HHS Public Access

Author manuscript

J Pediatr Rehabil Med. Author manuscript; available in PMC 2021 April 30.

Published in final edited form as:

J Pediatr Rehabil Med. 2017 December 11; 10(3-4): 189–194. doi:10.3233/PRM-170456.

Genetic Epidemiology of Neural Tube Defects

Philip J. Lupo[1,*], **A.J. Agopian**[2], **Heidi Castillo**[3], **Jonathan Castillo**[3], **Gerald H. Clayton**[4], **Nienke P. Dosa**[5], **Betsy Hopson**[6], **David B. Joseph**[7], **Brandon G. Rocque**[6], **William O. Walker**[8], **John S. Wiener**[9], **Laura E. Mitchell**[2]

[1]Department of Pediatrics, Section of Hematology-Oncology, Baylor College of Medicine, Houston, Texas, USA

[2]Department of Epidemiology, Human Genetics and Environmental Sciences, UTHealth School of Public Health, Houston, Texas, USA

[3]Department of Pediatrics, Section of Developmental Pediatrics, Baylor College of Medicine, Houston, Texas, USA

[4]Department of Physical Medicine and Rehabilitation, Children's Hospital Colorado, Aurora, Colorado, USA

[5]Department of Pediatrics, Center for Development Behavior and Genetics, State University of New York Upstate Medical University, Syracuse, New York, USA

[6]Department of Neurosurgery, University of Alabama at Birmingham, Birmingham, Alabama

[7]Department of Urology, University of Alabama at Birmingham, Birmingham, Alabama, USA

[8]Division of Developmental Medicine Seattle Children's Hospital, Seattle, Washington

[9]Division of Urology, Duke University Medical Center, Durham, North Carolina, USA

Abstract

It has been estimated that 60–70% of neural tube defects (NTDs) have a genetic component, but few causative genes have been identified. The lack of information on genes associated with non-syndromic NTDs in humans is especially notable as the "genomic revolution" has led to new tools (e.g., genome-wide genotyping arrays, next-generation sequencing) that are helping to elucidate the full spectrum of genetic variation (from common to rare) contributing to complex traits, including structural birth defects. However, the application of modern genomic approaches to the study of NTDs has lagged behind that of some other common structural birth defects. This may be due to the difficulty of assembling large study cohorts for anencephaly or spina bifida. The purpose of this review is to outline the evolution of genetic studies of NTDs, from studies of familial aggregation to candidate gene and genome-wide association studies, through whole-exome and whole-genome sequencing. Strategies for addressing gaps in NTD genetic research are also explored.

[*]Correspondence to: Philip J. Lupo, PhD, One Baylor Plaza, MS: BCM305, Houston, TX 77030, Telephone: 713-798-2960, Philip.Lupo@bcm.edu.

Keywords

Epidemiology; Genetics; Human Studies; Neural Tube Defects; Spina Bifida

Introduction

Neural tube defects (NTDs) are among the most frequent, most costly, and most deadly of all congenital anomalies (1, 2). The most common NTDs are anencephaly, which results from failure of fusion of the cranial neural tube, and myelomeningocele (commonly called spina bifida), which results from failure of fusion in the spinal region of the neural tube (2). While anencephaly is incompatible with life, individuals with other forms of NTDs typically live long lives due to medical advances over the past half century but exhibit a spectrum of neurological deficits that affect multiple organ systems as well as motor and/or sensory functions.

The number of infants born with NTDs varies temporally, by race/ethnicity, and by geographic region. For example, in recent years, approximately 1 in 1,000 infants is born with a NTD in the United States and many European countries is estimated to be 0.5–0.8 cases per 1,000, whereas in northern China, it has been reported to be as high as 10 per 1,000 (1, 3). In spite of their clinical and public health significance, the majority of the risk for NTDs cannot be accounted for by known risk factors (4).

One of the most important epidemiologic findings related to the etiology of NTDs is the protective effect of maternal periconceptional folic acid supplementation (2, 5). This finding has been translated into public health policies, including food fortification programs in many countries (6). While folic acid fortification has led to a 28% reduction in the birth of infants with anencephaly and spina bifida in the United States since mandatory fortification began in 1998 (7), NTDs continue to occur despite fortification.

There are other known causes of NTDs, including genetic syndromes (2, 5). For instance, NTDs can occur in children with certain chromosomal anomalies (e.g., trisomy 13, 18, and 21) (2, 5) and chromosomal deletion syndromes (e.g., 22q11 deletion syndrome), and there is evidence that NTDs are associated with Waardenburg syndrome (8). In addition, a few families have been observed with X-linked inheritance of anencephaly (9, 10), and anencephaly has recently been associated with mutations in *TRIM36* (11). While these syndromes and single gene defects account for only a small proportion of individuals with NTDs, the remainder without an identified syndrome are also thought to involve genetic factors because the risk of NTDs is increased in the relatives of individuals with the condition (see “Family History, Aggregation, and Linkage Studies”). In fact, it has been estimated that 60–70% of NTDs have a genetic component (1), but few causative genes have been identified.

The lack of information on genes associated with non-syndromic NTDs in humans is especially notable as the “genomic revolution” has led to new tools (e.g., genome-wide genotyping arrays, next-generation sequencing) that are helping to elucidate the full spectrum of genetic variation (from common to rare) contributing to complex traits,

including structural birth defects. The application of modern genomic approaches to the study of NTDs has, however, lagged behind that of some other common structural birth defects. For example, there has yet to be a published genome-wide association or whole-exome sequencing study of spina bifida (12). This lag may due to several factors including: (1) prenatal detection of NTDs leading to pregnancy terminations, (2) high mortality, and (3) reduced reproduction among individuals with these conditions that make assembling a large study cohort difficult. The purpose of this review is to outline the evolution of genetic studies of NTDs, from studies of familial aggregation to candidate gene and genome-wide association studies, through whole-exome and whole-genome sequencing. Strategies for addressing gaps in NTD genetic research are also explored.

Family History, Aggregation, and Linkage Studies

Having a family history of spina bifida or anencephaly is one of the strongest risk factors for these outcomes (5). Familial aggregation studies, largely conducted in the 1970s and 1980s, demonstrated that the risk for spina bifida or anencephaly, or both, was increased in the relatives of individuals with the condition: 3–8% in siblings (first-degree relatives); 1–2% in second-degree relatives; and 0.5% in third-degree relatives (13–17) – compared to 0.1% (or 1 per 1,000) in the United States. These studies clearly demonstrated: (1) increased risk of NTDs if other family members have NTDs, (2) risk increased with the number of relatives with the condition, which is not consistent with a single genetic locus underlying risk; (3) a non-linear decline in risk with decreasing degree of relationship; and (4) in most families (~95%), there was only one individual with spina bifida or anencephaly. Taken together, these familial patterns are consistent with multifactorial inheritance. More specifically, NTDs appear to be complex traits influenced by many genes and environmental factors that operate independently or through interactions rather than being attributable to the effects of a single genetic locus (5). However, studies to characterize the genetic epidemiology of NTDs have not yielded information on specific genes associated with these conditions. For instance, in one multicenter study, some chromosomal regions were identified, but to date, no strong susceptibility loci for NTDs have been confirmed (18). Interestingly, a very recent survey in the United States indicated that >16% of children with spina bifida have a family history of NTDs (19). While this must be confirmed in other studies, the higher proportion compared to previous studies could be suggestive of a greater role of genetics in populations where diets have been fortified with folic acid.

Genetic Association Studies

Study Design Considerations

The majority of genetic association studies of NTDs have used a case-control study design. In this approach, the frequency of variants in putative disease genes is compared between cases (i.e., individuals with the condition) and controls (i.e., individuals without the condition). This study design is particularly useful when studying rare outcomes, such as NTDs, and is often used in genetic association studies of other conditions. For instance, the case-control study design was used to identify genes associated with neuroblastoma (a relatively rare pediatric malignancy), which has led to improved therapeutic options for

these children (20). However, genetic association studies using the case-control design are vulnerable to a type of confounding referred to as “population stratification bias,” where a false association between a genotype and disease, or the masking of a genotypic effect, is induced by the existence of subgroups within a population (e.g., different racial or ethnic groups) that have different genotype frequencies and frequencies of disease (21).

Another study design emerged in the early 1990s that has proven to be very useful in genetic association studies of structural birth defects: the case-parent trio design (or child-parent trio). The trio is composed of the child with the condition and his or her biological parents. This design is particularly useful for studies of birth defects and conditions with early disease onset, since parents of children with these conditions are generally available. Several methods for analyzing the data generated in a case-parent trio study have been developed, including the transmission disequilibrium test (22, 23) and approaches using log-linear models (24). The child-parent trio design has the advantage (as compared to case-control studies) of being immune to population stratification bias when assessing the effects of the inherited genotype. Furthermore, this design can be used to assess maternal genetic effects (i.e., the effect of the maternal genotype on the phenotype of offspring) without incurring additional genotyping expenses (i.e., in the case-control design, evaluation of the maternal and case genotype would require genotyping cases and controls as well as the mothers of these individuals).

Candidate Gene Approaches

Regardless of the study design, early genetic association studies relied on a candidate gene approach (25). With this approach, candidate genes are selected based on current understanding of the disease. For example, given the known association of NTDs and folic acid, many candidate gene studies of NTDs focused on genes that are involved in folate metabolism (1, 2, 5, 26). Variants within the candidate gene (e.g., single-nucleotide polymorphisms or SNPs) are then genotyped and evaluated for their association with the condition of interest. While there have been a number of published studies implicating genes involved in folate metabolism, with the exception of the *MTHFR* C677T variant, these reports tend to characterized by weak and imprecise estimates of association, as well as a lack of consistent replication across studies. Notably, even for the *MTHFR* C677T variant, the observed association does not change the recommendation that women of childbearing age should take the standard dose of folic acid supplementation as per the general population guidelines (27).

Other candidate genes and candidate gene pathways have been explored in relation to NTD risk, including: genes associated with diabetes and obesity (maternal risk factors for NTDs) (28); genes identified in animal models of NTDs (e.g., *Pax3*) (29); genes that are involved in the metabolism of known teratogenic agents; and genes that have been implicated in the metabolism of compounds needed for embryonic development (2, 5). However, no candidate genes in these (or other) categories have been definitely linked to the risk of NTDs.

Genome-Wide Approaches

Advances in technology that permit affordable and reliable genotyping of millions of SNPs have provided the opportunity to expand beyond candidate gene association studies to an "agnostic" genome-wide approach, commonly referred to as genome-wide association studies or GWAS. In GWAS, hundreds of thousands or millions of SNPs are tested for association. Because of the enormous number of tests, the commonly accepted threshold for statistical significance in a GWAS is $p<5\times10^{-8}$, and thus very large study populations are required to provide adequate statistical power. Additionally, a tiered approach is typically used in GWAS, where a subset of SNPs from the first stage (i.e., discovery set) is moved to a second stage (i.e., replication set) for confirmation. This process limits the potential for false positives. Similar to candidate gene association studies, GWAS can use either a case-control or trio design.

In comparison to other diseases, there have been relatively few GWAS of structural birth defects (30–34). This is largely due to the difficulty of assembling the large study populations needed for GWAS (i.e., >1,000 affected individuals), especially as structural birth defects tend to be individually rare. Nonetheless, GWAS have been completed for some structural birth defects, and these studies have provided new insights regarding the genetic contribution to disease etiology. Notably, as of the writing of this review, there were no published GWAS of NTDs (see Table 2).

Other genome-wide approaches that may yield insights into the etiologies of NTDs include the analysis of copy-number variation. Rather than focusing on single base pairs (e.g., SNPs), when evaluating copy-number variants (CNVs), investigators interrogate structural variation involving the number of copies of specific regions of DNA, which can either be deleted or duplicated. These chromosomal deletions and duplications involve fairly large stretches of DNA. Previous assessments of pediatric neurodevelopmental conditions have demonstrated the importance of CNVs in human disease (35). However, as with GWAS, there are currently no published genome-wide assessments of CNVs among individuals with NTDs.

Whole-Exome and Whole-Genome Sequencing

Whole-exome and whole-genome sequencing (WES and WGS, respectively) studies have moved to the forefront of genomic research in recent years. As with the shift from candidate gene studies to GWAS, this is largely due to advances in technology that have led to reductions in the cost and time required to sequence DNA. The current focus of WES/WGS is on identification of rare mutations that have a large impact on disease risk. With that said, child-parent trios have reemerged as an important study design, partly because of the potential importance of *de novo* (i.e., new) mutations. New mutations have long been known to cause genetic disease, but their true contribution to disease burden in the absence of significant family history can only now begin to be determined using child-parent trio-based WES or WGS approaches. Notably, recent studies demonstrate that *de novo* mutations contribute to a range of rare and common pediatric phenotypes, including seemingly sporadic malformation syndromes, congenital heart defects, intellectual disability, autism, and schizophrenia (36–43). Furthermore, *de novo* mutations provide a mechanism by which

early-onset reproductively-lethal diseases remain prevalent in the population. However, *de novo* mutations do not explain the strong association between a family history of NTDs and the risk of these outcomes, so future assessments must still consider the role of inherited genetic variation. Additionally, when present, WES/WGS of several of multiplex families (in which many related individuals have NTDs) will also be informative in disentangling the genetics of these conditions. As with GWAS, there have been no large-scale efforts to conduct WES or WGS among those with spina bifida or anencephaly to identify the recurrent *de novo* mutations or novel inherited variants that play a role in the etiology of NTDs.

Conclusions and Future Directions

While there is strong evidence for a significant genetic component to the etiology of NTDs, little headway has been made to identify genetic variations related to these conditions. In fact, as highlighted in this review, understanding genetic susceptibility to NTDs continues to lag behind that of other common structural birth defects. This is in part due to the lack of large well-characterized study populations with biological samples collected with appropriate informed consent for more modern analytical techniques, such as GWAS, WES, and WGS. Future studies should not only take advantage of modern genomic approaches, but should also leverage existing study cohorts, including the National Spina Bifida Patient Registry (44), which has enrolled thousands of individuals with spina bifida with the goals of improving the health outcomes of people living with spina bifida and building a foundation for ongoing research. Another important avenue to explore in human populations is evaluating the >200 genes identified in animal models of NTDs (3). Conversely, candidate genes identified in genome-wide assessments must also be evaluated in animal models to understand the biological implications of these associations. Finally, while the focus of this review was on non-syndromic NTDs, a better understanding of the underlying biology (and modifier genes) of syndromic NTDs is also needed. Ultimately, the discovery of new disease-related genes is expected to result in: (1) new preventive approaches; (2) enhanced genetic counseling; and (3) improved prognostic information and new therapeutic strategies.

Acknowledgements

The authors would like to acknowledge Robert Roger Lebel, MD, FACMG for his review and comments. The authors have no conflict of interest to report.

References

1. Copp AJ, Adzick NS, Chitty LS, Fletcher JM, Holmbeck GN, Shaw GM. Spina bifida. Nat Rev Dis Primers. 2015;1:15007. [PubMed: 27189655]
2. Mitchell LE, Adzick NS, Melchionne J, Pasquariello PS, Sutton LN, Whitehead AS. Spina bifida. Lancet. 2004;364(9448):1885–95. [PubMed: 15555669]
3. Ross ME, Mason CE, Finnell RH. Genomic approaches to the assessment of human spina bifida risk. Birth Defects Res. 2017;109(2):120–8. [PubMed: 27883265]
4. Agopian AJ, Lupo PJ, Tinker SC, Canfield MA, Mitchell LE. Working towards a risk prediction model for neural tube defects. Birth Defects Res A Clin Mol Teratol. 2012;94(3):141–6. [PubMed: 22253139]

5. Mitchell LE. Epidemiology of neural tube defects. Am J Med Genet C Semin Med Genet. 2005;135C(1):88–94. [PubMed: 15800877]
6. Arth A, Kancherla V, Pachon H, Zimmerman S, Johnson Q, Oakley GP Jr. A 2015 global update on folic acid-preventable spina bifida and anencephaly. Birth Defects Res A Clin Mol Teratol. 2016;106(7):520–9. [PubMed: 27418029]
7. Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M, et al. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995–2011. MMWR Morb Mortal Wkly Rep. 2015;64(1):1–5. [PubMed: 25590678]
8. Nye JS, Balkin N, Lucas H, Knepper PA, McLone DG, Charrow J. Myelomeningocele and Waardenburg syndrome (type 3) in patients with interstitial deletions of 2q35 and the PAX3 gene: possible digenic inheritance of a neural tube defect. Am J Med Genet. 1998;75(4):401–8. [PubMed: 9482647]
9. Jensson O, Arnason A, Gunnarsdottir H, Petursdottir I, Fossdal R, Hreidarsson S. A family showing apparent X linked inheritance of both anencephaly and spina bifida. J Med Genet. 1988;25(4):227–9. [PubMed: 3285008]
10. Shaffer LG, Marazita ML, Bodurtha J, Newlin A, Nance WE. Evidence for a major gene in familial anencephaly. Am J Med Genet. 1990;36(1):97–101. [PubMed: 2333913]
11. Singh N, Kumble Bhat V, Tiwari A, Kodaganur SG, Tontanahal SJ, Sarda A, et al. A homozygous mutation in TRIM36 causes autosomal recessive anencephaly in an Indian family. Human molecular genetics. 2017;26(6):1104–14. [PubMed: 28087737]
12. Khokha MK, Mitchell LE, Wallingford JB. White paper on the study of birth defects. Birth Defects Res. 2017;109(2):180–5. [PubMed: 28398650]
13. Carter CO, David PA, Laurence KM. A family study of major central nervous system malformations in South Wales. J Med Genet. 1968;5(2):81–106. [PubMed: 4881170]
14. Carter CO, Evans K. Spina bifida and anencephalus in greater London. J Med Genet. 1973;10(3):209–34. [PubMed: 4590246]
15. Demenais F, Le Merrer M, Briard ML, Elston RC. Neural tube defects in France: segregation analysis. Am J Med Genet. 1982;11(3):287–98. [PubMed: 7081294]
16. Hunter AG. Neural tube defects in Eastern Ontario and Western Quebec: demography and family data. Am J Med Genet. 1984;19(1):45–63. [PubMed: 6388330]
17. Janerich DT, Piper J. Shifting genetic patterns in anencephaly and spina bifida. J Med Genet. 1978;15(2):101–5. [PubMed: 641940]
18. Speer MC, Melvin EC, Viles KD, Bauer KA, Rampersaud E, Drake C, et al. T locus shows no evidence for linkage disequilibrium or mutation in American Caucasian neural tube defect families. Am J Med Genet. 2002;110(3):215–8. [PubMed: 12116228]
19. Dupepe EB, Patel DM, Rocque BG, Hopson B, Arynchyna AA, Bishop ER, et al. Surveillance survey of family history in children with neural tube defects. J Neurosurg Pediatr. 2017:1–6.
20. Bosse KR, Maris JM. Advances in the translational genomics of neuroblastoma: From improving risk stratification and revealing novel biology to identifying actionable genomic alterations. Cancer. 2016;122(1):20–33. [PubMed: 26539795]
21. Campbell CD, Ogburn EL, Lunetta KL, Lyon HN, Freedman ML, Groop LC, et al. Demonstrating stratification in a European American population. Nat Genet. 2005;37(8):868–72. [PubMed: 16041375]
22. Schaid DJ, Sommer SS. Genotype relative risks: methods for design and analysis of candidate-gene association studies. Am J Hum Genet. 1993;53(5):1114–26. [PubMed: 8213835]
23. Spielman RS, McGinnis RE, Ewens WJ. Transmission test for linkage disequilibrium: the insulin gene region and insulin-dependent diabetes mellitus (IDDM). Am J Hum Genet. 1993;52(3):506–16. [PubMed: 8447318]
24. Weinberg CR, Wilcox AJ, Lie RT. A log-linear approach to case-parent-triad data: assessing effects of disease genes that act either directly or through maternal effects and that may be subject to parental imprinting. Am J Hum Genet. 1998;62(4):969–78. [PubMed: 9529360]
25. Patnala R, Clements J, Batra J. Candidate gene association studies: a comprehensive guide to useful in silico tools. BMC Genet. 2013;14:39. [PubMed: 23656885]

26. Yadav U, Kumar P, Yadav SK, Mishra OP, Rai V. “Polymorphisms in folate metabolism genes as maternal risk factor for neural tube defects: an updated meta-analysis”. Metab Brain Dis. 2015;30(1):7–24. [PubMed: 25005003]
27. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. Genetics in medicine : official journal of the American College of Medical Genetics. 2013;15(2):153–6.
28. Lupo PJ, Canfield MA, Chapa C, Lu W, Agopian AJ, Mitchell LE, et al. Diabetes and obesity-related genes and the risk of neural tube defects in the national birth defects prevention study. Am J Epidemiol. 2012;176(12):1101–9. [PubMed: 23132673]
29. Agopian AJ, Bhalla AD, Boerwinkle E, Finnell RH, Grove ML, Hixson JE, et al. Exon sequencing of PAX3 and T (brachyury) in cases with spina bifida. Birth Defects Res A Clin Mol Teratol. 2013;97(9):597–601. [PubMed: 23913553]
30. Agopian AJ, Mitchell LE, Glessner J, Bhalla AD, Sewda A, Hakonarson H, et al. Genome-wide association study of maternal and inherited loci for conotruncal heart defects. PLoS One. 2014;9(5):e96057. [PubMed: 24800985]
31. Birnbaum S, Ludwig KU, Reutter H, Herms S, Steffens M, Rubini M, et al. Key susceptibility locus for nonsyndromic cleft lip with or without cleft palate on chromosome 8q24. Nat Genet. 2009;41(4):473–7. [PubMed: 19270707]
32. Cordell HJ, Bentham J, Topf A, Zelenika D, Heath S, Mamasoula C, et al. Genome-wide association study of multiple congenital heart disease phenotypes identifies a susceptibility locus for atrial septal defect at chromosome 4p16. Nat Genet. 2013;45(7):822–4. [PubMed: 23708191]
33. Mitchell LE, Agopian AJ, Bhalla A, Glessner JT, Kim CE, Swartz MD, et al. Genome-wide association study of maternal and inherited effects on left-sided cardiac malformations. Human molecular genetics. 2015;24(1):265–73. [PubMed: 25138779]
34. van der Zanden LF, van Rooij IA, Feitz WF, Knight J, Donders AR, Renkema KY, et al. Common variants in DGKK are strongly associated with risk of hypospadias. Nat Genet. 2011;43(1):48–50. [PubMed: 21113153]
35. Thapar A, Cooper M. Copy number variation: what is it and what has it told us about child psychiatric disorders? J Am Acad Child Adolesc Psychiatry. 2013;52(8):772–4. [PubMed: 23880486]
36. Veltman JA, Brunner HG. De novo mutations in human genetic disease. Nat Rev Genet. 2012;13(8):565–75. [PubMed: 22805709]
37. de Ligt J, Willemsen MH, van Bon BW, Kleefstra T, Yntema HG, Kroes T, et al. Diagnostic exome sequencing in persons with severe intellectual disability. N Engl J Med. 2012;367(20):1921–9. [PubMed: 23033978]
38. Gregor A, Oti M, Kouwenhoven EN, Hoyer J, Sticht H, Ekici AB, et al. De novo mutations in the genome organizer CTCF cause intellectual disability. Am J Hum Genet. 2013;93(1):124–31. [PubMed: 23746550]
39. Hoischen A, van Bon BW, Gilissen C, Arts P, van Lier B, Steehouwer M, et al. De novo mutations of SETBP1 cause Schinzel-Giedion syndrome. Nat Genet. 2010;42(6):483–5. [PubMed: 20436468]
40. Hoischen A, van Bon BW, Rodriguez-Santiago B, Gilissen C, Vissers LE, de Vries P, et al. De novo nonsense mutations in ASXL1 cause Bohring-Opitz syndrome. Nat Genet. 2011;43(8):729–31. [PubMed: 21706002]
41. Ng SB, Bigham AW, Buckingham KJ, Hannibal MC, McMillin MJ, Gildersleeve HI, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010;42(9):790–3. [PubMed: 20711175]
42. Pagnamenta AT, Lise S, Harrison V, Stewart H, Jayawant S, Quaghebeur G, et al. Exome sequencing can detect pathogenic mosaic mutations present at low allele frequencies. J Hum Genet. 2012;57(1):70–2. [PubMed: 22129557]
43. Yang Y, Muzny DM, Xia F, Niu Z, Person R, Ding Y, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014;312(18):1870–9. [PubMed: 25326635]

44. Sawin KJ, Liu T, Ward E, Thibadeau J, Schechter MS, Soe MM, et al. The National Spina Bifida Patient Registry: profile of a large cohort of participants from the first 10 clinics. J Pediatr. 2015;166(2):444–50 e1. [PubMed: 25444012]

Table 1.

A sample of statistically significant findings from GWAS of structural birth defects

Birth defect	First author[A]	Year published	Cases in Discovery set	Locus, gene, or chromosome	Effect size (odds ratio)
Cleft lip with or without cleft palate	Birnbaum	2009	224	8q24	2.57 (het) 6.05 (hom)
Hypospadias	van der Zanden	2011	436	*DGKK*	2.46
Congenital heart defects	Cordell	2013	1,995	4p16	1.40[B]
Conotruncal heart defects	Agopian	2014	750	20p12.3 *SLC22A24*	5.24 (I) 1.85 (M)
Left-sided cardiac malformations	Mitchell	2015	377	Chr 16 Chr 10	2.65 (I) 1.64 (M)

Abbreviations: het=heterozygote; hom=homozygote; I=inherited; M=maternal

[A] References: (30–34)

[B] OR for atrial septal defects only

Table 2.

Genetic study designs and approaches that have been applied to neural tube defects versus other structural birth defects among published studies

Phenotype	Candidate Gene	Linkage Analysis	GWAS	WES/WGS
Neural tube defects	Applied	Not widely applied	Not applied	Not applied
Other birth defects	Applied	Applied	Applied	Applied

Abbreviations: GWAS=genome-wide association study; WES=whole-exome sequencing; WGS=whole-genome sequencing