

## 6 REFERENCES

1. Firth, H.V. & Wright, C.F. The Deciphering Developmental Disorders (DDD) study. *Dev Med Child Neurol* **53**, 702-3 (2011).
2. Markiewicz, K. & Pachalska, M. Diagnosis of severe developmental disorders in children under three years of age. *Med Sci Monit* **13**, CR89-99 (2007).
3. Wright, C.F. *et al.* Genetic diagnosis of developmental disorders in the DDD study: a scalable analysis of genome-wide research data. *Lancet* (2014).
4. Rehm, H.L. *et al.* ACMG clinical laboratory standards for next-generation sequencing. *Genet Med* **15**, 733-47 (2013).
5. Lee, H. *et al.* Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA* **312**, 1880-7 (2014).
6. DDD\_Study. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* **519**, 223-8 (2015).
7. van Karnebeek, C.D. *et al.* Etiology of mental retardation in children referred to a tertiary care center: a prospective study. *Am J Ment Retard* **110**, 253-67 (2005).
8. study, D.D.D. Large-scale discovery of novel genetic causes of developmental disorders. *Nature* (2014).
9. Boycott, K.M., Vanstone, M.R., Bulman, D.E. & MacKenzie, A.E. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. *Nat Rev Genet* **14**, 681-91 (2013).

- 
10. Amberger, J., Bocchini, C. & Hamosh, A. A new face and new challenges for Online Mendelian Inheritance in Man (OMIM(R)). *Hum Mutat* **32**, 564-7 (2011).
  11. Driscoll, D.A. & Gross, S.J. Screening for fetal aneuploidy and neural tube defects. *Genet Med* **11**, 818-21 (2009).
  12. Vorstman, J.A. & Ophoff, R.A. Genetic causes of developmental disorders. *Curr Opin Neurol* **26**, 128-36 (2013).
  13. Feuk, L., Carson, A.R. & Scherer, S.W. Structural variation in the human genome. *Nat Rev Genet* **7**, 85-97 (2006).
  14. Liehr, T. Uniparental disomy - clinical consequences due to imprinting and activation of recessive genes. *Mol Cytogenet* **7**, I21 (2014).
  15. Freeman, J.L. *et al.* Copy number variation: new insights in genome diversity. *Genome Res* **16**, 949-61 (2006).
  16. Poduri, A., Evrony, G.D., Cai, X. & Walsh, C.A. Somatic mutation, genomic variation, and neurological disease. *Science* **341**, 1237758 (2013).
  17. von Winiwarter, H. Etudes sur la spermatogenese humaine. *Arch. de Biol.* **XXVII**, p.91 (1912).
  18. Barr, M.L. & Bertram, E.G. A morphological distinction between neurones of the male and female, and the behaviour of the nucleolar satellite during accelerated nucleoprotein synthesis. *Nature* **163**, 676 (1949).
  19. Hsu, T.C. Mammalian chromosomes in vitro. IV. Some human neoplasms. *J Natl Cancer Inst* **14**, 905-33 (1954).
  20. Eagle, H. Nutrition needs of mammalian cells in tissue culture. *Science* **122**, 501-14 (1955).
  21. Levan, A. Chromosome studies on some human tumors and tissues of normal origin, grown in vivo and in vitro at the Sloan-Kettering Institute. *Cancer* **9**, 648-63 (1956).
  22. Giemsa, G. Eine Vereinfachung und Vervollkommnung meiner Methylenblau Eosin Farbemethode zur Erzielung der Romanowsky Nochtschen Chromatinfärbung. *Centralblatt für Bakteriologie* **32**, 307-313 (1904).

- 
23. Seabright, M. A rapid banding technique for human chromosomes. *Lancet* **2**, 971-2 (1971).
  24. Yunis, J.J., Sawyer, J.R. & Ball, D.W. Characterization of banding patterns of metaphase-prophase G-banded chromosomes and their use in gene mapping. *Cytogenet Cell Genet* **22**, 679-83 (1978).
  25. Mattei, M.G., Mattei, J.F., Ayme, S. & Giraud, F. X-autosome translocations: cytogenetic characteristics and their consequences. *Hum Genet* **61**, 295-309 (1982).
  26. Hook, E.B. Exclusion of chromosomal mosaicism: tables of 90%, 95% and 99% confidence limits and comments on use. *Am J Hum Genet* **29**, 94-7 (1977).
  27. Mayall, B.H. *et al.* The DNA-based human karyotype. *Cytometry* **5**, 376-85 (1984).
  28. Kwok, P.Y. & Gu, Z. Single nucleotide polymorphism libraries: why and how are we building them? *Mol Med Today* **5**, 538-43 (1999).
  29. Pardue, M.L. & Gall, J.G. Molecular hybridization of radioactive DNA to the DNA of cytological preparations. *Proc Natl Acad Sci U S A* **64**, 600-4 (1969).
  30. Langer, P.R., Waldrop, A.A. & Ward, D.C. Enzymatic synthesis of biotin-labeled polynucleotides: novel nucleic acid affinity probes. *Proc Natl Acad Sci U S A* **78**, 6633-7 (1981).
  31. Kallioniemi, A. *et al.* Comparative genomic hybridization for molecular cytogenetic analysis of solid tumors. *Science* **258**, 818-21 (1992).
  32. Oostlander, A.E., Meijer, G.A. & Ylstra, B. Microarray-based comparative genomic hybridization and its applications in human genetics. *Clin Genet* **66**, 488-95 (2004).
  33. Wang, D.G. *et al.* Large-scale identification, mapping, and genotyping of single-nucleotide polymorphisms in the human genome. *Science* **280**, 1077-82 (1998).
  34. LaFramboise, T. Single nucleotide polymorphism arrays: a decade of biological, computational and technological advances. *Nucleic Acids Res* **37**, 4181-93 (2009).
  35. Bruno, D.L. *et al.* Pathogenic aberrations revealed exclusively by single nucleotide polymorphism (SNP) genotyping data in 5000 samples tested by molecular karyotyping. *J Med Genet* **48**, 831-9 (2011).

- 
36. Conlin, L.K. *et al.* Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis. *Hum Mol Genet* **19**, 1263-75 (2010).
  37. Wiszniewska, J. *et al.* Combined array CGH plus SNP genome analyses in a single assay for optimized clinical testing. *Eur J Hum Genet* **22**, 79-87 (2014).
  38. Peiffer, D.A. *et al.* High-resolution genomic profiling of chromosomal aberrations using Infinium whole-genome genotyping. *Genome Res* **16**, 1136-48 (2006).
  39. Steemers, F.J. *et al.* Whole-genome genotyping with the single-base extension assay. *Nat Methods* **3**, 31-3 (2006).
  40. Hsu, L. *et al.* Denoising array-based comparative genomic hybridization data using wavelets. *Biostatistics* **6**, 211-26 (2005).
  41. Huang, T., Wu, B., Lizardi, P. & Zhao, H. Detection of DNA copy number alterations using penalized least squares regression. *Bioinformatics* **21**, 3811-7 (2005).
  42. Pique-Regi, R. *et al.* Sparse representation and Bayesian detection of genome copy number alterations from microarray data. *Bioinformatics* **24**, 309-18 (2008).
  43. Broet, P. & Richardson, S. Detection of gene copy number changes in CGH microarrays using a spatially correlated mixture model. *Bioinformatics* **22**, 911-8 (2006).
  44. Marioni, J.C., Thorne, N.P. & Tavare, S. BioHMM: a heterogeneous hidden Markov model for segmenting array CGH data. *Bioinformatics* **22**, 1144-6 (2006).
  45. Wang, K. *et al.* PennCNV: an integrated hidden Markov model designed for high-resolution copy number variation detection in whole-genome SNP genotyping data. *Genome Res* **17**, 1665-74 (2007).
  46. Hoque, M.O., Lee, C.C., Cairns, P., Schoenberg, M. & Sidransky, D. Genome-wide genetic characterization of bladder cancer: a comparison of high-density single-nucleotide polymorphism arrays and PCR-based microsatellite analysis. *Cancer Res* **63**, 2216-22 (2003).
  47. Altug-Teber, O. *et al.* A rapid microarray based whole genome analysis for detection of uniparental disomy. *Hum Mutat* **26**, 153-9 (2005).

48. Illumina.  
[http://www.illumina.com/Documents/products/appnotes/appnote\\_cytogenetics.pdf](http://www.illumina.com/Documents/products/appnotes/appnote_cytogenetics.pdf).  
(2010).
49. Gonzalez, J.R. *et al.* A fast and accurate method to detect allelic genomic imbalances underlying mosaic rearrangements using SNP array data. *BMC Bioinformatics* **12**, 166 (2011).
50. Jacobs, K.B. *et al.* Detectable clonal mosaicism and its relationship to aging and cancer. *Nat Genet* **44**, 651-8 (2012).
51. Baugher, J.D., Baugher, B.D., Shirley, M.D. & Pevsner, J. Sensitive and specific detection of mosaic chromosomal abnormalities using the Parent-of-Origin-based Detection (POD) method. *BMC Genomics* **14**, 367 (2013).
52. Sanger, F., Nicklen, S. & Coulson, A.R. DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A* **74**, 5463-7 (1977).
53. Prober, J.M. *et al.* A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides. *Science* **238**, 336-41 (1987).
54. Karger, B.L. & Guttman, A. DNA sequencing by CE. *Electrophoresis* **30 Suppl 1**, S196-202 (2009).
55. Mardis, E.R. Next-generation sequencing platforms. *Annu Rev Anal Chem (Palo Alto Calif)* **6**, 287-303 (2013).
56. Schadt, E.E., Turner, S. & Kasarskis, A. A window into third-generation sequencing. *Hum Mol Genet* **19**, R227-40 (2010).
57. Li, H. & Durbin, R. Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* **25**, 1754-60 (2009).
58. Li, H. *et al.* The Sequence Alignment/Map format and SAMtools. *Bioinformatics* **25**, 2078-9 (2009).
59. Phillips, K.A., Pletcher, M.J. & Ladabaum, U. Is the "\$1000 Genome" really \$1000? Understanding the full benefits and costs of genomic sequencing. *Technol Health Care* (2015).
60. Ng, S.B. *et al.* Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* **461**, 272-6 (2009).

- 
61. Yang, Y. *et al.* Clinical whole-exome sequencing for the diagnosis of mendelian disorders. *N Engl J Med* **369**, 1502-11 (2013).
  62. Fromer, M. *et al.* Discovery and statistical genotyping of copy-number variation from whole-exome sequencing depth. *Am J Hum Genet* **91**, 597-607 (2012).
  63. Alkan, C. *et al.* Personalized copy number and segmental duplication maps using next-generation sequencing. *Nat Genet* **41**, 1061-7 (2009).
  64. Chiang, D.Y. *et al.* High-resolution mapping of copy-number alterations with massively parallel sequencing. *Nat Methods* **6**, 99-103 (2009).
  65. Goringe, K.L. & Campbell, I.G. High-resolution copy number arrays in cancer and the problem of normal genome copy number variation. *Genes Chromosomes Cancer* **47**, 933-8 (2008).
  66. Yoon, S., Xuan, Z., Makarov, V., Ye, K. & Sebat, J. Sensitive and accurate detection of copy number variants using read depth of coverage. *Genome Res* **19**, 1586-92 (2009).
  67. Tuzun, E. *et al.* Fine-scale structural variation of the human genome. *Nat Genet* **37**, 727-32 (2005).
  68. Kidd, J.M. *et al.* Mapping and sequencing of structural variation from eight human genomes. *Nature* **453**, 56-64 (2008).
  69. Jiang, Y., Wang, Y. & Brudno, M. PRISM: pair-read informed split-read mapping for base-pair level detection of insertion, deletion and structural variants. *Bioinformatics* **28**, 2576-83 (2012).
  70. Ye, K., Schulz, M.H., Long, Q., Apweiler, R. & Ning, Z. Pindel: a pattern growth approach to detect break points of large deletions and medium sized insertions from paired-end short reads. *Bioinformatics* **25**, 2865-71 (2009).
  71. Price, T.S. *et al.* SW-ARRAY: a dynamic programming solution for the identification of copy-number changes in genomic DNA using array comparative genome hybridization data. *Nucleic Acids Res* **33**, 3455-64 (2005).

- 
72. Ashoor, G., Poon, L., Syngelaki, A., Mosimann, B. & Nicolaides, K.H. Fetal fraction in maternal plasma cell-free DNA at 11-13 weeks' gestation: effect of maternal and fetal factors. *Fetal Diagn Ther* **31**, 237-43 (2012).
73. Chiu, R.W. *et al.* Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proc Natl Acad Sci U S A* **105**, 20458-63 (2008).
74. Fan, H.C., Blumenfeld, Y.J., Chitkara, U., Hudgins, L. & Quake, S.R. Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc Natl Acad Sci U S A* **105**, 16266-71 (2008).
75. Rampasek, L., Arbabi, A. & Brudno, M. Probabilistic method for detecting copy number variation in a fetal genome using maternal plasma sequencing. *Bioinformatics* **30**, i212-8 (2014).
76. Jacobs, P.A. & Strong, J.A. A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* **183**, 302-3 (1959).
77. Ford, C.E., Jones, K.W., Polani, P.E., De Almeida, J.C. & Briggs, J.H. A sex-chromosome anomaly in a case of gonadal dysgenesis (Turner's syndrome). *Lancet* **1**, 711-3 (1959).
78. Lejeune, J., Gautier, M. & Turpin, R. [Study of somatic chromosomes from 9 mongoloid children]. *C R Hebd Seances Acad Sci* **248**, 1721-2 (1959).
79. Patau, K., Smith, D.W., Therman, E., Inhorn, S.L. & Wagner, H.P. Multiple congenital anomaly caused by an extra autosome. *Lancet* **1**, 790-3 (1960).
80. Edwards, J.H., Harnden, D.G., Cameron, A.H., Crosse, V.M. & Wolff, O.H. A new trisomic syndrome. *Lancet* **1**, 787-90 (1960).
81. Carr, D.H. Genetic basis of abortion. *Annu Rev Genet* **5**, 65-80 (1971).
82. Lejeune, J. *et al.* [3 Cases of Partial Deletion of the Short Arm of a 5 Chromosome]. *C R Hebd Seances Acad Sci* **257**, 3098-102 (1963).
83. van Karnebeek, C.D., Jansweijer, M.C., Leenders, A.G., Offringa, M. & Hennekam, R.C. Diagnostic investigations in individuals with mental retardation: a systematic literature review of their usefulness. *Eur J Hum Genet* **13**, 6-25 (2005).
84. Hansteen, I.L., Varslot, K., Steen-Johnsen, J. & Langard, S. Cytogenetic screening of a new-born population. *Clin Genet* **21**, 309-14 (1982).

- 
85. Maeda, T., Ohno, M., Matsunobu, A., Yoshihara, K. & Yabe, N. A cytogenetic survey of 14,835 consecutive liveborns. *Jinrui Idengaku Zasshi* **36**, 117-29 (1991).
  86. Iafrate, A.J. *et al.* Detection of large-scale variation in the human genome. *Nat Genet* **36**, 949-51 (2004).
  87. Sebat, J. *et al.* Large-scale copy number polymorphism in the human genome. *Science* **305**, 525-8 (2004).
  88. Redon, R. *et al.* Global variation in copy number in the human genome. *Nature* **444**, 444-54 (2006).
  89. Pang, A.W. *et al.* Towards a comprehensive structural variation map of an individual human genome. *Genome Biol* **11**, R52 (2010).
  90. Stranger, B.E. *et al.* Relative impact of nucleotide and copy number variation on gene expression phenotypes. *Science* **315**, 848-53 (2007).
  91. Huang, N., Lee, I., Marcotte, E.M. & Hurles, M.E. Characterising and predicting haploinsufficiency in the human genome. *PLoS Genet* **6**, e1001154 (2010).
  92. Korbel, J.O. *et al.* The current excitement about copy-number variation: how it relates to gene duplications and protein families. *Curr Opin Struct Biol* **18**, 366-74 (2008).
  93. Kleinjan, D.A. & van Heyningen, V. Long-range control of gene expression: emerging mechanisms and disruption in disease. *Am J Hum Genet* **76**, 8-32 (2005).
  94. Lupski, J.R. & Stankiewicz, P. Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. *PLoS Genet* **1**, e49 (2005).
  95. Cheung, S.W. *et al.* Development and validation of a CGH microarray for clinical cytogenetic diagnosis. *Genet Med* **7**, 422-32 (2005).
  96. Shaffer, L.G. *et al.* Targeted genomic microarray analysis for identification of chromosome abnormalities in 1500 consecutive clinical cases. *J Pediatr* **149**, 98-102 (2006).
  97. Rickman, L. *et al.* Prenatal detection of unbalanced chromosomal rearrangements by array CGH. *J Med Genet* **43**, 353-61 (2006).



98. Sahoo, T. *et al.* Prenatal diagnosis of chromosomal abnormalities using array-based comparative genomic hybridization. *Genet Med* **8**, 719-27 (2006).
99. Hochstenbach, R. *et al.* Array analysis and karyotyping: workflow consequences based on a retrospective study of 36,325 patients with idiopathic developmental delay in the Netherlands. *Eur J Med Genet* **52**, 161-9 (2009).
100. Reddy, U.M. *et al.* Karyotype versus microarray testing for genetic abnormalities after stillbirth. *N Engl J Med* **367**, 2185-93 (2012).
101. Miller, D.T. *et al.* Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* **86**, 749-64 (2010).
102. Cooper, G.M. *et al.* A copy number variation morbidity map of developmental delay. *Nat Genet* **43**, 838-46 (2011).
103. Schinzel, A. Catalogue of unbalanced chromosome aberrations in man. (W. de Gruyter, Berlin; New York, 1984).
104. Firth, H.V. *et al.* DECIPHER: Database of Chromosomal Imbalance and Phenotype in Humans Using Ensembl Resources. *Am J Hum Genet* **84**, 524-33 (2009).
105. Yamazawa, K., Ogata, T. & Ferguson-Smith, A.C. Uniparental disomy and human disease: an overview. *Am J Med Genet C Semin Med Genet* **154C**, 329-34 (2010).
106. Zlotogora, J. Parents of children with autosomal recessive diseases are not always carriers of the respective mutant alleles. *Hum Genet* **114**, 521-6 (2004).
107. Kotzot, D. Complex and segmental uniparental disomy updated. *J Med Genet* **45**, 545-56 (2008).
108. Boue, A., Boue, J., Cure, S., Deluchat, C. & Perraudin, N. In vitro cultivation of cells from aneuploid human embryos. Initiation of cell lines and longevity of the cultures. *In Vitro* **11**, 409-13 (1975).
109. Engel, E. A new genetic concept: uniparental disomy and its potential effect, isodisomy. *Am J Med Genet* **6**, 137-43 (1980).
110. Dracopoli, N.C. & Fogh, J. Loss of heterozygosity in cultured human tumor cell lines. *J Natl Cancer Inst* **70**, 83-7 (1983).

- 
111. Yokota, J., Wada, M., Shimosato, Y., Terada, M. & Sugimura, T. Loss of heterozygosity on chromosomes 3, 13, and 17 in small-cell carcinoma and on chromosome 3 in adenocarcinoma of the lung. *Proc Natl Acad Sci U S A* **84**, 9252-6 (1987).
112. Koufos, A. *et al.* Loss of heterozygosity in three embryonal tumours suggests a common pathogenetic mechanism. *Nature* **316**, 330-4 (1985).
113. Spence, J.E. *et al.* Uniparental disomy as a mechanism for human genetic disease. *Am J Hum Genet* **42**, 217-26 (1988).
114. Elder, F.F., Nichols, M.M., Hood, O.J. & Harrison, W.R., 3rd. Unbalanced translocation (15;17)(q13;13.3) with apparent Prader-Willi syndrome but without Miller-Dieker syndrome. *Am J Med Genet* **20**, 519-24 (1985).
115. Schinzel, A., Robinson, W.P., Bottani, A., Yagang, X. & Prader, A. Prader-Willi or Angelman syndrome in familial 15q11----q13 deletion of maternal origin? *Hum Genet* **88**, 361-2 (1992).
116. Vidaud, M. & Lavergne, J.M. [Prenatal diagnosis of hemophilia A and B]. *Rev Prat* **39**, 2689-96 (1989).
117. Engel, E. & DeLozier-Blanchet, C.D. Uniparental disomy, isodisomy, and imprinting: probable effects in man and strategies for their detection. *Am J Med Genet* **40**, 432-9 (1991).
118. Ledbetter, D.H. & Engel, E. Uniparental disomy in humans: development of an imprinting map and its implications for prenatal diagnosis. *Hum Mol Genet* **4 Spec No**, 1757-64 (1995).
119. Robinson, W.P. *et al.* Cytogenetic and age-dependent risk factors associated with uniparental disomy 15. *Prenat Diagn* **16**, 837-44 (1996).
120. Field, L.L., Tobias, R., Robinson, W.P., Paisey, R. & Bain, S. Maternal uniparental disomy of chromosome 1 with no apparent phenotypic effects. *Am J Hum Genet* **63**, 1216-20 (1998).
121. Robinson, W.P. Mechanisms leading to uniparental disomy and their clinical consequences. *Bioessays* **22**, 452-9 (2000).

122. Shaffer, L.G. *et al.* American College of Medical Genetics statement of diagnostic testing for uniparental disomy. *Genet Med* **3**, 206-11 (2001).
123. Liehr, T. & Unique. Uniparental disomy (UPD) in clinical genetics : a guide for clinicians and patients. (2014).
124. Liehr, T. Cytogenetic contribution to uniparental disomy (UPD). *Mol Cytogenet* **3**, 8 (2010).
125. Eggermann, T., Soellner, L., Buiting, K. & Kotzot, D. Mosaicism and uniparental disomy in prenatal diagnosis. *Trends Mol Med* **21**, 77-87 (2015).
126. Papenhausen, P. *et al.* UPD detection using homozygosity profiling with a SNP genotyping microarray. *Am J Med Genet A* **155A**, 757-68 (2011).
127. Ford, C.E., Polani, P.E., Briggs, J.H. & Bishop, P.M. A presumptive human XXY/XX mosaic. *Nature* **183**, 1030-2 (1959).
128. Hsu, L.Y. *et al.* Incidence and significance of chromosome mosaicism involving an autosomal structural abnormality diagnosed prenatally through amniocentesis: a collaborative study. *Prenat Diagn* **16**, 1-28 (1996).
129. Kotzot, D. Complex and segmental uniparental disomy (UPD): review and lessons from rare chromosomal complements. *J Med Genet* **38**, 497-507 (2001).
130. Laurie, C.C. *et al.* Detectable clonal mosaicism from birth to old age and its relationship to cancer. *Nat Genet* **44**, 642-50 (2012).
131. Rodriguez-Santiago, B. *et al.* Mosaic uniparental disomies and aneuploidies as large structural variants of the human genome. *Am J Hum Genet* **87**, 129-38 (2010).
132. Liehr, T. <http://www.fish.uniklinikum-jena.de/UPD.html>. Vol. 2012 (2013).
133. South, S.T., Lee, C., Lamb, A.N., Higgins, A.W. & Kearney, H.M. ACMG Standards and Guidelines for constitutional cytogenomic microarray analysis, including postnatal and prenatal applications: revision 2013. *Genet Med* **15**, 901-9 (2013).
134. El-Fishawy, P. & State, M.W. The genetics of autism: key issues, recent findings, and clinical implications. *Psychiatr Clin North Am* **33**, 83-105 (2010).
135. Robinson, P.N. *et al.* The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. *Am J Hum Genet* **83**, 610-5 (2008).

- 
136. Plon, S.E. *et al.* Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat* **29**, 1282-91 (2008).
137. King, D.A. *et al.* A novel method for detecting uniparental disomy from trio genotypes identifies a significant excess in children with developmental disorders. *Genome Res* **24**, 673-87 (2014).
138. Kirin, M. *et al.* Genomic runs of homozygosity record population history and consanguinity. *PLoS One* **5**, e13996 (2010).
139. Ting, J.C. *et al.* Visualization of uniparental inheritance, Mendelian inconsistencies, deletions, and parent of origin effects in single nucleotide polymorphism trio data with SNP trio. *Hum Mutat* **28**, 1225-35 (2007).
140. Schroeder, C. *et al.* UPDtool: a tool for detection of iso- and heterodisomy in parent-child trios using SNP microarrays. *Bioinformatics* **29**, 1562-4 (2013).
141. Danecek, P. *et al.* The variant call format and VCFtools. *Bioinformatics* **27**, 2156-8 (2011).
142. MacArthur, D.G. *et al.* A systematic survey of loss-of-function variants in human protein-coding genes. *Science* **335**, 823-8 (2012).
143. Evangelou, E., Trikalinos, T.A., Salanti, G. & Ioannidis, J.P. Family-based versus unrelated case-control designs for genetic associations. *PLoS Genet* **2**, e123 (2006).
144. Li, J. *et al.* CONTRA: copy number analysis for targeted resequencing. *Bioinformatics* **28**, 1307-13 (2012).
145. Love, M.I. *et al.* Modeling read counts for CNV detection in exome sequencing data. *Stat Appl Genet Mol Biol* **10**(2011).
146. Abecasis, G.R. *et al.* An integrated map of genetic variation from 1,092 human genomes. *Nature* **491**, 56-65 (2012).
147. Sherry, S.T. *et al.* dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res* **29**, 308-11 (2001).

- 
148. Teo, Y.Y. *et al.* A genotype calling algorithm for the Illumina BeadArray platform. *Bioinformatics* **23**, 2741-6 (2007).
149. Purcell, S. *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* **81**, 559-75 (2007).
150. Barnes, C. *et al.* A robust statistical method for case-control association testing with copy number variation. *Nat Genet* **40**, 1245-52 (2008).
151. Conrad, D.F. *et al.* Origins and functional impact of copy number variation in the human genome. *Nature* **464**, 704-12 (2010).
152. McLaren, W. *et al.* Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor. *Bioinformatics* **26**, 2069-70 (2010).
153. Ramu, A. *et al.* DeNovoGear: de novo indel and point mutation discovery and phasing. *Nat Methods* **10**, 985-7 (2013).
154. Eilers, P.H. & de Menezes, R.X. Quantile smoothing of array CGH data. *Bioinformatics* **21**, 1146-53 (2005).
155. Mills, R.E. *et al.* Mapping copy number variation by population-scale genome sequencing. *Nature* **470**, 59-65 (2011).
156. Li, L.H. *et al.* Long contiguous stretches of homozygosity in the human genome. *Hum Mutat* **27**, 1115-21 (2006).
157. Astle, W. & Balding, D.J. Population Structure and Cryptic Relatedness in Genetic Association Studies. *Statistical Science* **24**, 451-471 (2009).
158. Temple, I.K., Cockwell, A., Hassold, T., Pettay, D. & Jacobs, P. Maternal uniparental disomy for chromosome 14. *J Med Genet* **28**, 511-4 (1991).
159. Balciuniene, J. *et al.* Alpha-tectorin involvement in hearing disabilities: one gene--two phenotypes. *Hum Genet* **105**, 211-6 (1999).
160. Sagong, B., Park, H.J., Lee, K.Y. & Kim, U.K. Identification and functional characterization of novel compound heterozygotic mutations in the TECTA gene. *Gene* **492**, 239-43 (2012).
161. Moreno, J.C. *et al.* Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. *N Engl J Med* **347**, 95-102 (2002).

- 
162. Carvalho, C.M. *et al.* Absence of Heterozygosity Due to Template Switching during Replicative Rearrangements. *Am J Hum Genet* **96**, 555-64 (2015).
163. Horn, D., Schottmann, G. & Meinecke, P. Hyperphosphatasia with mental retardation, brachytelephalangy, and a distinct facial gestalt: Delineation of a recognizable syndrome. *Eur J Med Genet* **53**, 85-8 (2010).
164. Isidor, B., Pichon, O., Baron, S., David, A. & Le Caignec, C. Deletion of the CUL4B gene in a boy with mental retardation, minor facial anomalies, short stature, hypogonadism, and ataxia. *Am J Med Genet A* **152A**, 175-80 (2010).
165. Uldall, P., Alving, J., Hansen, L.K., Kibaek, M. & Buchholt, J. The misdiagnosis of epilepsy in children admitted to a tertiary epilepsy centre with paroxysmal events. *Arch Dis Child* **91**, 219-21 (2006).
166. Koch, M.C. *et al.* Evidence for genetic homogeneity in autosomal recessive generalised myotonia (Becker). *J Med Genet* **30**, 914-7 (1993).
167. Trip, J. *et al.* In tandem analysis of CLCN1 and SCN4A greatly enhances mutation detection in families with non-dystrophic myotonia. *Eur J Hum Genet* **16**, 921-9 (2008).
168. Yamatogi, Y. & Ohtahara, S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome; its overview referring to our 16 cases. *Brain Dev* **24**, 13-23 (2002).
169. Wolff, M., Casse-Perrot, C. & Dravet, C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. *Epilepsia* **47 Suppl 2**, 45-8 (2006).
170. Kearney, J.A. *et al.* A gain-of-function mutation in the sodium channel gene Scn2a results in seizures and behavioral abnormalities. *Neuroscience* **102**, 307-17 (2001).
171. Singh, N.A. *et al.* A role of SCN9A in human epilepsies, as a cause of febrile seizures and as a potential modifier of Dravet syndrome. *PLoS Genet* **5**, e1000649 (2009).
172. Caldovic, L. *et al.* Restoration of ureagenesis in N-acetylglutamate synthase deficiency by N-carbamylglutamate. *J Pediatr* **145**, 552-4 (2004).

- 
173. Krakow, D. *et al.* Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. *Nat Genet* **36**, 405-10 (2004).
174. Carmichael, H., Shen, Y., Nguyen, T., Hirschhorn, J. & Dauber, A. Whole exome sequencing in a patient with uniparental disomy of chromosome 2 and a complex phenotype. *Clin Genet* (2012).
175. Kotzot, D. & Utermann, G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. *Am J Med Genet A* **136**, 287-305 (2005).
176. Quinlan, A.R. & Hall, I.M. BEDTools: a flexible suite of utilities for comparing genomic features. *Bioinformatics* **26**, 841-2 (2010).
177. Koehler, K.E., Hawley, R.S., Sherman, S. & Hassold, T. Recombination and nondisjunction in humans and flies. *Hum Mol Genet* **5 Spec No**, 1495-504 (1996).
178. King, D.A. *et al.* Mosaic structural variation in children with developmental disorders. *Hum Mol Genet* (2015).
179. Lupski, J.R. Genomic disorders: structural features of the genome can lead to DNA rearrangements and human disease traits. *Trends Genet* **14**, 417-22 (1998).
180. Biesecker, L.G. & Spinner, N.B. A genomic view of mosaicism and human disease. *Nat Rev Genet* **14**, 307-20 (2013).
181. Lupski, J.R. Genetics. Genome mosaicism--one human, multiple genomes. *Science* **341**, 358-9 (2013).
182. Lindhurst, M.J. *et al.* A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med* **365**, 611-9 (2011).
183. Behjati, S. *et al.* A Pathogenic Mosaic TP53 Mutation in Two Germ Layers Detected by Next Generation Sequencing. *PLoS One* **9**, e96531 (2014).
184. Machiela, M.J. & Chanock, S.J. Detectable clonal mosaicism in the human genome. *Semin Hematol* **50**, 348-59 (2013).
185. Robberecht, C., Fryns, J.P. & Vermeesch, J.R. Piecing together the problems in diagnosing low-level chromosomal mosaicism. *Genome Med* **2**, 47 (2010).

- 
186. Olshen, A.B., Venkatraman, E.S., Lucito, R. & Wigler, M. Circular binary segmentation for the analysis of array-based DNA copy number data. *Biostatistics* **5**, 557-72 (2004).
187. Pique-Regi, R., Caceres, A. & Gonzalez, J.R. R-Gada: a fast and flexible pipeline for copy number analysis in association studies. *BMC Bioinformatics* **11**, 380 (2010).
188. Van Loo, P. *et al.* Allele-specific copy number analysis of tumors. *Proc Natl Acad Sci U S A* **107**, 16910-5 (2010).
189. Baumbusch, L.O. *et al.* Comparison of the Agilent, ROMA/NimbleGen and Illumina platforms for classification of copy number alterations in human breast tumors. *BMC Genomics* **9**, 379 (2008).
190. Nik-Zainal, S. *et al.* The life history of 21 breast cancers. *Cell* **149**, 994-1007 (2012).
191. Xia, R., Vattathil, S. & Scheet, P. Identification of allelic imbalance with a statistical model for subtle genomic mosaicism. *PLoS Comput Biol* **10**, e1003765 (2014).
192. Ballif, B.C. *et al.* Detection of low-level mosaicism by array CGH in routine diagnostic specimens. *Am J Med Genet A* **140**, 2757-67 (2006).
193. Cheung, S.W. *et al.* Microarray-based CGH detects chromosomal mosaicism not revealed by conventional cytogenetics. *Am J Med Genet A* **143A**, 1679-86 (2007).
194. Pham, J. *et al.* Somatic mosaicism detected by exon-targeted, high-resolution aCGH in 10,362 consecutive cases. *Eur J Hum Genet* **22**, 969-78 (2014).
195. Zhong, Q. & Layman, L.C. Genetic considerations in the patient with Turner syndrome--45,X with or without mosaicism. *Fertil Steril* **98**, 775-9 (2012).
196. Smith, B.H. *et al.* Cohort Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its participants and their potential for genetic research on health and illness. *Int J Epidemiol* **42**, 689-700 (2013).



197. Boyd, A. *et al.* Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *Int J Epidemiol* **42**, 111-27 (2013).
198. Haworth, C.M., Davis, O.S. & Plomin, R. Twins Early Development Study (TEDS): a genetically sensitive investigation of cognitive and behavioral development from childhood to young adulthood. *Twin Res Hum Genet* **16**, 117-25 (2013).
199. Liu, P. *et al.* Passage number is a major contributor to genomic structural variations in mouse iPSCs. *Stem Cells* **32**, 2657-67 (2014).
200. Narva, E. *et al.* High-resolution DNA analysis of human embryonic stem cell lines reveals culture-induced copy number changes and loss of heterozygosity. *Nat Biotechnol* **28**, 371-7 (2010).
201. Robinson, W.P. *et al.* Origin and outcome of pregnancies affected by androgenetic/biparental chimerism. *Hum Reprod* **22**, 1114-22 (2007).
202. Shin, S.Y., Yoo, H.W., Lee, B.H., Kim, K.S. & Seo, E.J. Identification of the mechanism underlying a human chimera by SNP array analysis. *Am J Med Genet A* **158A**, 2119-23 (2012).
203. Reik, W. & Walter, J. Genomic imprinting: parental influence on the genome. *Nat Rev Genet* **2**, 21-32 (2001).
204. Zweier, C. *et al.* Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). *Am J Hum Genet* **80**, 994-1001 (2007).
205. Schinzel, A. *Catalogue of unbalanced chromosome aberrations in man*, xx, 913 p. (W. de Gruyter, Berlin ; New York, 2001).
206. Steinbach, P. *et al.* The dup(3q) syndrome: report of eight cases and review of the literature. *Am J Med Genet* **10**, 159-77 (1981).
207. Reynolds, J.F. *et al.* Isochromosome 12p mosaicism (Pallister mosaic aneuploidy or Pallister-Killian syndrome): report of 11 cases. *Am J Med Genet* **27**, 257-74 (1987).
208. Shinawi, M. *et al.* Recurrent reciprocal 16p11.2 rearrangements associated with global developmental delay, behavioural problems, dysmorphism, epilepsy, and abnormal head size. *J Med Genet* **47**, 332-41 (2010).

- 
209. Phelan, M.C. *et al.* 22q13 deletion syndrome. *Am J Med Genet* **101**, 91-9 (2001).
210. Daber, R. *et al.* Mosaic trisomy 17: variable clinical and cytogenetic presentation. *Am J Med Genet A* **155A**, 2489-95 (2011).
211. Gogiel, M. *et al.* Genome-wide paternal uniparental disomy mosaicism in a woman with Beckwith-Wiedemann syndrome and ovarian steroid cell tumour. *Eur J Hum Genet* **21**, 788-91 (2013).
212. Willis, M.J., Bird, L.M., Dell'Aquila, M. & Jones, M.C. Expanding the phenotype of mosaic trisomy 20. *Am J Med Genet A* **146**, 330-6 (2008).
213. Schmeisser, M.J. *et al.* The Nedd4-binding protein 3 (N4BP3) is crucial for axonal and dendritic branching in developing neurons. *Neural Dev* **8**, 18 (2013).
214. Mavrogiannis, L.A. *et al.* Haploinsufficiency of the human homeobox gene ALX4 causes skull ossification defects. *Nat Genet* **27**, 17-8 (2001).
215. Gilissen, C. *et al.* Genome sequencing identifies major causes of severe intellectual disability. *Nature* (2014).
216. Endler, G., Greinix, H., Winkler, K., Mitterbauer, G. & Mannhalter, C. Genetic fingerprinting in mouthwashes of patients after allogeneic bone marrow transplantation. *Bone Marrow Transplant* **24**, 95-8 (1999).
217. Staaf, J. *et al.* Segmentation-based detection of allelic imbalance and loss-of-heterozygosity in cancer cells using whole genome SNP arrays. *Genome Biol* **9**, R136 (2008).
218. Forsberg, L.A. *et al.* Mosaic loss of chromosome Y in peripheral blood is associated with shorter survival and higher risk of cancer. *Nat Genet* **46**, 624-8 (2014).
219. Forsberg, L.A. *et al.* Age-related somatic structural changes in the nuclear genome of human blood cells. *Am J Hum Genet* **90**, 217-28 (2012).
220. Koboldt, D.C., Steinberg, K.M., Larson, D.E., Wilson, R.K. & Mardis, E.R. The next-generation sequencing revolution and its impact on genomics. *Cell* **155**, 27-38 (2013).

- 
221. Meynert, A.M., Ansari, M., FitzPatrick, D.R. & Taylor, M.S. Variant detection sensitivity and biases in whole genome and exome sequencing. *BMC Bioinformatics* **15**, 247 (2014).
222. Lee, C., Iafrate, A.J. & Brothman, A.R. Copy number variations and clinical cytogenetic diagnosis of constitutional disorders. *Nat Genet* **39**, S48-54 (2007).
223. Plagnol, V. *et al.* A robust model for read count data in exome sequencing experiments and implications for copy number variant calling. *Bioinformatics* **28**, 2747-54 (2012).
224. Magi, A. *et al.* EXCAVATOR: detecting copy number variants from whole-exome sequencing data. *Genome Biol* **14**, R120 (2013).
225. Sathirapongsasuti, J.F. *et al.* Exome sequencing-based copy-number variation and loss of heterozygosity detection: ExomeCNV. *Bioinformatics* **27**, 2648-54 (2011).
226. Krumm, N. *et al.* Copy number variation detection and genotyping from exome sequence data. *Genome Res* **22**, 1525-32 (2012).
227. Backenroth, D. *et al.* CANOES: detecting rare copy number variants from whole exome sequencing data. *Nucleic Acids Res* **42**, e97 (2014).
228. Lonigro, R.J. *et al.* Detection of somatic copy number alterations in cancer using targeted exome capture sequencing. *Neoplasia* **13**, 1019-25 (2011).
229. Amarasinghe, K.C. *et al.* Inferring copy number and genotype in tumour exome data. *BMC Genomics* **15**, 732 (2014).
230. Kaye, J. *et al.* Managing clinically significant findings in research: the UK10K example. *Eur J Hum Genet* **22**, 1100-4 (2014).
231. Chen, K. *et al.* BreakDancer: an algorithm for high-resolution mapping of genomic structural variation. *Nat Methods* **6**, 677-81 (2009).
232. Choate, K.A. *et al.* Frequent somatic reversion of KRT1 mutations in ichthyosis with confetti. *J Clin Invest* **125**, 1703-7 (2015).
233. Snape, K. *et al.* Mutations in CEP57 cause mosaic variegated aneuploidy syndrome. *Nat Genet* **43**, 527-9 (2011).
234. Guilherme, R.S. *et al.* Mechanisms of ring chromosome formation, ring instability and clinical consequences. *BMC Med Genet* **12**, 171 (2011).

- 
235. Knijnenburg, J. *et al.* Ring chromosome formation as a novel escape mechanism in patients with inverted duplication and terminal deletion. *Eur J Hum Genet* **15**, 548-55 (2007).
236. Abyzov, A., Urban, A.E., Snyder, M. & Gerstein, M. CNVnator: an approach to discover, genotype, and characterize typical and atypical CNVs from family and population genome sequencing. *Genome Res* **21**, 974-84 (2011).
237. Plaiasu, V., Ochiana, D., Motei, G. & Georgescu, A. A rare chromosomal disorder - isochromosome 18p syndrome. *Maedica (Buchar)* **6**, 132-6 (2011).
238. Wulfsberg, E.A., Weaver, R.P., Cunniff, C.M., Jones, M.C. & Jones, K.L. Chromosome 10qter deletion syndrome: a review and report of three new cases. *Am J Med Genet* **32**, 364-7 (1989).
239. Conlin, L.K. *et al.* Utility of SNP arrays in detecting, quantifying, and determining meiotic origin of tetrasomy 12p in blood from individuals with Pallister-Killian syndrome. *Am J Med Genet A* **158A**, 3046-53 (2012).
240. Choo, S., Teo, S.H., Tan, M., Yong, M.H. & Ho, L.Y. Tissue-limited mosaicism in Pallister-Killian syndrome -- a case in point. *J Perinatol* **22**, 420-3 (2002).
241. Piotrowski, A. *et al.* Somatic mosaicism for copy number variation in differentiated human tissues. *Hum Mutat* **29**, 1118-24 (2008).
242. O'Huallachain, M., Karczewski, K.J., Weissman, S.M., Urban, A.E. & Snyder, M.P. Extensive genetic variation in somatic human tissues. *Proc Natl Acad Sci U S A* **109**, 18018-23 (2012).
243. Abraham, J.E. *et al.* Saliva samples are a viable alternative to blood samples as a source of DNA for high throughput genotyping. *BMC Med Genomics* **5**, 19 (2012).
244. Daksis, J.I. & Erikson, G.H. Heteropolymeric triplex-based genomic assay to detect pathogens or single-nucleotide polymorphisms in human genomic samples. *PLoS One* **2**, e305 (2007).
245. Ayoglu, B. *et al.* Affinity proteomics within rare diseases: a BIO-NMD study for blood biomarkers of muscular dystrophies. *EMBO Mol Med* **6**, 918-36 (2014).

246. Garcia-Closas, M. *et al.* Collection of genomic DNA from adults in epidemiological studies by buccal cytobrush and mouthwash. *Cancer Epidemiol Biomarkers Prev* **10**, 687-96 (2001).
247. Drost, M. *et al.* Genetic screens to identify pathogenic gene variants in the common cancer predisposition Lynch syndrome. *Proc Natl Acad Sci U S A* **110**, 9403-8 (2013).
248. Hassold, T., Merrill, M., Adkins, K., Freeman, S. & Sherman, S. Recombination and maternal age-dependent nondisjunction: molecular studies of trisomy 16. *Am J Hum Genet* **57**, 867-74 (1995).
249. Gravholt, C.H. Chapter 44 - Sex-Chromosome Abnormalities. in *Emery and Rimoin's Principles and Practice of Medical Genetics (Sixth Edition)* (eds. Rimoin, D. & Korf, R.P.) 1-32 (Academic Press, Oxford, 2013).
250. Lynch, M. Rate, molecular spectrum, and consequences of human mutation. *Proc Natl Acad Sci U S A* **107**, 961-8 (2010).
251. Papavassiliou, P. *et al.* The phenotype of persons having mosaicism for trisomy 21/Down syndrome reflects the percentage of trisomic cells present in different tissues. *Am J Med Genet A* **149A**, 573-83 (2009).
252. Choate, K.A. *et al.* Mitotic recombination in patients with ichthyosis causes reversion of dominant mutations in KRT10. *Science* **330**, 94-7 (2010).
253. McDermott, D.H. *et al.* Chromothriptic cure of WHIM syndrome. *Cell* **160**, 686-99 (2015).
254. Crow, J.F. Two centuries of genetics: a view from halftime. *Annu Rev Genomics Hum Genet* **1**, 21-40 (2000).
255. Tripp, S.G., M. Economic Impact of the Human Genome Project. (2011).
256. Meldrum, D.R. Tech.Sight. Sequencing genomes and beyond. *Science* **292**, 515-7 (2001).
257. Hayden, E.C. Technology: The \$1,000 genome. *Nature* **507**, 294-5 (2014).
258. Sboner, A., Mu, X.J., Greenbaum, D., Auerbach, R.K. & Gerstein, M.B. The real cost of sequencing: higher than you think! *Genome Biol* **12**, 125 (2011).
259. Michaud, M. Illumina Is Dominting The Sequencing Market. (2015).

- 
260. Stoddart, D., Heron, A.J., Mikhailova, E., Maglia, G. & Bayley, H. Single-nucleotide discrimination in immobilized DNA oligonucleotides with a biological nanopore. *Proc Natl Acad Sci U S A* **106**, 7702-7 (2009).
261. Eid, J. *et al.* Real-time DNA sequencing from single polymerase molecules. *Science* **323**, 133-8 (2009).
262. Hsi-Yang Fritz, M., Leinonen, R., Cochrane, G. & Birney, E. Efficient storage of high throughput DNA sequencing data using reference-based compression. *Genome Res* **21**, 734-40 (2011).
263. Li, Y. *et al.* Structural variation in two human genomes mapped at single-nucleotide resolution by whole genome de novo assembly. *Nat Biotechnol* **29**, 723-30 (2011).
264. Dunn, W.B., Broadhurst, D.I., Atherton, H.J., Goodacre, R. & Griffin, J.L. Systems level studies of mammalian metabolomes: the roles of mass spectrometry and nuclear magnetic resonance spectroscopy. *Chem Soc Rev* **40**, 387-426 (2011).
265. Bibby, K. & Peccia, J. Identification of viral pathogen diversity in sewage sludge by metagenome analysis. *Environ Sci Technol* **47**, 1945-51 (2013).
266. Robinson, P.N. & Mundlos, S. The human phenotype ontology. *Clin Genet* **77**, 525-34 (2010).
267. Ferry, Q. *et al.* Diagnostically relevant facial gestalt information from ordinary photos. *Elife* **3**, e02020 (2014).
268. Bamshad, M.J. *et al.* Exome sequencing as a tool for Mendelian disease gene discovery. *Nat Rev Genet* **12**, 745-55 (2011).
269. Dietz, H.C. New therapeutic approaches to mendelian disorders. *N Engl J Med* **363**, 852-63 (2010).
270. Garg, S.K. *et al.* Systemic delivery of MeCP2 rescues behavioral and cellular deficits in female mouse models of Rett syndrome. *J Neurosci* **33**, 13612-20 (2013).
271. Jiang, J. *et al.* Translating dosage compensation to trisomy 21. *Nature* **500**, 296-300 (2013).

272. Buchanan, A., Sachs, A., Toler, T. & Tsipis, J. NIPT: current utilization and implications for the future of prenatal genetic counseling. *Prenat Diagn* **34**, 850-7 (2014).
273. Hill, M. *et al.* Evaluation of non-invasive prenatal testing (NIPT) for aneuploidy in an NHS setting: a reliable accurate prenatal non-invasive diagnosis (RAPID) protocol. *BMC Pregnancy Childbirth* **14**, 229 (2014).
274. Gupta, K. Disability-selective abortion: denying human rights to make a "perfect world"? *Indian J Med Ethics* **10**, 70-1 (2013).
275. Yurkiewicz, I.R., Korf, B.R. & Lehmann, L.S. Prenatal whole-genome sequencing--is the quest to know a fetus's future ethical? *N Engl J Med* **370**, 195-7 (2014).
276. Liang, P. *et al.* CRISPR/Cas9-mediated gene editing in human trippronuclear zygotes. *Protein Cell* **6**, 363-72 (2015).
277. Cyranoski, D. & Reardon, S. Embryo editing sparks epic debate. *Nature* **520**, 593-4 (2015).
278. Jin, F. *et al.* A high-resolution map of the three-dimensional chromatin interactome in human cells. *Nature* **503**, 290-4 (2013).
279. Ohno, S. So much "junk" DNA in our genome, in *Evolution of Genetic Systems.*, (Gordon and Breach, New York, 1972).
280. Palazzo, A.F. & Gregory, T.R. The case for junk DNA. *PLoS Genet* **10**, e1004351 (2014).
281. An integrated encyclopedia of DNA elements in the human genome. *Nature* **489**, 57-74 (2012).
282. van Berkum, N.L. *et al.* Hi-C: a method to study the three-dimensional architecture of genomes. *J Vis Exp* (2010).
283. Riethoven, J.J. Regulatory regions in DNA: promoters, enhancers, silencers, and insulators. *Methods Mol Biol* **674**, 33-42 (2010).
284. Dekker, J., Marti-Renom, M.A. & Mirny, L.A. Exploring the three-dimensional organization of genomes: interpreting chromatin interaction data. *Nat Rev Genet* **14**, 390-403 (2013).

---

285. Ahn, C.P. *et al.* The Tenth Data Release of the Sloan Digital Sky Survey: First Spectroscopic Data from the Sdss-Iii Apache Point Observatory Galactic Evolution Experiment. *Astrophysical Journal Supplement Series* **211**(2014).

}