |
| Anorectal atresia/stenosis + Limb deficiency + Hydrocephaly | 5 | 7.7 |
| Oral cleft + Limb deficiency + Hydrocephaly | 5 | 7.5 |
| CHD + Anotia/microtia + Hydrocephaly | 5 | 7.5 |
| CHD + Esophageal atresia + Intestinal atresia/stenosis  | 10 | 7.4 |
| Anorectal atresia/stenosis + Esophageal atresia + Hydrocephaly | 5 | 7.4 |
| Limb deficiency + Renal agenesis/hypoplasia  | 21 | 7.2 |
| CHD + Sacral agenesis  | 44 | 7.1 |
| NTD + Omphalocele  | 30 | 6.5 |
| CHD + Anorectal atresia/stenosis + Intestinal atresia/stenosis  | 13 | 6.5 |
| CHD + Esophageal atresia  | 237 | 6.2 |
| CHD + Esophageal atresia + Anotia/microtia | 9 | 6.1 |
| CHD + Oral cleft + Eye defect | 14 | 5.9 |
| CHD + Limb deficiency + Hydrocephaly | 7 | 5.8 |
| CHD + Anorectal atresia/stenosis + Hypospadias | 7 | 5.8 |
| Esophageal atresia + Choanal atresia  | 11 | 5.8 |
| Anotia/microtia + Eye defect  | 17 | 5.8 |
| Esophageal atresia + Limb deficiency  | 59 | 5.6 |
| Esophageal atresia + Intestinal atresia/stenosis  | 33 | 5.4 |
| CHD + Esophageal atresia + Hydrocephaly | 6 | 5.4 |
| Anorectal atresia/stenosis + Limb deficiency  | 84 | 5.2 |
| CHD + NTD + Eye defect | 5 | 5.0 |
| Oral cleft + DWM/Cerebellar hypoplasia  | 27 | 5.0 |
| CHD + Limb deficiency + Diaphragmatic hernia  | 8 | 4.9 |
| Oral cleft + Anotia/microtia  | 65 | 4.9 |
| CHD + Oral cleft + Esophageal atresia | 15 | 4.7 |
| HD + DWM/Cerebellar hypoplasia  | 63 | 4.6 |
| Esophageal atresia + Hydrocephaly  | 25 | 4.6 |
| CHD + Anorectal atresia/stenosis  | 286 | 4.5 |
| Oral cleft + Esophageal atresia + Limb deficiency | 5 | 4.5 |
| CHD + Anorectal atresia/stenosis + Hydrocephaly | 7 | 4.4 |
| Anotia/microtia + Renal agenesis/hypoplasia  | 5 | 4.3 |
| Esophageal atresia + Cloacal exstrophy  | 5 | 4.3 |
| CHD + Anorectal atresia/stenosis + Diaphragmatic hernia  | 9 | 4.3 |
| Oral cleft + Choanal atresia  | 14 | 4.2 |
| Oral cleft + Limb deficiency + NTD | 6 | 4.2 |
| Limb deficiency + Cloacal exstrophy  | 5 | 4.1 |
| Limb deficiency + Anotia/microtia  | 29 | 4.1 |
| CHD + Anorectal atresia/stenosis + Anotia/microtia | 9 | 4.1 |
| Hydrocephaly + Craniosynostosis  | 15 | 4.0 |
| CHD + Oral cleft + Hydrocephaly | 7 | 4.0 |
| Diaphragmatic hernia + Omphalocele  | 12 | 4.0 |
| Anotia/microtia + Hydrocephaly  | 11 | 3.9 |
| Limb deficiency + Choanal atresia  | 8 | 3.9 |
| Hydrocephaly + DWM/Cerebellar hypoplasia  | 6 | 3.8 |
| Hydrocephaly + Eye defect  | 12 | 3.7 |
| CHD + Cloacal exstrophy  | 19 | 3.7 |
| Oral cleft + Anorectal atresia/stenosis + Limb deficiency | 6 | 3.7 |
| CHD + Choanal atresia  | 31 | 3.6 |
| NTD + Holoprosencephaly  | 6 | 3.5 |
| NTD + Renal agenesis/hypoplasia  | 8 | 3.4 |
| CHD + Oral cleft + Limb deficiency | 17 | 3.3 |
| CHD + Limb deficiency + Intestinal atresia/stenosis  | 5 | 3.2 |
| CHD + Omphalocele  | 76 | 3.2 |
| Oral cleft + Sacral agenesis  | 8 | 3.1 |
| Limb deficiency + Holoprosencephaly  | 7 | 3.1 |
| CHD + Limb deficiency + Eye defect | 5 | 3.1 |
| CHD + Diaphragmatic hernia  | 136 | 3.0 |
| CHD + Anotia/microtia  | 109 | 3.0 |
| Oral cleft + Eye defect  | 45 | 3.0 |
| Esophageal atresia + Renal agenesis/hypoplasia  | 8 | 3.0 |
| CHD + Limb deficiency + NTD | 8 | 3.0 |
| Anorectal atresia/stenosis + Intestinal atresia/stenosis  | 29 | 2.9 |
| Oral cleft + Hydrocephaly  | 35 | 2.9 |
| CHD + Oral cleft + Anorectal atresia/stenosis  | 15 | 2.8 |
| Esophageal atresia + Anotia/microtia  | 16 | 2.8 |
| Limb deficiency + Hydrocephaly  | 19 | 2.8 |
| CHD + Hydrocephaly  | 82 | 2.8 |
| CHD + Holoprosencephaly  | 27 | 2.8 |
| Limb deficiency + Omphalocele  | 15 | 2.7 |
| Oral cleft + Limb deficiency  | 79 | 2.6 |
| Anorectal atresia/stenosis + Choanal atresia  | 7 | 2.6 |
| Anorectal atresia/stenosis + Hydrocephaly  | 21 | 2.5 |
| CHD + Limb deficiency  | 176 | 2.5 |
| CHD + Anorectal atresia/stenosis + Eye defect | 5 | 2.4 |
| Hypospadias + DWM/Cerebellar hypoplasia  | 5 | 2.4 |
| Limb deficiency + NTD  | 38 | 2.3 |
| CHD + Oral cleft + Hypospadias | 8 | 2.3 |
| CHD + Renal agenesis/hypoplasia  | 28 | 2.2 |
| CHD + Intestinal atresia/stenosis  | 88 | 2.1 |
| Oral cleft + NTD  | 82 | 2.1 |
| Anorectal atresia/stenosis + Anotia/microtia  | 18 | 2.0 |
| CHD + Eye defect  | 76 | 2.0 |
| Anorectal atresia/stenosis + NTD  | 36 | 2.0 |
| CHD + Oral cleft + Diaphragmatic hernia  | 5 | 1.9 |
| Limb deficiency + Diaphragmatic hernia  | 17 | 1.8 |
| Oral cleft + Esophageal atresia  | 33 | 1.7 |
| Anorectal atresia/stenosis + Hypospadias  | 36 | 1.7 |
| NTD + Anotia/microtia  | 11 | 1.7 |
| Anorectal atresia/stenosis + Holoprosencephaly  | 5 | 1.7 |
| NTD + ABS-LBWC  | 5 | 1.6 |
| CHD + Oral cleft  | 337 | 1.6 |
| Oral cleft + Omphalocele  | 15 | 1.5 |
| CHD + Oral cleft + NTD | 8 | 1.5 |
| Anorectal atresia/stenosis + Omphalocele  | 10 | 1.4 |
| CHD + Anorectal atresia/stenosis + NTD | 5 | 1.4 |
| Anorectal atresia/stenosis + Diaphragmatic hernia  | 15 | 1.4 |
| Limb deficiency + Intestinal atresia/stenosis  | 11 | 1.3 |
| Limb deficiency + Eye defect  | 10 | 1.2 |
| Oral cleft + Renal agenesis/hypoplasia  | 6 | 1.2 |
| Hypospadias + Omphalocele  | 5 | 1.2 |
| Anorectal atresia/stenosis + DWM/Cerebellar hypoplasia  | 5 | 1.2 |
| Craniosynostosis + Eye defect  | 5 | 1.2 |
| CHD + Biliary atresia  | 12 | 1.1 |
| Esophageal atresia + Omphalocele  | 5 | 1.1 |
| NTD + Gastroschisis  | 10 | 1.1 |
| Esophageal atresia + Craniosynostosis  | 8 | 1.0 |
| ABS-LBWC = Amniotic band syndrome and limb-body wall complex; CHD = congenital heart defect; DWM = Dandy-Walker malformation; NTD = neural tube defect |