

## Papers published by members of the International Clearinghouse for Birth Defects Surveillance and Research and appeared in the Medline in the period January - August 2007

### ANNEREN G

Gustavsson P, Schoumans J, Staaf J, Borg A, Nordenskjold M, Anneren G. **Duplication 16q12.1-q22.1 characterized by array CGH in a girl with spina bifida.** Eur J Med Genet. 2007 May-Jun;50(3):237-41. Epub 2007 Feb 21.

Department of Molecular Medicine and Surgery, Center for Molecular Medicine, L8:02, Karolinska University Hospital, S-171 76 Stockholm, Sweden.

We report a 7-year-old girl with spina bifida carrying a complex chromosome abnormality resulting in duplication 16q12.1-q22.1. An abnormal karyotype was identified involving the long arm of chromosome 11 and fluorescent in situ hybridization (FISH) to metaphase chromosomes revealed an insertion of part of chromosome 16 on chromosome 11. A detailed mapping of the chromosome abnormality using whole genome array based comparative genomic hybridization (CGH) of the patient DNA revealed a duplication 16q12.1-q22.1 corresponding to gain of 19.8Mb of DNA without any detectable loss of genetic material on chromosome 11. The karyotype is defined as 46,XX,der(11)ins(11;16)(q13;q12.1q22.1). We present here the clinical findings and a fine mapping of the associated structural chromosome abnormalities. We suggest that a gene dosage imbalance of 16q12.1-q22.1 is associated with spina bifida in the patient.

### BAKKER M

Bakker MK, de Walle HE, Dequito A, van den Berg PB, de Jong-van den Berg LT. **Selection of controls in case-control studies on maternal medication use and risk of birth defects.** Birth Defects Res A Clin Mol Teratol. 2007 Jul 31;

EUROCAT Registration of Congenital Anomalies, Department of Genetics, University. Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

**BACKGROUND:** In case-control studies on teratogenic risks of maternal drug use during pregnancy, the use of normal or malformed controls may lead to recall-bias or selection bias. This can be avoided by using controls with a genetic disorder. However, researchers are hesitant to use these as controls because it is unknown whether their selection is independent of exposure status. The aim of this study is to investigate whether first trimester drug use among mothers of children with genetic disorders is representative for the "general pregnant population".

**METHODS:** From a birth defects registry 565 mothers of infants with a genetic disorder born between 1998-2004 were selected (the "genetic population"). The first trimester exposure rate was calculated for prescription-only drugs as the number of exposed women per 100. By calculating the rate ratio (RR) and 95% CI, the exposure rates in the genetic population were compared with those in the "source population" obtained from a population-based prescription database and consisting of 10,870 mothers who gave birth to a child between 1998-2004.

**RESULTS:** The mean age at birth was 32.1 for the genetic population and 29.6 for the source population ( $p = .000$ ). In the genetic population, a higher use was found for antimigraine medication (RR = 2.7, 95% CI = 1.0-7.8) and for ovulation stimulants (RR = 1.6, 95% CI = 1.0-2.6). After adjustment for maternal age, the difference in use of ovulation stimulants disappeared.

**CONCLUSIONS:** Except for antimigraine medication, first trimester drug use among mothers of infants with genetic disorders is representative for the general pregnant population.

### BIANCHI F

Calzolari E, Pierini A, Astolfi G, Bianchi F, Neville AJ, Rivieri F. **Associated anomalies in multi-malformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries.** Am. J. Med. Genet. A. 2007 Mar 15;143(6):528-37.

Medical Genetics Section, University of Ferrara, Ferrara, Italy.

We studied 5,449 cases of cleft lip (CL) with or without cleft palate (CL/P) identified between 1980 and 2000 from the EUROCAT network of 23 registers (nearly 6 million births) in 14 European countries. We investigated specific types of defects associated with clefts. Among CL/P cases (prevalence = 9.1 per 10,000), 1,996 (36.6%) affected only the lip (CL) and 3,453 (63.4%) involved CL and palate (CLP). A total of 3,860 CL/P cases (70.8%) occurred as isolated anomalies and 1,589 (29.2%) were associated with other defects such as multiple congenital anomalies of unknown origin (970), chromosomal (455) and recognized syndromes (164). Associated malformations were more frequent in infants who had CLP (34.0%) than in infants with CL only (20.8%). Among multi-malformed infants, 2 unrelated anomalies were found in 351 cases, 3 in 242 cases, and 4 or more in 377 cases. Among 5,449 CL/P cases, 4,719 were live births (LB) (86.6%), 203 stillbirths (SB) (3.7%), while 508 (9.3%) were terminations of pregnancy (ToP). CL/P occurred significantly more frequently in males (M/F = 1.70), especially among total isolated cases (M/F = 1.87) and CLP isolated cases (M/F = 1.92). The study confirmed that musculoskeletal, cardiovascular, and central nervous system defects are frequently associated with CL/P. An association with reduction anomalies of the brain was found. This association suggests that clinicians should seek to identify structural brain anomalies in these patients with CL/P as the potential functional consequences may be important for rehabilitation and clinical management.

## BOWER C

O'Leary CM, Heuzenroeder L, Elliott EJ, Bower C. **A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries, 2006.** Med. J. Aust. 2007 May 7;186(9):466-71.

Department of Population Sciences and Centre for Child Health Research, Telethon Institute for Child Health Research and University of Western Australia, Perth, WA, Australia. colleeno@ichr.uwa.edu.au

It is well accepted that heavy alcohol consumption during pregnancy is a risk factor for fetal alcohol spectrum disorder, but research findings for exposure to low to moderate alcohol levels during pregnancy are equivocal, allowing a range of interpretations. The 2001 guideline from the National Health and Medical Research Council (NHMRC) for low-risk drinking for "women who are pregnant or might soon become pregnant" recommends fewer than seven standard drinks per week, and no more than two standard drinks on any one day. This position has polarised health professional and consumer opinion in Australia. The NHMRC guidelines on alcohol are scheduled for review in 2007. We surveyed the alcohol and pregnancy policies and clinical practice guidelines of Australia and six other English-speaking countries to identify current policy. Documents were obtained through Internet searches and direct contact with the relevant organisations. The policies and guidelines varied both across and within countries, and the NHMRC guideline, while not universally supported in Australia, is in step with the policies of the United Kingdom and Canada. Research is needed to elucidate the true association between low to moderate alcohol consumption and fetal harm, the impact of different policies on rates of maternal alcohol consumption during pregnancy, and any untoward outcomes of an abstinence message, to inform and underpin future policy development in Australia

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Haynes A, Bower C, Bulsara MK, Finn J, Jones TW, Davis EA. **Perinatal risk factors for childhood Type 1 diabetes in Western Australia—a population-based study (1980-2002).** Diabet. Med. 2007 May;24(5):564-70.

Department of Endocrinology & Diabetes, Princess Margaret Hospital, and Telethon Institute of Child Health Research, Centre for Child Health Research, Perth, Western Australia, Australia.

AIMS: To investigate perinatal risk factors for childhood Type 1 diabetes in Western Australia, using a complete population-based cohort.

METHODS: Children born between 1980 and 2002 and diagnosed with Type 1 diabetes aged < 15 years (n=940) up to 31 December 2003 were identified using a prospective population-based diabetes register with a case ascertainment rate of 99.8%. Perinatal data were obtained for all live births in Western Australia from 1980 to 2002 (n = 558 633) and record linkage performed to identify the records of cases.

RESULTS: The incidence of Type 1 diabetes increased by 13% for each 5-year increase in maternal age [adjusted incidence rate ratio (IRR) 1.13, 95% confidence interval (CI) 1.05, 1.21], by 13% for every 500-g increase in birth weight (adjusted IRR 1.13, 95% CI 1.04, 1.23). The incidence decreased with increasing birth order (adjusted IRR 0.89, 95% CI 0.82, 0.96) and increasing gestational age (adjusted IRR 0.84, 95%

CI 0.77, 0.93). A higher incidence of Type 1 diabetes was associated with an urban vs. non-urban maternal address at the time of birth (adjusted IRR 1.38, 95% CI 1.18, 1.63), but no association was found with socio-economic status of the area.

**CONCLUSIONS: A higher incidence of Type 1 diabetes was associated with increasing maternal age, higher birth weight, lower gestational age, lower birth order and urban place of residence at the time of birth.**

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Milne E, Laurvick CL, Blair E, Bower C, de Klerk N. **Fetal Growth and Acute Childhood Leukemia: Looking Beyond Birth Weight.** Am J Epidemiol. 2007 Apr 18;

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Perth, Western Australia.

The authors examined the relation between birth weight, intrauterine growth, and risk of childhood leukemia using population-based linked health data from Western Australia. **A cohort of 576,593 infants born in 1980-2004 were followed from birth to diagnosis of acute lymphoblastic leukemia (ALL) (n = 243) or acute myeloid leukemia (AML) (n = 36) before their 15th birthday,** death, or the end of follow-up (December 31, 2005). Data were analyzed using Cox regression. Risk of ALL was positively associated with the proportion of optimal birth weight-a measure of the appropriateness of fetal growth-particularly among children younger than 5 years; the hazard ratio for a 1-standard-deviation increase in proportion of optimal birth weight was 1.25 (95% confidence interval: 1.07, 1.47). Among children younger than 5 years not classified as having high birth weight (defined as >3,500 g, >3,800 g, and >4,000 g), a 1-unit increase in proportion of optimal birth weight was associated with an approximately 40% increase in ALL risk. This suggests that **accelerated growth, rather than high birth weight per se, is involved in the etiology of ALL. These findings are consistent with a role for insulin-like growth factor I in the causal pathway.** Findings for AML were inconclusive, probably because of small numbers.

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Nassar N, Bower C, Barker A. **Increasing prevalence of hypospadias in Western Australia, 1980-2000.** Arch Dis Child. 2007 Apr 3;

Telethon Institute for Child Health Research, Australia.

**OBJECTIVES:** Hypospadias, a common birth defect, has shown widespread variation in reported rates and temporal trends across countries over the last 30 years. The aim of this study was to determine the prevalence and trends of hypospadias in an Australian population. Design, setting, patients: Population-based study of all male infants born in Western Australia (WA) between 1980 and 2000 diagnosed with hypospadias and notified to the WA Birth Defects Registry.

**MAIN OUTCOME MEASURES:** Prevalence of hypospadias, birth outcome and association with other congenital anomalies; stratified by degree-of-severity.

**RESULTS:** A total of 1788 cases of hypospadias were registered in WA in 1980-2000 with **overall prevalence of 34.8 (95%Confidence Interval, 33.2 to 36.4) cases per 10,000 births.** The prevalence increased 2.0% per annum (1.2% to 2.8%) from 27.9 in 1980 to 43.2 per 10,000 births in 2000 (P<0.001). Hypospadias was diagnosed as mild in 84% of cases, 11% were moderate- severe and 5% unspecified; with moderate-severe hypospadias almost doubling over time (P<0.01). There were 1465 (82%) cases of isolated hypospadias and 18% with co-existing anomalies. Infants with co-existing genital (Relative Risk(RR) 4.5; 3.3 to 6.1) or non- genital (RR 1.5; 1.0 to 2.2) anomalies were more likely to have moderate-severe hypospadias compared with isolated cases.

**CONCLUSION:** This study overcomes many limitations of previous reports. Hypospadias affects one in 231 births and has increased significantly over the last 20 years. Future investigation of aetiology of hypospadias is important to identify potentially modifiable risk factors and ensure optimal male reproductive health in the future.

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Blair E, Al Asedy F, Badawi N, Bower C. **Is cerebral palsy associated with birth defects other than cerebral defects?** Dev Med Child Neurol. 2007 Apr;49(4):252-8.

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, Australia. eve@ichr.uwa.edu.au

The objective of the study was to identify the origin (s) of the association between cerebral palsy (CP) and birth defects in the absence of cerebral birth defects. Data from the 1980 to 1994 Western Australian birth cohorts (355 659 neonatal survivors) were linked to the Cerebral Palsy Register (941 links) and the Birth Defects Registry (17070 links). Associations between CP (congenital or acquired) and birth defects (cerebral or exclusively non-cerebral) were estimated. The origin of the association between non-cerebral defects and acquired CP was investigated with an observational study, and the origin of the association between non-cerebral defects and congenital CP was investigated with a blinded case-control study of births with non-cerebral defects with or without CP. **With non-cerebral defects, the odds ratio for CP was 4.8 (95% CI 3.1-7.4) if acquired and 4.7 (3.9-5.7) if congenital. For acquired CP, the association arose primarily as a result of cardiac defects. For congenital CP, the association arose partly from ascertainment bias and partly from defects known to be associated with cerebral defects (but not identified in these data).** However, a significant portion remained unexplained. **The presence of non-cerebral defects should heighten clinical alertness to the possibility of CP and of cerebral birth defects.**

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Colvin L, Payne J, Parsons D, Kurinczuk JJ, Bower C. **Alcohol consumption during pregnancy in nonindigenous west Australian women.** Alcohol. Clin. Exp. Res. 2007 Feb;31(2):276-84.

Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Australia. lync@ichr.uwa.edu.au

**BACKGROUND:** High alcohol intake in pregnancy has been linked to abnormal fetal development. There are limited published data in Australia on standard drinks of alcohol consumed on a typical occasion during the periconceptional period or pregnancy.

**METHODS:** During 1995 to 1997, a **10% random sample of all nonindigenous women** giving birth in Western Australia was surveyed 12 weeks after delivery (N=4,839). Women were asked questions about alcohol consumption in each of the 4 time periods: the 3 months before pregnancy and each trimester of pregnancy. Questions were framed to measure volume, frequency, and type of alcoholic beverage.

**RESULTS:** 46.7% of the women had not planned their pregnancy. Most women (79.8%) reported drinking alcohol in the 3 months before pregnancy, with 58.7% drinking alcohol in at least 1 trimester of pregnancy. The proportion of women consuming 1 to 2 drinks on a typical occasion did not change much during pregnancy, but the number of occasions declined. Although the proportion of women consuming **more than 2 standard drinks** on a typical occasion declined after the first trimester, **19.0%** of women consumed this amount in at least 1 trimester of pregnancy and **4.3% of women consumed 5 or more standard drinks on a typical occasion in at least 1 trimester of pregnancy.** In the first trimester of pregnancy, 14.8% of women drank outside the current Australian guideline for alcohol consumption in pregnancy, decreasing to 10% in the second and third trimesters.

**CONCLUSIONS:** Women generally reduced their average alcohol consumption and the number of standard drinks on a typical occasion as their pregnancy progressed, although **10 to 14% were drinking outside current guidelines for pregnancy.** It is important that all women of child-bearing age are aware, well before they consider pregnancy, of the risks of drinking alcohol during pregnancy so they can make informed decisions about their alcohol consumption in pregnancy.

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Petterson B, Bourke J, Leonard H, Jacoby P, Bower C. **Co-occurrence of birth defects and intellectual disability.** Paediatr Perinat Epidemiol. 2007 Jan;21(1):65-75.

Telethon Institute for Child Health Research, Centre for Child Health Research, University of Western Australia, West Perth, WA 6872, Australia.

This study used population-based databases to ascertain birth defects and intellectual disability (ID), defined as full IQ < 70, in children born in Western Australia during 1980-99. Of the children surviving to 1 year (n = 474 285), 4.9% had birth defects and 1.3% ID. **ID was identified in 7.9% of children with birth defects.** After adjusting for sex, mother's age, race, parity, plurality, birthweight and gestational age the prevalence ratio (PR) [95% confidence interval (CI)] for ID in children with birth defects compared with those with no birth defects **was 7.6 [7.2, 8.0].** Those with chromosomal anomalies comprised 3.2% of the group with birth defects. The percentage ID (and PR [95% CI]) in specific categories were: **Down's syndrome 97% (84.5 [79.4, 90.0]), sex chromosome anomalies 30.3% (31.0 [23.8, 40.3]), other chromosomal anomalies 64.2%**

(54.2 [47.2, 62.3]). Birth defects were categorised according to system in the 96.8% of children with non-chromosomal anomalies. The percentage with ID (and PR [95% CI]) for birth defects in each system were: spina bifida 18.8 (16.7 [12.2, 23.0]); nervous (except spina bifida) 38.6 (33.4 [30.3, 36.9]); cardiovascular 4.2 (4.1 [3.5, 4.8]); gastro-intestinal 2.2 (2.0 [1.5, 2.7]); urogenital 2.6 (2.4 [2.0, 2.8]); musculo-skeletal 3.6 (4.0 [3.5, 4.6]); other non-chromosomal 7.0 (7.3 [6.5, 8.3]); and multiple systems 12.3 (10.2 [8.6, 12.2]). Birth defects were present in 30.2% of children with ID (27.7% of children with mild/moderate ID (IQ 40-69) and 54% of children with severe ID (IQ < 40)). Adjusted PRs for birth defects in children with any ID, mild/moderate ID and severe ID compared with children with normal intellectual function were 6.0 [5.8, 6.3], 5.5 [5.3, 5.8] and 10.5 [9.7, 11.4] respectively. The data are useful for those providing services for children with developmental disabilities especially for predicting family support and respite and accommodation requirements for children and adults with severe ID.

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## CANFIELD MA

Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A; National Birth Defects Prevention Study. **Prepregnancy obesity as a risk factor for structural birth defects.** Arch Pediatr Adolesc Med. 2007 Aug;161(8):745-50.

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**OBJECTIVE:** To describe the relation between maternal obesity, overweight and underweight status, and 16 categories of structural birth defects.

**DESIGN:** An ongoing multisite, case-control study. Clinical geneticists reviewed all of the cases, excluding those that had or were strongly suspected to have a single-gene disorder or chromosomal abnormality. Mothers with preexisting diabetes were also excluded. Body mass index was based on maternal report of height and weight prior to pregnancy.

**SETTING:** Eight participating states in the United States.

**PARTICIPANTS:** Mothers enrolled in the National Birth Defects Prevention Study who had index pregnancies between October 1, 1997, and December 31, 2002.

**MAIN EXPOSURE:** Maternal obesity.

**MAIN OUTCOME MEASURES:** Crude and adjusted odds ratios.

**RESULTS:** Mothers of offspring with spina bifida, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele were significantly more likely to be obese than mothers of controls, with odds ratios ranging between 1.33 and 2.10. Mothers of offspring with gastroschisis were significantly less likely to be obese than mothers of controls.

**CONCLUSIONS:** To our knowledge, this is the first population-based study of its scale to examine prepregnancy obesity and a range of structural birth defects. These results suggest a weak to moderate positive association of maternal obesity with 7 of 16 categories of birth defects and a strong inverse association with gastroschisis. The mechanisms underlying these associations are not yet understood but may be related to undiagnosed diabetes.

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Case AP, Ramadhani TA, Canfield MA, Wicklund CA. **Awareness and Attitudes Regarding Prenatal Testing among Texas Women of Childbearing Age.** J Genet Couns. 2007 Aug 3;

Birth Defects Epidemiology & Surveillance Branch, Texas Department of State, Health Services, Mail Code 1964, 1100 W. 49th Street, Austin, TX, 78756, USA, amy.case@dshs.state.tx.us.

Despite increased visibility and availability of prenatal testing procedures, very little is known about the attitudes among the populace toward these procedures. Using a computer assisted telephone interview of pregnant and non-pregnant women of childbearing age we analyze awareness and attitudes regarding prenatal tests among a diverse group of women of childbearing age in Texas. We also examine maternal characteristics associated with awareness and the willingness to undergo these procedures. While 89% were aware that such tests are available, younger, black and less educated women were less likely to know about prenatal tests for birth defects. Seventy-two percent of respondents said they would want their baby tested while Hispanic and black women were significantly more likely to express an interest than non-Hispanic whites. This study demonstrates the variability of knowledge and beliefs and confirms the

importance of taking time to understand an individual's personal beliefs, knowledge and attitudes about prenatal diagnosis.

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Rasmussen SA, Yazdy MM, Carmichael SL, Jamieson DJ, Canfield MA, Honein MA. **Maternal thyroid disease as a risk factor for craniosynostosis.** *Obstet Gynecol.* 2007 Aug;110(2 Pt 1):369-77.

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA. skr9@cdc.gov

**OBJECTIVE:** To study the relationship between maternal thyroid disease and craniosynostosis using data from the National Birth Defects Prevention Study, a multisite, case-control study.

**METHODS:** Case infants (n=431) were identified through population-based birth defects surveillance systems at eight sites and had craniosynostosis verified by radiographic imaging. Control infants (n=4,094) consisted of a random sample of live births with no major birth defects from the same population as the case infants. Information on thyroid disease was based on self-report: mothers who reported either a thyroid disorder or use of a medication to treat a thyroid disorder during pregnancy were considered to have thyroid disease. Using an unconditional logistic regression model, we considered potential confounding factors (maternal age, race or ethnicity, smoking, body mass index, preexisting diabetes, plurality, gravidity, family history, infant sex).

**RESULTS:** Among case mothers, 19 (4.4%) were classified as having thyroid disease, compared with 65 (1.6%) of control mothers. **Maternal thyroid disease was associated with craniosynostosis after controlling for maternal age (adjusted odds ratio 2.47, 95% confidence interval 1.46-4.18)**, the only factor that remained significant in the final model.

**CONCLUSION:** These data provide additional evidence that maternal thyroid disease (most likely Graves' disease) or its treatment is associated with craniosynostosis. Given the frequency of maternal thyroid disease, this association warrants further investigation.

**LEVEL OF EVIDENCE:** II.

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Case AP, Ramadhani TA, Canfield MA, Beverly L, Wood R. **Folic acid supplementation among diabetic, overweight, or obese women of childbearing age.** *J Obstet Gynecol Neonatal Nurs.* 2007 Jul-Aug;36(4):335-41.

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**OBJECTIVE:** To examine whether obese, overweight, or diabetic women were equally likely to supplement with folic acid as normal-weight or nondiabetic women.

**DESIGN:** **Texas Behavioral Risk Factor Surveillance System** was used to compare folic acid supplementation rates among obese, overweight, or diabetic women to those of normal-weight or nondiabetic women.

**PARTICIPANTS:** Responses from nonpregnant Texas women of ages 18 to 44 were analyzed.

**MAIN OUTCOME MEASURES:** Odds ratios were calculated for association between diabetes, body mass index, and folic acid supplementation.

**RESULTS:** Of 6,835 participants, **35% reported daily folic acid supplementation. Obese women were less likely to supplement, even after adjustment for other factors.**

**CONCLUSIONS:** All women of childbearing age, but especially those who are obese or diabetic, should be encouraged to take folic acid daily to reduce the risk of neural tube defects.

## **CASTILLA EE**

Vieira AR, Cooper ME, Marazita ML, Orioli IM, Castilla EE. **Interferon regulatory factor 6 (IRF6) is associated with oral-facial cleft in individuals that originate in South America.** *Am J Med Genet A.* 2007 Sep 1;143(17):2075-8.

Department of Oral Biology and Center for Craniofacial and Dental Genetics, School of Dental Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania.

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Schuler-Faccini L, Soares RC, de Sousa AC, Maximino C, Luna E, Schwartz IV, Waldman C, Castilla EE. **New cases of thalidomide embryopathy in Brazil.** Birth Defects Res A Clin Mol Teratol. 2007 Aug 3;

Federal University of Rio Grande do Sul Genetics Department; Fundacao Faculdade Federal de Ciencias Medicas, Clinical Genetics Department, Porto Alegre, Brazil.

Thalidomide is the best known human teratogen. Although withdrawn from the market in 1961, thalidomide was remarketed after 1965 in several countries, for the treatment of erythema nodosum leprosum. Thalidomide has a potent immunomodulatory property and has now a number of approved and off-label uses in dermatologic, oncologic, infectious and gastrointestinal conditions. In the U.S., FDA approved the use of thalidomide in 1998, but no cases of thalidomide embryopathy were registered after that. Since 1996 no new cases were reported in Latin America. However, **the Teratogen Information Service (TIS) Porto Alegre, recorded three new cases of thalidomide embryopathy born in Brazil since 2005.** Considering that **these three cases were not registered through a systematic surveillance system,** but that came to our attention through a series of coincidental random events, it can be assumed that the actual occurrence of affected babies by thalidomide continues being as frequent as denounced ten years ago.

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Amorim MR, Lima MA, Castilla EE, Orioli IM. **Non-Latin European descent could be a requirement for association of NTDs and MTHFR variant 677C > T: A meta-analysis.** Am J Med Genet A. 2007 Aug 1;143(15):1726-32.

Estudo Colaborativo Latino Americano de Malformaciones Congénitas: ECLAMC at Departamento de Genética, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

There are several studies that have found a positive association between neural tube defects (NTDs) and the common mutation 677C > T of 5,10-methylenetetrahydrofolate reductase (MTHFR), and others that have not found such an association. We updated the meta-analyses of the published data about NTDs and MTHFR 677C > T variant from January 1994 to October 2005 identifying 170 potentially relevant studies. After applying pertinent exclusion criteria, 37 different populations from 32 studies were included in the meta-analysis, with a total of 3,530 cases and 6,296 controls. Further we stratified the data according to geographical region and ethnicity, and produced two separated meta-analyses for non-Latin European and Latin European descent populations. **The general (odds ratio 1.41; 95% confidence interval 1.24-1.59), and the non-Latin European meta-analyses (1.62; 1.38-1.90) indicate an association of TT genotype and NTDs; no association was demonstrated for Latin European populations (1.16; 0.95-1.43).** The examination of non-Latin European studies revealed that the association of TT genotype with NTD has only been proven for Irish populations, both by case-control studies, and by family-based tests, such as the allele transmission disequilibrium test (TDT).

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El-Jaick KB, Fonseca RF, Moreira MA, Ribeiro MG, Bolognese AM, Dias SO, Pereira ET, Castilla EE, Orioli IM. **Single median maxillary central incisor: New data and mutation review.** Birth Defects Res A Clin Mol Teratol. 2007 Aug;79(8):573-80.

Estudo Colaborativo Latino Americano de Malformaciones Congénitas: ECLAMC at Departamento de Genética, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil.

**BACKGROUND:** Single median maxillary central incisor (SMMCI) is a rare anomaly that may occur alone or associated with other conditions, frequently as part of the holoprosencephaly (HPE) spectrum. However, it has been suggested that SMMCI alone, or associated with some midline defects, may be considered a different entity from HPE (OMIM: 147250). Families with SMMCI, without HPE cases, are difficult to counsel for the risk of HPE in future generations because the same midline defects described as part of the "SMMCI syndrome" can also be part of the HPE spectrum.

**METHODS:** We screened five cases of SMMCI for mutations in three HPE genes, SHH, TGIF, and SIX3. **RESULTS:** A missense mutation c.686C>T was found in the gene SIX3 of one patient, which did not differ from the accepted 20% of known HPE gene mutations among all HPE cases. Our results and an extensive literature review of gene mutations in patients with SMMCI showed that 27/28 of them were in HPE genes:

SHH (n = 21), SIX3 (n = 3), TGIF (n = 1), GLI2 (n = 1), and PTCH (n = 1), and only one in the SALL4 gene. CONCLUSIONS: The clinical findings in patients with SMMCI without HPE in families with mutations in HPE genes cannot be distinguished from the findings reported in the SMMCI syndrome. Therefore, **persons with SMMCI and their relatives should be carefully investigated for related midline disorders, especially of the HPE spectrum, and all known HPE genes screened.**

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Rittler M, Castilla EE, Chambers C, Lopez-Camelo JS. **Risk for gastroschisis in primigravidity, length of sexual cohabitation, and change in paternity.** Birth Defects Res A Clin Mol Teratol. 2007 Mar 14;

Latinâ American Collaborative Study of Congenital Malformations, WHO Collaborating Centre for the Prevention of Birth Defects (ECLAMC) at Hospital Materno Infantil, Buenos Aires, Argentina.

BACKGROUND: Maternal epidemiologic similarities between gastroschisis and preeclampsia have led to the objective of evaluating the risk for gastroschisis related to primigravidity, change in paternity, and length of cohabitation, considered as risk factors for preeclampsia.

METHODS: The subjects were 288 newborns with isolated gastroschisis and 576 normal controls, matched by maternal age. They were ascertained in the Estudio Colaborativo Latino Americano de Malformaciones Congenitas hospital network of 10 South American countries between 1982 and 2005. Epidemiologic variables were compared among controls, between primigravidas and multigravidas, between multigravidas who had and had not changed partners, and between mothers with short and long cohabitation times with their partners. Risks associated with primigravidity, short cohabitation time, and changing paternity, as well as their combinations, were calculated. An eventual interaction between maternal age and the three risk factors was assessed.

RESULTS: Only a **short cohabitation time showed a significant OR for gastroschisis** (OR = 2.36, 95% CI: 1.52-3.66, p < .001), whereas ORs were not significant for primigravidity (OR = 1.40, 95% CI: 0.84-2.35, p = .192) nor for changing paternity (OR = 1.20, 95% CI: 0.49-3.10, p = .752). **The risk was highest for multigravidas who had changed partners** (OR = 8.71, 95% CI: 2.93-21.12, p <.001), followed by multigravidas who had not changed partners (OR = 3.99, 95% CI: 1.07-15.43, p = .049), and by primigravidas (OR = 3.02, 95% CI: 1.58-5.76, p =.001), **all having cohabitated for a short time.** Maternal age did not modify these risks.

CONCLUSIONS: **Three groups at risk for a child with gastroschisis were identified, all having in common a short cohabitation time. Antigenic or "modern" lifestyle-related factors might be involved in the origin of gastroschisis.**

## CORREA A

Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A; **Prepregnancy obesity as a risk factor for structural birth defects.** Arch Pediatr Adolesc Med. 2007 Aug;161(8):745-50.

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[See Canfield M](#)

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Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, Rasmussen SA; the National Birth Defects Prevention Study. **Maternal Periconceptional Alcohol Consumption and Risk of Orofacial Clefts.** Am J Epidemiol. 2007 Jul 3;

Department of Epidemiology, The University of Iowa, Iowa City, IA.

Using data from the National Birth Defects Prevention Study, the authors investigated the association between maternal reports of periconceptional alcohol consumption and clefting. Cases with a cleft lip, cleft palate, or both and unaffected controls delivered from 1997 through 2002 were ascertained. Interview reports of alcohol consumption were obtained from 1,749 (75.1%) case and 4,094 (68.2%) control mothers. Adjusted odds ratios and 95% confidence intervals were calculated to assess associations. Compared with odds ratios for mothers with no reported consumption, those for mothers who consumed alcohol tended to be near to (cleft lip, cleft lip with cleft palate) or to exceed (cleft palate) unity. The odds ratios associated with

binge drinking were elevated but did not demonstrate significantly increased risk for any phenotype; however, the odds ratios differed by the type of alcohol consumed, particularly for cleft palate (distilled spirits > wine > beer). These odds ratios were further increased among mothers with no reported folic acid intake. Although **these findings suggest that the association between alcohol consumption and clefting might be most influenced by the type of beverage consumed and folic acid intake, they are preliminary and might reflect chance associations.** Such findings need exploration in additional, large studies.

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Calvert GM, Alarcon WA, Chelminski A, Crowley MS, Barrett R, Correa A, Higgins S, Leon HL, Correia J, Becker A, Allen RH, Evans E. **Case report: three farmworkers who gave birth to infants with birth defects closely grouped in time and place-Florida and North Carolina, 2004-2005.** Environ. Health Perspect. 2007 May;115(5):787-91.

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CONTEXT: There is little evidence linking adverse reproductive effects to exposure to specific pesticides during pregnancy.

CASE PRESENTATION: In February 2005, **three infants with congenital anomalies were identified in Collier County, Florida, who were born within 8 weeks of one another and whose mothers worked for the same tomato grower.** The mothers worked on the grower's Florida farms in 2004 before transferring to its North Carolina farms. All three worked during the period of organogenesis in fields recently treated with several pesticides. The Florida and North Carolina farms were inspected by regulatory agencies, and in each state a large number of violations were identified and record fines were levied.

DISCUSSION: Despite the suggestive evidence, a causal link could not be established between pesticide exposures and the birth defects in the three infants. Nonetheless, the prenatal pesticide exposures experienced by the mothers of the three infants is cause for concern. Farmworkers need greater protections against pesticides. These include increased efforts to publicize and comply with both the U.S. Environmental Protection Agency's Worker Protection Standard and pesticide label requirements, enhanced procedures to ensure pesticide applicator competency, and recommendations to growers to adopt work practices to reduce pesticide exposures.

RELEVANCE TO PROFESSIONAL PRACTICE: The findings from this report reinforce the need to reduce pesticide exposures among farmworkers. In addition, they support the need for epidemiologic studies to examine the role of pesticide exposure in the etiology of congenital anomalies.

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Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL. **Noninherited Risk Factors and Congenital Cardiovascular Defects: Current Knowledge. A Scientific Statement From the American Heart Association Council on Cardiovascular Disease in the Young. Endorsed by the American Academy of Pediatrics.** Circulation. 2007 May 22;

Prevention of congenital cardiovascular defects has been hampered by a lack of information about modifiable risk factors for abnormalities in cardiac development. Over the past decade, there have been major breakthroughs in the understanding of inherited causes of congenital heart disease, including the identification of specific genetic abnormalities for some types of malformations. Although relatively less information has been available on noninherited modifiable factors that may have an adverse effect on the fetal heart, there is a growing body of epidemiological literature on this topic. This statement summarizes the currently available literature on potential fetal exposures that might alter risk for cardiovascular defects. Information is summarized for periconceptional multivitamin or folic acid intake, which may reduce the risk of cardiac disease in the fetus, and for additional types of potential exposures that may increase the risk, including maternal illnesses, maternal therapeutic and nontherapeutic drug exposures, environmental exposures, and paternal exposures. Information is highlighted regarding definitive risk factors such as maternal rubella; phenylketonuria; pregestational diabetes; exposure to thalidomide, vitamin A congeners, or retinoids; and indomethacin tocolysis. Caveats regarding interpretation of possible exposure-outcome relationships from case-control studies are given because this type of study has provided most of the available information. Guidelines for prospective parents that could reduce the likelihood that their child will have a major cardiac malformation are given. Issues related to pregnancy monitoring are discussed. Knowledge gaps and future sources of new information on risk factors are described.

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Browne ML, Bell EM, Druschel CM, Gensburg LJ, Mitchell AA, Lin AE, Romitti PA, Correa A. **Maternal caffeine consumption and risk of cardiovascular malformations.** Birth Defects Res A Clin Mol Teratol. 2007 Apr 2;

Bureau of Environmental & Occupational Epidemiology, New York State Department of Health, Troy, New York.

**BACKGROUND:** The physiologic effects and common use of caffeine during pregnancy call for examination of maternal caffeine consumption and risk of birth defects. Epidemiologic studies have yielded mixed results, but such studies have grouped etiologically different defects and have not evaluated effect modification.

**METHODS:** The large sample size and precise case classification of the National Birth Defects Prevention Study allowed us to examine caffeine consumption and specific cardiovascular malformation (CVM) case groups. We studied consumption of caffeinated coffee, tea, soda, and chocolate to estimate total caffeine intake and separately examined exposure to each caffeinated beverage. Smoking, alcohol, vasoactive medications, folic acid supplement use, and infant gender were evaluated for effect modification. Maternal interview reports for 4,196 CVM case infants overall and 3,957 control infants were analyzed.

**RESULTS:** We did not identify any significant positive associations between maternal caffeine consumption and CVMs. For tetralogy of Fallot, nonsignificant elevations in risk were observed for moderate (but not high) caffeine intake overall and among nonsmokers (ORs of 1.3 to 1.5). Risk estimates for both smoking and consuming caffeine were less than the sum of the excess risks for each exposure. We observed an inverse trend between coffee intake and risk of atrial septal defect; however, this single significant pattern of association might have been a chance finding.

**CONCLUSIONS:** Our study found no evidence for an appreciable teratogenic effect of caffeine with regard to CVMs.

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Malik S, Cleves MA, Zhao W, Correa A, Hobbs CA; National Birth Defects Prevention Study. **Association between congenital heart defects and small for gestational age.** Pediatrics. 2007 Apr;119(4):e976-82.

Arkansas Center for Birth Defects Research and Prevention, Little Rock, AR, USA.

**OBJECTIVES:** Infants with congenital heart defects may experience inhibited growth during fetal life. In a large case-control study, we addressed the hypothesis that infants with congenital heart defects are more likely to be small for gestational age than infants without congenital heart defects after controlling for selected maternal and infant characteristics.

**METHODS:** Using data from population-based birth defect registries, the National Birth Defects Prevention Study enrolled infants with nonsyndromic congenital heart defects (case subjects) and infants without congenital heart defects or any other birth defect (control subjects). Small for gestational age was defined as birth weight below the 10<sup>th</sup> percentile for gestational age and gender. Association between congenital heart defects and small for gestational age was examined by conditional logistic regression adjusting for maternal covariates related to fetal growth.

**RESULTS:** Live-born singleton infants with congenital heart defects (case subjects, n = 3395) and live-born singleton infants with no birth defect (control subjects, n = 3924) were included in this study. Case subjects had lower birth weights compared with control subjects. Small for gestational age was observed among 15.2% of case subjects and among only 7.8% of control subjects. Congenital heart defect infants were significantly more likely to be small for gestational age than control infants.

**CONCLUSIONS:** Infants with congenital heart defects are approximately twice as likely to be small for gestational age as control subjects. Small for gestational age status may affect clinical management decisions, therapeutic response, and prognosis of neonates with congenital heart defects. Although the etiology of growth retardation among infants with congenital heart defects is uncertain, further exploration may uncover a common pathogenesis or causal relationship between congenital heart defects and small for gestational age.

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Gardner BR, Strickland MJ, Correa A. **Application of the automated spatial surveillance program to birth defects surveillance data.** Birth Defects Res A Clin Mol Teratol. 2007 Mar 26;

National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

**BACKGROUND:** Although many birth defects surveillance programs incorporate georeferenced records into their databases, practical methods for routine spatial surveillance are lacking. **We present a macroprogram written for the software package R designed for routine exploratory spatial analysis of birth defects data, the Automated Spatial Surveillance Program (ASSP), and present an application of this program using spina bifida prevalence data for metropolitan Atlanta.**

**METHODS:** Birth defects surveillance data were collected by the Metropolitan Atlanta Congenital Defects Program. We generated ASSP maps for two groups of years that correspond roughly to the periods before (1994-1998) and after (1999-2002) folic acid fortification of flour. ASSP maps display census tract-specific spina bifida prevalence, smoothed prevalence contours, and locations of statistically elevated prevalence. We used these maps to identify areas of elevated prevalence for spina bifida.

**RESULTS:** We identified a large area of potential concern in the years following fortification of grains and cereals with folic acid. This area overlapped census tracts containing large numbers of Hispanic residents.

**CONCLUSIONS:** **The potential utility of ASSP for spatial disease monitoring was demonstrated by the identification of areas of high prevalence of spina bifida and may warrant further study and monitoring.** We intend to further develop ASSP so that it becomes practical for routine spatial monitoring of birth defects.

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Honein MA, Rasmussen SA, Reefhuis J, Romitti PA, Lammer EJ, Sun L, Correa A. **Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts.** Epidemiology. 2007 Mar;18(2):226-33.

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**BACKGROUND:** Smoking during pregnancy has been associated with orofacial clefts in numerous studies. However, most previous studies have not been able to assess the relation between maternal smoking and specific phenotypes (eg, bilateral clefts).

**METHODS:** We examined the association between periconceptional maternal smoking, environmental tobacco smoke (ETS) exposure, and cleft lip with or without cleft palate (CLP) (n = 933) and cleft palate only (CPO) (n = 528) compared with infants with no major birth defects (n = 3390). Infants were born between 1 October 1997 and 31 December 2001, and exposures were ascertained from maternal telephone interviews for the National Birth Defects Prevention Study. We excluded infants who had a first-degree relative with an orofacial cleft. Effect estimates were adjusted for folic acid use, study site, prepregnancy obesity, alcohol use, gravidity, and maternal age, education, and race/ethnicity.

**RESULTS:** Periconceptional smoking was associated with CLP (odds ratio = 1.3; 95% confidence interval = 1.0-1.6), and more strongly associated with **bilateral CLP (1.7; 1.2-2.6)**, with a weaker association observed for CPO. **Heavy maternal smoking (25+ cigarettes/day) was associated with CLP (1.8; 1.0-3.2), bilateral CLP (4.2; 1.7-10.3), and CPO with Pierre Robin sequence (2.5; 0.9-7.0).** ETS exposure was not associated with CLP or CPO.

**CONCLUSIONS:** **This study confirmed the modest association between smoking and orofacial clefts that has been consistently reported, and identified specific phenotypes most strongly affected.**

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Correa A, Cragan JD, Kucik ME, Alverson CJ, Gilboa SM, Balakrishnan R, Strickland MJ, Duke CW, O'Leary LA, Riehle-Colarusso T, Siffel C, Gambrell D, Thompson D, Atkinson M, Chitra J. **Reporting birth defects surveillance data 1968-2003.** Birth Defects Res. Part A Clin. Mol. Teratol. 2007 Feb;79(2):65-186.

**No abstract available**

## DE VIGAN C

Khoshnood B, De Vigan C, Goffinet F, Leroy V. **Prenatal screening and diagnosis of congenital toxoplasmosis: a review of safety issues and psychological consequences for women who undergo screening.** *Prenat. Diagn.* 2007 May;27(5):395-403.

INSERM, UMR S149, IFR 69, Epidemiological Research Unit on Perinatal and Women's Health, Villejuif, F-94807 France. khoshnood@vjf.inserm.fr

As part of the EUROTOXO initiative, this review focuses on the potential risks associated with prenatal testing for congenital toxoplasmosis. We first review the evidence on the risks of adverse events associated with amniocentesis, which is required for definitive diagnosis of toxoplasmosis infection in the fetus, and for which the most important risk is fetal loss. To date, there has been only one randomized trial to document risks associated with amniocentesis. This trial, which was conducted in 1986, reported a procedure-related rate of fetal loss of 1.0% (95% CI, 0.3-1.5). However, evidence from available controlled studies suggests that the pregnancy loss associated with mid-trimester amniocentesis may be lower. **Potential psychological consequences of prenatal testing for congenital toxoplasmosis include parental anxiety due to false positive results and uncertainties related to prognosis of children with a prenatal diagnosis of congenital toxoplasmosis.** Parental anxiety may be particularly important in screening strategies that include more frequent screenings, which may in turn entail substantial, and at times unnecessary, anxiety or other negative consequences for women and their families. These negative psychological outcomes should be balanced against the benefits of testing, which can allow women to make an informed choice regarding the pregnancy.

## FELDKAMP M

Feldkamp ML, Carey JC, Sadler TW. **Development of gastroschisis: review of hypotheses, a novel hypothesis, and implications for research.** *Am. J. Med. Genet. A.* 2007 Apr 1;143(7):639-52.

Department of Pediatrics, Division of Medical Genetics, University of Utah Health Sciences Center, Salt Lake City, UT 84132, USA. mfeldkamp@utah.gov

Gastroschisis, a ventral body wall defect, is a continuing challenge and concern to researchers, clinicians, and epidemiologists seeking to identify its cause(s) and pathogenesis. Concern has been renewed in recent years because, unlike most other birth defects, rates of gastroschisis are reportedly increasing in many developed and developing countries. No tenable explanation or specific causes have been identified for this trend. Rates of gastroschisis are particularly high among pregnancies of very young women. Such an intriguing association, not observed to this degree with other birth defects, may afford clues to the defect's cause. Understanding the causes of gastroschisis may provide insight to the defect's origin. In pursuing such causal studies, it would be helpful to understand the embryogenesis of gastroschisis. To date, four main embryologic hypotheses have been proposed: (1) Failure of mesoderm to form in the body wall; (2) Rupture of the amnion around the umbilical ring with subsequent herniation of bowel; (3) Abnormal involution of the right umbilical vein leading to weakening of the body wall and gut herniation; and (4) Disruption of the right vitelline (yolk sac) artery with subsequent body wall damage and gut herniation. Although based on embryological phenomena, these hypotheses do not provide an adequate explanation for how gastroschisis would occur. Therefore, we propose an alternative hypothesis, based on well described embryonic events. Specifically, we propose that abnormal folding of the body wall results in a ventral body wall defect through which the gut herniates, leading to the clinical presentation of gastroschisis. This hypothesis potentially explains the origin of gastroschisis as well as that of other developmental defects of the ventral wall.

## GATT M

Savona-Ventura C, Gatt M, Zammit K, Grima S. **Twin pregnancy outcomes in the Maltese Islands.** *Int J Gynaecol Obstet.* 2007 Sep;98(3):255-6. Epub 2007 Jun 27.

Department of Obstetrics-Gynecology, Department of Health, Malta.

**No abstract available**

## IRGENS LM

Andersen GL, Irgens LM, Haagaas I, Skranes JS, Meberg AE, Vik T. **Cerebral palsy in Norway: Prevalence, subtypes and severity.** Eur J Paediatr Neurol. 2007 Jun 14;

Habilitation Center, Vestfold Hospital, TÅnsberg, Norway.

**BACKGROUND/AIM:** To describe prevalence, subtypes and severity of cerebral palsy (CP) in Norway using criteria proposed by the Surveillance of Cerebral Palsy in Europe (SCPE) network.

**MATERIAL:** All children in Norway with CP born in January 1996-December 1998 were registered in the Cerebral Palsy Registry of Norway. The Medical Birth Registry of Norway provided the perinatal data.

**RESULTS:** A total of 374 children with CP were identified with a prevalence of 2.1 per 1000 live births. Detailed information was obtained from 294 (79%) children. Median age at clinical assessment was 6.9 years (range: 1.9-10.2 years). Thirty-three percent of the children had spastic unilateral CP, 49% spastic bilateral, 6% dyskinetic, 5% ataxic CP and 7% were not classified. Severely impaired vision and hearing were present in 5% and 4% of the children, respectively. Active epilepsy was present in 28%, mental retardation in 31% and severely impaired or no speech in 28% children. The most severe impairments in gross motor function were observed in children with low Apgar scores, and the most severe impairments in fine motor function in children born at term, with normal birth weight and low Apgar scores.

**CONCLUSION:** Compared with other populations, the prevalence of CP as well as the proportions of subtypes and gross motor impairments were similar, whereas fine motor impairments and associated impairments were more common. The classification of children with mixed forms of CP is still a challenge. Children were more severely affected if Apgar scores were low, and if they were born at term.

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Thompson JM, Irgens LM, Skjaerven R, Rasmussen S. **Placenta weight percentile curves for singleton deliveries.** BJOG. 2007 Jun;114(6):715-20.

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**OBJECTIVE:** To produce population-based, gender- and gestational-age-specific centile curves for placental weight.

**DESIGN:** Population study.

**SETTING:** Medical Birth Registry of Norway.

**POPULATION:** All singleton live births in Norway from 1 January 1999 to 31 December 2002.

**METHODS:** In a cohort of children born in Norway, placental weights and the ratio of the birthweight to the placental weight were analysed to produce percentile curves.

**MAIN OUTCOME MEASURES:** Placental weight, birthweight-to-placental weight ratio.

**RESULTS:** Tables and figures are presented for placental percentiles curves according to gestational age and gender. Also, tables and figures are presented for the ratio of birthweight to placental weight.

**CONCLUSIONS** To our knowledge, this is the first time that population percentile curves have been produced for placental weights and hence for the ratio of birthweight to placental weight. These percentile curves may act as a reference for other populations as well until population-specific curves can be produced.

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Tollanes MC, Thompson JM, Daltveit AK, Irgens LM. **Cesarean section and maternal education; secular trends in Norway, 1967-2004.** Acta Obstet Gynecol Scand. 2007;86(7):840-8.

Section for Epidemiology and Medical Statistics, Department of Public Health and Primary Health Care, University of Bergen, Norway. mette.tollanes@isf.uib.no

**BACKGROUND:** Worldwide rising cesarean section rates over the past decades have caused much concern. Studies on the association between cesarean section and maternal social background have reported conflicting results.

**METHODS:** A cohort study, comprising 837,312 birth order one deliveries notified to the population-based Medical Birth Registry of Norway during 1967-2004. The relative risk of cesarean section (from 1988 onwards planned and emergency caesarean section) according to maternal educational level was assessed in all deliveries, in an obstetric low-risk group and within groups of medical/obstetric high-risk conditions.

**RESULTS:** Throughout the study period, the lowest educated had the highest risk of cesarean section, followed by the medium educational group. In all deliveries, the adjusted relative risk of cesarean section for the lowest versus the highest educated increased from 1.16 (95% CI 1.09-1.23) in the 1967-76 period to

1.34 (95% CI 1.27-1.42) in the 1996-2004 period, and in the obstetric low risk group from 1.19 (95% CI 1.10-1.30) to 1.50 (95% CI 1.38-1.63). From 1988 onwards, the lowest educated had the highest risk of both planned and emergency cesarean section, followed by the medium educational group.

CONCLUSION: The lowest educated had the highest risk of cesarean section, followed by the medium educational group, and the differences gradually increased during 1967-2004. This trend could be accounted for by increasing vulnerability of the lowest educational group due to a strong social migration, and by increased occurrence of cesarean section on maternal request among the lowest educated in recent years.

## HALLIDAY J

Chew C, Halliday JL, Riley MM, Penny DJ. **Population-based study of antenatal detection of congenital heart disease by ultrasound examination.** *Ultrasound Obstet Gynecol.* 2007 Jun;29(6):619-24.

Department of Cardiology, Royal Children's Hospital, Australia and New Zealand Children's Heart Research Centre, Parkville, Australia.

OBJECTIVES: Ultrasound-based screening is widely employed for the detection of congenital malformations in utero including congenital heart disease (CHD), but there is widespread variability in the efficacy of screening programs. We aimed to evaluate current antenatal detection rates of selected congenital heart defects in Victoria.

METHODS: Data were collected from the Victorian Perinatal Data Collection Unit and Birth Defects Registry. There were 631 209 births in Victoria (1993-2002), of which 4897 cases had CHD. Cases included live births, stillbirths and termination of pregnancies because of CHD. We reviewed all cases from 1999 to 2002 with atrioventricular septal defect, simple coarctation of the aorta, double-inlet or -outlet ventricle, hypoplastic left heart syndrome, simple transposition of the great arteries (TGA), tetralogy of Fallot and truncus arteriosus. Outcome measures were antenatal diagnosis, pregnancy outcome and associated malformations.

RESULTS: The overall birth prevalence of CHD from 1993 to 2002 in Victoria was 7.8/1000. The antenatal detection rate for the seven selected defects from 1999 to 2002 was 52.8%. All but 4.8% of the cases had an ultrasound examination at > 13 weeks' gestation. Antenatal detection was highest for hypoplastic left heart syndrome (84.6%) and lowest for simple TGA (17.0%).

CONCLUSIONS: This study shows wide variation in the antenatal detection rate of CHD in Victoria. The low antenatal detection rate of TGA, a defect that should be detected easily, demonstrates suboptimal routine obstetric anomaly scanning.

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Muggli EE, Halliday JL. **Folic acid and risk of twinning: a systematic review of the recent literature, July 1994 to July 2006.** *Med. J. Aust.* 2007 Mar 5;186(5):243-8.

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OBJECTIVE: To assess the evidence of an association between periconceptional folic acid (FA) supplementation or fortification of foods with FA and the risk of twinning, using the Food Standards Australia New Zealand (FSANZ) framework for assessing evidence when substantiating nutrition, health and related claims on foods.

DATA SOURCES: The Cochrane Library Database, MEDLINE, MEDLINE in Process, EMBASE, PubMed National Library of Medicine, and CINAHL were searched to identify systematic reviews and primary intervention and observational studies published from 1 July 1994 to 7 July 2006.

STUDY SELECTION: One prospective and five retrospective cohort studies that assessed the rate of twinning in populations exposed to FA through supplementation, and six retrospective registry-based cohort studies examining twinning rates after fortification of foods with FA.

DATA EXTRACTION: Two reviewers appraised eligible studies and evaluated data independently.

DATA SYNTHESIS: The best maximal risk estimates of twinning after FA supplementation were an adjusted odds ratio (adjOR) of 1.26 (95% CI, 0.91-1.73) for preconceptional supplementation and dizygotic twinning and an adjOR of 1.02 (95% CI, 0.85-1.24) for overall twinning. Data from four FA fortification studies in the United States that allowed for calculation of an annual percentage increase showed a maximal annual increase in twinning rates of 4.6%.

**CONCLUSIONS:** Overall, under the FSANZ framework, there is possible evidence for a relationship between periconceptional FA intake and increased twinning. To support this tentative relationship, more well designed, long-term follow-up studies are needed in places where fortification with FA has been introduced, focusing on dose-response and obtaining accurate data on infertility treatments.

## **LOWRY B**

De Wals P, Tairou F, Van Allen MI, Uh SH, Lowry RB, Sibbald B, Evans JA, Van den Hof MC, Zimmer P, Crowley M, Fernandez B, Lee NS, Niyonsenga T. **Reduction in neural-tube defects after folic acid fortification in Canada.** N Engl J Med. 2007 Jul 12;357(2):135-42.

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**BACKGROUND:** In 1998, folic acid fortification of a large variety of cereal products became mandatory in Canada, a country where the prevalence of neural-tube defects was historically higher in the eastern provinces than in the western provinces. We assessed changes in the prevalence of neural-tube defects in Canada before and after food fortification with folic acid was implemented.

**METHODS:** The study population included live births, stillbirths, and terminations of pregnancies because of fetal anomalies among women residing in seven Canadian provinces from 1993 to 2002. On the basis of published results of testing of red-cell folate levels, the study period was divided into prefortification, partial-fortification, and full-fortification periods. We evaluated the relationship between baseline rates of neural-tube defects in each province and the magnitude of the decrease after fortification was implemented.

**RESULTS:** A total of 2446 subjects with neural-tube defects were recorded among 1.9 million births. The prevalence of neural-tube defects decreased from 1.58 per 1000 births before fortification to 0.86 per 1000 births during the full-fortification period, a 46% reduction (95% confidence interval, 40 to 51). The magnitude of the decrease was proportional to the prefortification baseline rate in each province, and geographical differences almost disappeared after fortification began. **The observed reduction in rate was greater for spina bifida (a decrease of 53%) than for anencephaly and encephalocele (decreases of 38% and 31%, respectively).**

**CONCLUSIONS:** Food fortification with folic acid was associated with a significant reduction in the rate of neural-tube defects in Canada. **The decrease was greatest in areas in which the baseline rate was high.**

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Lowry RB, Sibbald B, Bedard T. **Stability of prevalence rates of anorectal malformations in the Alberta Congenital Anomalies Surveillance System 1990-2004.** J Pediatr Surg. 2007 Aug;42(8):1417-21.

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**BACKGROUND/PURPOSE:** Anorectal malformations appeared to be increasing in the province of Alberta, Canada. To assess whether this was a significant trend, with the possibility of these having a teratogenic origin, we examined the frequency of anorectal malformations **over a 15-year period.**

**METHODS:** We examined the records of the Alberta Congenital Anomaly Surveillance System, which is a semiactive surveillance system using the British Paediatric Association and the Royal College of Paediatrics and Child Health expansions of the International Classification of Diseases-Ninth Revision and the International Classification of Diseases-10th Revision.

**RESULTS:** The **overall rate was 1/2162 (4.63/10,000 total births)** with a marked male predominance (1.7:1). Approximately two thirds of the 273 cases had 1 or more malformations.

**CONCLUSION:** Although there was an **increasing trend in the rate from 1999 especially for the multiples, this was not significant.** In view of the advances in syndrome identification and molecular diagnostics, consideration should be given to a detailed review of the family history and appropriate testing not only for multiple cases but also for isolated ones.

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Lowry RB, Gould DB, Walter MA, Savage PR. **Absence of PITX2, BARX1, and FOXC1 mutations in De Hauwere syndrome (Axenfeld-Rieger anomaly, hydrocephaly, hearing loss): A 25-year follow up.** Am. J. Med. Genet. A. 2007 Jun 1;143(11):1227-30.

Department of Medical Genetics, Alberta Children's Hospital & University of Calgary, Calgary, Alberta, Canada.

This study reports a 25-year follow-up of a patient with De Hauwere syndrome (Axenfeld-Rieger anomaly, hydrocephalus, and hearing loss) whose intelligence is normal. Short stature and hyperlaxity of joints later leading to severe joint pain were noted. Mutation analysis of candidate genes known or suspected to be associated with Axenfeld-Rieger eye malformations was performed. This included complete sequencing for PITX2, BARX1 and the forkhead domain of FOXC1. The results of these analyses were negative and suggest that De Hauwere syndrome is caused by a different gene.

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Lowry RB. **The Fetal Alert Network.** J Obstet Gynaecol Can. 2007 Apr;29(4):307.  
Alberta Congenital Anomalies Surveillance System, Alberta Children's Hospital, Calgary AB.

**No abstract available**

## **MARTINEZ FRIAS ML**

Martinez-Frias ML; Grupo de trabajo del ECEMC. **Folic acid dose in the prevention of congenital defects.** [Article in Spanish]. Med Clin (Barc). 2007 Apr 28;128(16):609-16.

Facultad de Medicina, Universidad Complutense de Madrid, Centro de Investigacion sobre Anomalias Congénitas (CIAC), Instituto de Salud Carlos III, Madrid, Espana. mlmartinez.frias@isciii.es

**BACKGROUND AND OBJECTIVE:** Synthetic folic acid (FA) is in the form of pteroylmonoglutamate (PGA), a form that does not occur in nature, where it is in form of pteroylpolyglutamate, mainly as 5-methyltetrahydrofolate. The organism transforms PGA into 5-methyltetrahydrofolate, and it has been detected that this process is saturated at doses of 0.4 mg of PGA. Recently, some concern has been expressed on the use of higher than recommended doses of FA, because of the possibility of saturating the biotransformation process and the consequent plasmatic accumulation of unmetabolized synthetic FA. The objective of this study is to analyze the doses of synthetic FA that are being currently used in Spain, as well as its secular and geographic distribution.

**PATIENTS AND METHODS:** The study was based on 16,761 mothers of non-malformed infants from the data base of the Spanish Collaborative Study of Congenital Malformations. All forms of folates (folic or folinic) have been considered under the general term of FA.

**RESULTS:** Although an increasing trend in the proportion of mothers using FA in the last study period (2003-2004), **only 17.37% of the mothers had FA supplements since before pregnancy.** Among the rest, 71.13% started using FA once they knew they were pregnant, and 11.50% never took this vitamin. In addition, more than 70% of mothers who took FA ingested doses of 4 mg or more. The results by Spanish Autonomic Regions are quite similar, with more that 50% of the mothers (of the period 2003-2004), in the great majority of the Regions, taking mean daily doses of FA that are between 12.5 and 20-fold higher than the recommended 0.4 mg/day.

**CONCLUSIONS:** Most of women are having FA after conception, or do not ingest FA at all. Most of those women who take FA use doses much higher than recommended. The results of this study show that it is necessary to spread these aspects among the health professionals implicated.

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Mejàs C, Rodríguez-Pinilla E, Fernández Martín P, Martínez-Frías ML. **Side effects of selective serotonin reuptake inhibitors use during the third trimester of pregnancy and guidelines.** [Article in Spanish] Med Clin (Barc). 2007 Apr 21;128(15):584-9.

Sección de Teratología Clínica y Servicios de Información Telefónica sobre Teratógenos (SITTE y SITE). Centro de Investigación sobre Anomalias Congénitas (CIAC). Instituto de Salud Carlos III. Madrid. Espana. site@isciii.es.

Selective Serotonin Reuptake Inhibitors (SSRIs) have become the drug of choice for the treatment of depression and have shown to be effective in the treatment for other mental disorders. Recently, several articles have reported about the adverse effects observed in newborns after maternal exposure to these drugs during the last trimester of pregnancy. In this work, **a review of literature is presented**, regarding the above mentioned adverse effects. Moreover, some guidelines for the rational use of these drugs during the last trimester of pregnancy and for the management of prenatally exposed newborns are provided.

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Rodríguez L, Zollino M, Mansilla E, Martínez-Fernández ML, Pérez P, Murdolo M, Martínez-Frías ML. **The first 4p euchromatic variant in a healthy carrier having an unusual reproductive history.** Am. J. Med. Genet. A. 2007 May 1;143(9):995-8.

Estudio Colaborativo Español de Malformaciones Congénitas del Centro de Investigación sobre Anomalías Congénitas, Instituto de Salud Carlos III, Ministerio de Sanidad y Consumo, Madrid, Spain. laura@isciii.es

We report on the molecular cytogenetics studies in a healthy couple who had had three pregnancies which ended in a termination of pregnancy (TOP). In two of them, prenatal sonogram showed fetal dwarfism and in the third one, a chromosome alteration was found in the amniocentesis. A previous pregnancy ended in a healthy girl. A high-resolution G-band karyotype (550-850 bands), together with Fluorescence in situ Hybridization (FISH) techniques, detected in the father a 4p interstitial euchromatic duplication. This chromosome duplication appears to be a previously undescribed euchromatic variant (EV). We discuss the possibility that the 4p paternal EV could be involved in the clinical and genetic findings of the three TOPs.

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Martínez-Frías ML. **Postmarketing analysis of medicines: methodology and value of the Spanish case-control study and surveillance system in preventing birth defects.** Drug Saf. 2007;30(4):307-16.

Spanish Collaborative Study of Congenital Malformations and the Research Center of Congenital Anomalies, Instituto de Salud Carlos III, Facultad de Medicina de la Universidad Complutense de Madrid, Madrid, Spain. mlmartinez.frias@isciii.es

There are many surveillance systems of congenital defects all over the world; several of them have developed specific approaches to generate and test selected hypotheses regarding human teratogens. However, to the best of our knowledge, none of them have a permanent and systematised programme for the study of the risk and safety of drugs. The aim of this article is to describe the research programme on the potential effects of drugs in pregnancy followed by the Spanish Collaborative Study of Congenital Malformations (ECEMC), which is a permanent ongoing case-control study and surveillance system. The programme to analyse drugs includes a continuous and systematic study on the potential effects of medicines used during pregnancy. This programme has several characteristics that make it different from other current systems: (i) the collection of numerous datapoints (up to 312 per infant) in a case-control design; (ii) the use of a versatile and specific coding of birth defects; (iii) a specific programme for the continuous analysis of the potential effects of each type of drugs used during pregnancy that has been developed specifically for the ECEMC methodology, including its dysmorphological coding system. **The description of the ECEMC's approach to surveillance of the effects of drug use during pregnancy may help researches in this area, particularly those using data from birth defects registries.**

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Rouhani P, Fleming LE, Frías J, Martínez-Frías ML, Bermejo E, Mendioroz J. **Pilot study of socioeconomic class, nutrition and birth defects in Spain.** Matern Child Health J. 2007 Jul;11(4):403-5. Epub 2007 Feb 21.

Department of Epidemiology & Public Health, University of Miami Miller School of Medicine, 1801 NW 9th Avenue, Highland Professional Building, Suite 200, Miami, FL, 33136, USA, lfleming@med.miami.edu.

Research has indicated that the appropriate intake of folic acid, a B vitamin, before and during early pregnancy has been shown to prevent 50-70% of neural-tube defects. Increased NTD incidence has long been reported to occur more frequently among women of lower socioeconomic (SES). Since consumption of

the folate-rich Mediterranean diet in Spain does not vary by socio-economic status (SES), we hypothesized that there would be no social class effect on NTD occurrence. Using data from a Spanish hospital-based birth defects registry, we studied the risk of Neural Tube Defects (NTDs) in 980 cases and 774 controls between 1980 and 2003. **Our analysis showed that the risk of NTDs did not vary by SES. This finding suggests that increased access to folate and nutrition education might benefit women of lower SES in the US.**

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Martinez-Frias ML, Cormier-Daire V, Cohn DH, Mendioroz J, Bermejo E, Mansilla E. **Dyggve-Melchior-Clausen syndrome: presentation of a case with a mutation of possible Spanish origin.** [Article in Spanish]. Med Clin (Barc). 2007 Feb 3;128(4):137-40.

ECEMC, Centro de Investigación sobre Anomalías Congénitas (CIAC), Instituto de Salud Carlos III, Madrid, Espana. mlmartinez.frias@isciii.es

**BACKGROUND AND OBJECTIVE:** The Dyggve-Melchior-Clausen syndrome is a progressive spondyloepimetaphyseal dysplasia characterized by a short trunk dwarfism, barrel chest, sternal protrusion, kyphoscoliosis, severe platyspondyly, with a central constriction, irregular iliac wings with a lacy appearance, rhizomelic shortening of the limbs, microcephaly, coarse face, and variable mental retardation. This condition is extremely rare and the diagnosis is difficult without any previous experience on it. It is inherited as an autosomal recessive condition, its gene (DYM) having been mapped in the 18q12-21.1 chromosomal region. At least 21 different mutations of this gene have been reported.

**MATERIAL AND METHODS:** We describe an affected Spanish child and include his molecular analysis. We also review the current knowledge on this syndrome.

**RESULTS:** The diagnosis of this patient, based on his clinical and radiological features, was later confirmed by analysis of the DYM gene mutations. The patient had two different mutations, one inherited from the mother and the other inherited from the father.

**CONCLUSIONS:** One of the mutations of this patient (exon 8) is extremely rare and has mostly been reported in patients with Spanish ancestors (from Chile, Argentina, Guam islands and a French patient with Spanish ancestors). These observations, together with that of the patient described here, led us to consider this mutation as having a possible Spanish/Portuguese origin. This condition may be more frequent in Spain than previously thought, especially due to misdiagnosis. This is important in order to undertake quaternary prevention, which is quite necessary for rare syndromes with polysystemic affectation

## **MERLOB P**

Amir A, Merlob P, Linder N, Sirota L, Klinger G. **Mortality of full-term infants during the first month of life in a tertiary care hospital.** J Perinatol. 2007 Aug 23;

Department of Neonatal Intensive Care, Schneider Children's Medical Center of Israel, Petah Tiqva, Israel.

**OBJECTIVE:** The neonatal mortality rate is disproportionately influenced by preterm infants and does not reflect the rate in full-term infants. Our objectives were to estimate the full-term neonatal mortality rate and to identify causes of death in full-term infants during the first month of life. Study

**DESIGN:** A retrospective study of full-term infant deaths during a 6-year period from 2000 to 2005, in a tertiary medical center.

**RESULT:** During the study period there were 44 703 full-term births and 31 deaths, representing a **mortality rate of 0.69 per 1000 live births.** The **main cause of death was congenital anomalies (64.5%),** specifically cardiac anomalies. Other causes were chromosomal anomalies or syndromes (12.9%), labor complications (12.9%), infections (3.2%), congenital diseases (3.2%) and metabolic disorders (3.2%).

**CONCLUSION:** The mortality rate of full-term infants may be lower than previous estimates. Efforts aimed at decreasing mortality among full-term infants should focus on prenatal diagnosis.

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Dubnov-Raz G, Merlob P, Geva-Dayan K, Blumenthal D, Finkelstein Y. **Increased rate of major birth malformations in infants with neonatal "asymmetric crying face": a hospital-based cohort study.** Am. J. Med. Genet. A. 2007 Feb 15;143(4):305-10.

Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. gald@clalit.org.il

**Asymmetric crying face (ACF) is a minor anomaly found in 3-8 per 1,000 births**, which may be associated with other anomalies. Previous studies on this topic included small groups of selected subjects, resulting in large variations in findings. The aim of this study was to examine the characteristics and associated anomalies of newborn infants with ACF compared with the general population of newborn infants. The study included newborn infants delivered between 1993 and 2003 at the Department of Neonatology of Rabin Medical Center, Israel. Charts of all newborns diagnosed with ACF were reviewed for obstetric and neonatal details, then compared with non-ACF newborns. **ACF was diagnosed in 258 of 67,289 newborns (0.38%), with left-side predominance (77%). Major malformations were found in 7% of ACF infants, 3.5-fold higher than in the total Israeli population.** Mild anomalies were present in 15% of the ACF group, and deformations in 4.6%. There was a higher rate of forceps deliveries in the ACF group (RR = 2.73, 95% CI = 1.37-5.42). ACF was more prevalent among females, and the male:female ratio was lower in the ACF group (0.86 vs. 1.06, P = 0.05). The rate of low-birth-weight infants was 3.9% among ACF infants and 9.6% in the control group (RR = 0.41, 95% CI = 0.23-0.76). No significant between-group difference was found for rates of primiparity, macrosomia, prematurity, postmaturity, or size-for-gestational-age. Thus, ACF is associated with a high rate of major malformations. This should prompt clinicians to seek for additional birth defects in ACF infants.

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Lonardo F, Sabba G, Luquetti DV, Monica MD, Scarano G. **Al-Awadi/Raas-Rothschild syndrome: Two new cases and review.** Am J Med Genet A. 2007 Apr 12;

Medical Genetics Department, Gaetano Rummo Hospital, Benevento, Italy.

Al-Awadi/Raas-Rothschild syndrome, an autosomal recessive disorder, is characterized by severe malformations of the upper and lower limbs, and a hypoplastic pelvis. We describe two new cases with the typical manifestations, report some new findings, review the relevant literature, and present minimal criteria for the diagnosis. A single homozygous WNT7A mutation was identified by Woods et al. [2006]: 1179C --> T, resulting in Arg292Cys with complete loss of WNT7A function.

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Ballarati L, Rossi E, Bonati MT, Gimelli S, Maraschio P, Finelli P, Giglio S, Lapi E, Bedeschi MF, Gueneri S, Arrigo G, Patricelli MG, Mattina T, Guzzardi O, Pecile V, Police A, Scarano G, Larizza L, Zuffardi O, Giardino D. **13q Deletion and central nervous system anomalies: further insights from karyotype-phenotype analyses of 14 patients.** J. Med. Genet. 2007 Jan;44(1):e60.

**BACKGROUND:** Chromosome 13q deletion is associated with varying phenotypes, which seem to depend on the location of the deleted segment. Although various attempts have been made to link the 13q deletion intervals to distinct phenotypes, there is still no acknowledged consensus correlation between the monosomy of distinct 13q regions and specific clinical features.

**METHODS:** 14 Italian patients carrying partial de novo 13q deletions were studied. Molecular-cytogenetic characterisation was carried out by means of array-comparative genomic hybridisation (array-CGH) or fluorescent in situ hybridisation (FISH).

**RESULTS:** Our 14 patients showed mental retardation ranging from profound-severe to moderate-mild: eight had central nervous system (CNS) anomalies, including neural tube defects (NTDs), six had eye abnormalities, nine had facial dysmorphisms and 10 had hand or feet anomalies. The size of the deleted regions varied from 4.2 to 75.7 Mb.

**CONCLUSION:** This study is the first systematic molecular characterisation of de novo 13q deletions, and offers a karyotype-phenotype correlation based on detailed clinical studies and molecular determinations of the deleted regions. Analyses confirm that patients lacking the 13q32 band are the most seriously affected, and critical intervals have been preliminarily assigned for CNS malformations. Dose-sensitive genes proximal to q33.2 may be involved in NTDs. The minimal deletion interval associated with the Dandy-Walker malformation (DWM) was narrowed to the 13q32.2-33.2 region, in which the ZIC2 and ZIC5 genes proposed as underlying various CNS malformations are mapped.

## **MORGAN M**

Durning P, Chestnutt IG, Morgan MZ. **The relationship between orofacial clefts and material deprivation in Wales.** Cleft Palate Craniofac. J. 2007 Mar;44(2):203-7.

Cardiff and Vale National Health Service Trust, Cardiff, UK.

**OBJECTIVE:** This study investigated the relationship between material deprivation and the incidence of orofacial clefts (OFC) in South, West, and Central Wales, U.K.

**DESIGN AND SETTING:** The South, West, and Central Wales Orofacial-Cleft Register served as the primary data source for the study. Data on all children born with an orofacial cleft between 1982 and 2003 were geocoded to one of 844 geographic wards. National census data, similarly geocoded, served as the population denominator. Townsend's index of material deprivation was used to assign wards to one of seven levels of deprivation. This permitted investigation of the association of orofacial clefts with material deprivation.

**RESULTS:** Between 1982 and 2003, there were 831 babies born with an orofacial cleft, equating to 109 clefts per 100,000 live births. The incidence of orofacial clefts ranged from 82 per 100,000 (95% confidence interval [C.I.] 64 to 102 per 100,000) in babies born to mothers residing in the least deprived areas to 127 per 100,000 (95% C.I., 112 to 144 per 100,000) in those living in the most deprived areas, a significant linear trend being apparent ( $p < .001$ ). A statistically significant **risk of 1.55 (95% C.I., 1.18 to 2.04)** for orofacial clefts was apparent between most and least deprived septiles of deprivation.

**CONCLUSIONS:** **This study provides further evidence of an association between material deprivation and orofacial clefts.** Further work is required to elicit the degree to which potential risk factors contribute to this association and to determine how deprivation predisposes to orofacial clefts.

## RITVANEN A

Suutarla S, Rautio J, Ritvanen A, Ala-Mello S, Jero J, Klockars T. **Microtia in Finland: comparison of characteristics in different populations.** *Int J Pediatr Otorhinolaryngol.* 2007 Aug;71(8):1211-7. Epub 2007 Jun 4.

Department of Otorhinolaryngology, Kymenlaakso Central Hospital, Kotka, Finland.

**OBJECTIVE:** To compare the characteristics of microtia in Finland and in other populations.

**METHODS:** Retrospective case series and patient questionnaire of 190 microtia patients referred for reconstruction of the earlobe to the Helsinki University Central Hospital during the years 1980-2005.

**RESULTS:** **The prevalence in Finland is 4.34/10,000** and varied in other populations from 0.83 to 17.4/10,000. Microtia is seen more in males (58%), as unilateral (88.4%), right-sided (59.5%) and it is almost always associated with aural atresia or stenosis (93%). There is conductive hearing loss in 96% and sensorineural hearing loss in 8% of the affected ears. 11% of the patients had congenital heart defects, and 5% had anomalies of extremities.

**CONCLUSIONS:** **There is variation in the prevalence and characteristics of microtia in different populations.**

## SCARANO G

Selicorni A, Russo S, Gervasini C, Castronovo P, Milani D, Cavalleri F, Bentivegna A, Masciadri M, Domi A, Divizia M, Sforzini C, Tarantino E, Memo L, Scarano G, Larizza L. **Clinical score of 62 Italian patients with Cornelia de Lange syndrome and correlations with the presence and type of NIPBL mutation.** *Clin Genet.* 2007 Aug;72(2):98-108.

I Clinica Pediatrica, Fondazione Policlinico Mangiagalli Regina Elena, Milan, Italy.

Cornelia de Lange syndrome (CdLS) is a rare multisystem disorder characterized by facial dysmorphisms, upper limb abnormalities, growth and cognitive retardation. About half of all patients with CdLS carry mutations in the NIPBL gene. The first Italian CdLS cohort involving 62 patients (including 4 related members) was screened for NIPBL mutations after a clinical evaluation using a quantitative score that integrates auxological, malformation and neurodevelopmental parameters. The patients were classified as having an overall 'severe', 'moderate' or 'mild' phenotype. NIPBL screening showed 26 mutations so classified: truncating (13), splice-site (8), missense (3), in-frame deletion (1) and regulatory (1). **The truncating mutations were most frequently found in the patients with a high clinical score, whereas most of the splice-site and all missense mutations clustered in the low-medium score groups.** The NIPBL-negative group included patients covering the entire clinical spectrum. The prevalence of a severe phenotype in the mutated group and a mild phenotype in the non-mutated group was statistically significant. In terms of the isolated clinical signs, the statistically significant differences between the mutation-positive and mutation-negative individuals were pre- and post-natal growth deficits, limb reduction, and delayed speech development. The proposed score seems to be a valuable means of prioritizing the patients with CdLS to undergo an NIPBL mutation test.

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Lonardo F, Parenti G, Luquetti DV, Annunziata I, Della Monica M, Perone L, De Gregori M, Zuffardi O, Brunetti-Pierrri N, Andria G, Scarano G. **Contiguous gene syndrome due to an interstitial deletion in Xp22.3 in a boy with ichthyosis, chondrodysplasia punctata, mental retardation and ADHD.** Eur J Med Genet. 2007 Jul-Aug;50(4):301-8. Epub 2007 May 21.

U.O.C. di Genetica Medica, A.O.R.N. "Gaetano Rummo", S.S. di Citogenetica Medica e Genetica Molecolare, Via dell'Angelo, 1, I-82100 Benevento, Italy.

Microdeletions of Xp22.3 can result in contiguous gene syndromes, showing the variable association of apparently unrelated clinical manifestations such as ichthyosis, chondrodysplasia punctata, hypogonadotropic hypogonadism, anosmia, ocular albinism, short stature and mental retardation. We report on a boy with ichthyosis, dysmorphic features and mental retardation with ADHD. The patient was born at term after a pregnancy complicated by threatened abortion; decreased fetal movements and low estril serum levels were reported during the last trimester. The boy was referred to us at the age of 13years. He presented with aggressive and hyperactive behavior. He had dry hair, a flat face, bilateral lens opacities, a small nose with hypoplastic tip, alae nasi and nares, a high-arched palate with a very small cleft, mixed dentition with 7 unerupted permanent teeth, left sensorineural and right mixed hearing loss with a calcified plaque of the tympanic membrane, marked shortness of terminal phalanges of hands and feet, ichthyosis of trunk and limbs. The genomic interval between AFM248th5 and KAL1 was investigated. PCR analysis showed a deletion in Xp22.3, with the distal breakpoint between the marker AFM248th5 and PABX and the proximal one between DXS278 and KAL1. Array-CGH and FISH analysis confirmed the interstitial deletion (of about 5.5Mb) and refined the breakpoints. We discuss the phenotype of our patient in relationship to the deleted segment and the possibility of mental retardation and ADHD genes in the region.

## SULLIVAN E

Tracy SK, Dahlen H, Caplice S, Laws P, Wang YA, Tracy MB, Sullivan E. **Birth centers in Australia: a national population-based study of perinatal mortality associated with giving birth in a birth center.** Birth. 2007 Sep;34(3):194-201.

Australian Institute of Health and Welfare National Perinatal Statistics Unit, University of New South Wales, Sydney, New South Wales, Australia.

**BACKGROUND:** Perinatal mortality is a rare outcome among babies born at term in developed countries after normal uncomplicated pregnancies; consequently, the numbers involved in large databases of routinely collected statistics provide a meaningful evaluation of these uncommon events. The National Perinatal Data Collection records the place of birth and information on the outcomes of pregnancy and childbirth for all women who give birth each year in Australia.

**AIM:** To describe the perinatal mortality associated with giving birth in "alongside hospital" birth centers in Australia during 1999 to 2002 using nationally collected data.

**METHODS:** This population-based study included all 1,001,249 women who gave birth in Australia during 1999 to 2002. Of these women, 21,800 (2.18%) gave birth in a birth center. Selected perinatal outcomes (including stillbirths and neonatal deaths) were described for the 4-year study period separately for first-time mothers and for women having a second or subsequent birth. A further comparison was made between deaths of low-risk term babies born in hospitals compared with deaths of term babies born in birth centers. **RESULTS:** The total perinatal death rate attributed to birth centers was significantly lower than that attributed to hospitals (1.51/1,000 vs 10.03/1,000). The perinatal mortality rate among term births to primiparas in birth centers compared with term births among low-risk primiparas in hospitals was 1.4 versus 1.9 per 1,000; the perinatal mortality rate among term births to multiparas in birth centers compared with term births among low-risk multiparas in hospitals was 0.6 versus 1.6 per 1,000.

**CONCLUSIONS:** This study using Australian national data showed that **the overall rate of perinatal mortality was lower in alongside hospital birth centers than in hospitals irrespective of the mother's parity.**

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Tracy SK, Tracy MB, Dean J, Laws P, Sullivan E. **Spontaneous preterm birth of liveborn infants in women at low risk in Australia over 10 years: a population-based study.** BJOG. 2007 Jun;114(6):731-5.

Australian Institute of Health and Welfare National Perinatal Statistics Unit, University of New South Wales, Randwick, Australia. stracy@ozemail.com.au

**OBJECTIVES:** To describe a 10-year trend in preterm birth.

**DESIGN:** Population-based study.

**SETTING:** Australia.

**POPULATION:** All women who gave birth during 1994-03.

**METHODS:** The proportion of spontaneous preterm births (greater than or equal to 22 weeks of gestation and less than 37 completed weeks of gestation) was calculated by dividing the number of women who had a live spontaneous preterm birth (excluding elective caesarean section and induction of labour) by the total number of women who had a live birth after spontaneous onset of labour (excluding elective caesarean section and induction of labour). This method was repeated for the selected population of women at low risk.

**MAIN OUTCOME MEASURE:** Preterm birth rates among the overall population of women; preterm birth among all women with a spontaneous onset of labour; and preterm birth in a selected population of women who were either primiparous or multiparous, non-Indigenous; aged 20-40 years and who gave birth to a live singleton baby after the spontaneous onset of labour.

**RESULTS:** Over the 10-year study period, the proportion of all women having a live preterm birth in Australia increased by 12.1% (from 5.9% in 1994 to 6.6% in 2003). Among women with a spontaneous onset of labour, there was an increase of 18.3% (from 5.7 to 6.7%). Among the selected population of low-risk women after the spontaneous onset of labour, the rate increased by 10.7% (from 5.6 to 6.2%) among first time mothers and by 19.2% (4.4-5.2%) among selected multiparous women.

**CONCLUSIONS:** Over the 10-year period of 1994-03, the rate of spontaneous preterm birth among low-risk women having a live singleton birth has risen in Australia.

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Tracy SK, Sullivan E, Wang YA, Black D, Tracy M. **Birth outcomes associated with interventions in labour amongst low risk women: A population-based study.** *Women Birth.* 2007 Jun;20(2):41-8.

Australian Institute of Health and Welfare, National Perinatal Statistics Unit, School of Women's and children's Health, Faculty of Medicine, University of New South Wales, Sydney, NSW 2031, Australia.

**INTRODUCTION:** Despite concern over high rates of operative birth in many countries, particularly amongst low risk healthy women, the obstetric antecedents of operative birth are poorly described. We aimed to determine the association between interventions introduced during labour with interventions in the birth process amongst women of low medical risk.

**METHODS:** We undertook a population-based descriptive study of all low risk women amongst the 753,895 women who gave birth in Australia during 2000-2002. Adjusted odds ratios (AOR) were calculated using multinomial logistic regression to describe the association between mode of birth and each of four labour intervention subgroups separately for primiparous and multiparous women.

**RESULTS:** We observed increased rates of operative birth in association with each of the interventions offered during the labour process. For first time mothers the association was particularly strong.

**CONCLUSIONS:** This study underlines the need for better clinical evidence of the effects of epidurals and pharmacological agents introduced in labour. At a population level it demonstrates the magnitude of the fall in rates of unassisted vaginal birth in association with a cascade of interventions in labour and interventions at birth particularly amongst women with no identified risk markers and having their first baby. This information may be useful for women wanting to explore other methods of influencing the course of labour and the management of pain in labour, especially in their endeavour to achieve a normal vaginal birth.

## **SZUNYOGH M**

Puhò EH, Szunyogh M, Métneki J, Czeizel AE. **Drug treatment during pregnancy and isolated orofacial clefts in hungary.** *Cleft Palate Craniofac. J.* 2007 Mar;44(2):194-202.

National Center for Healthcare Audit and Improvement, Department of Human Genetics and Teratology and the Foundation for the Community Control of Hereditary Diseases, Budapest, Hungary.

**OBJECTIVE:** To evaluate the possible association between all kinds of drug treatments during pregnancy and isolated cleft lip with or without cleft palate (CL/P) and posterior cleft palate (PCP) in the offspring.

**SETTING:** The dataset of the large population-based Hungarian Case-Control Surveillance of Congenital Abnormalities, 1980-1996, was evaluated.

**PARTICIPANTS:** One thousand three hundred seventy-four cases with isolated CL/P and 601 with PCP, plus 38,151 population controls (without birth defects) and 20,868 malformed controls with other defects. **Intervention:** In this observation case-control study the data collection was based on prospective medical records particularly prenatal logbook, retrospective maternal data via a self-reported questionnaire, and home visits of nonresponding mothers.

**MAIN OUTCOME MEASURES:** Isolated CL/P and PCP associated with drug treatments during pregnancy.

**RESULTS:** An increased risk for isolated CL/P was found in cases born to mothers treated with amoxicillin, phenytoin, oxprenolol, and thiethylperazine during the second and third month of pregnancy, i.e., the critical period of isolated CL/P. Risk of isolated PCP was increased in mothers with oxytetracycline and carbamazepine treatment during the third and fourth month of pregnancy, i.e., the critical period of PCP.

**CONCLUSIONS:** This study confirmed the orofacial cleft (OFC) inducing effect of phenytoin, carbamazepine, oxytetracycline, and thiethylperazine and suggested a possible association between OFCs and oxprenolol and amoxicillin. However, drugs may have only a limited role in the origin of isolated OFCs.

## TENCONI R

Zollino M, Lecce R, Murdolo M, Orteschi D, Marangi G, Selicorni A, Midro A, Sorge G, Zampino G, Memo L, Battaglia D, Petersen M, Pandelia E, Gyftodimou Y, Faravelli F, Tenconi R, Garavelli L, Mazzanti L, Fischetto R, Cavalli P, Savasta S, Rodriguez L, Neri G. **Wolf-Hirschhorn syndrome-associated chromosome changes are not mediated by olfactory receptor gene clusters nor by inversion polymorphism on 4p16.** Hum Genet. 2007 Aug 4;

Istituto di Genetica Medica, Policlinico A. Gemelli, Universita Cattolica Sacro Cuore, L.go F. Vito, 1, 00168, Rome, Italy, mzollino@rm.unicatt.it.

The basic genomic defect in Wolf-Hirschhorn syndrome (WHS), including isolated 4p deletions and various unbalanced de novo 4p;autosomal translocations and above all t(4p;8p), is heterogeneous. Olfactory receptor gene clusters (ORs) on 4p were demonstrated to mediate a group of WHS-associated t(4p;8p)dn translocations. The breakpoint of a 4-Mb isolated deletion was also recently reported to fall within the most distal OR. However, it is still unknown whether ORs mediate all 4p-autosomal translocations, or whether they are involved in the origin of isolated 4p deletions. Another unanswered question is whether a parental inversion polymorphism on 4p16 can act as predisposing factor in the origin of WHS-associated rearrangements. We investigated the involvement of the ORs in the origin of 73 WHS-associated rearrangements. No hotspots for rearrangements were detected. Breakpoints on 4p occurred within the proximal or the distal olfactory receptor gene cluster in 8 of 73 rearrangements (11%). These were five t(4p;8p) translocations, one t(4p;7p) translocation and two isolated terminal deletions. ORs were not involved in one additional t(4p;8p) translocation, in a total of nine different 4p;autosomal translocations and in the majority of isolated deletions. The presence of a parental inversion polymorphism on 4p was investigated in 30 families in which the 4p rearrangements, all de novo, were tested for parental origin (7 were maternal and 23 paternal). It was detected only in the mothers of 3 t(4p;8p) cases. We conclude that WHS-associated chromosome changes are not usually mediated by low copy repeats. The 4p16.3 inversion polymorphism is not a risk factor for their origin.

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Pandit B, Sarkozy A, Pennacchio LA, Carta C, Oishi K, Martinelli S, Pogna EA, Schackwitz W, Ustaszewska A, Landstrom A, Bos JM, Ommen SR, Esposito G, Lepri F, Faul C, Mundel P, Lopez Siguero JP, Tenconi R, Selicorni A, Rossi C, Mazzanti L, Torrente I, Marino B, Digilio MC, Zampino G, Ackerman MJ, Dallapiccola B, Tartaglia M, Gelb BD. **Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy.** Nat Genet. 2007 Aug;39(8):1007-12. Epub 2007 Jul 1.

Center for Molecular Cardiology, Department of Pediatrics and Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, New York 10029, USA.

Noonan and LEOPARD syndromes are developmental disorders with overlapping features, including cardiac abnormalities, short stature and facial dysmorphism. Increased RAS signaling owing to PTPN11, SOS1 and KRAS mutations causes approximately 60% of Noonan syndrome cases, and PTPN11 mutations cause 90% of LEOPARD syndrome cases. Here, we report that 18 of 231 individuals with Noonan syndrome without known mutations (corresponding to 3% of all affected individuals) and two of six individuals with LEOPARD syndrome without PTPN11 mutations have missense mutations in RAF1, which encodes a serine-threonine

kinase that activates MEK1 and MEK2. Most mutations altered a motif flanking Ser259, a residue critical for autoinhibition of RAF1 through 14-3-3 binding. Of 19 subjects with a RAF1 mutation in two hotspots, 18 (or 95%) showed hypertrophic cardiomyopathy (HCM), compared with the 18% prevalence of HCM among individuals with Noonan syndrome in general. Ectopically expressed RAF1 mutants from the two HCM hotspots had increased kinase activity and enhanced ERK activation, whereas non-HCM-associated mutants were kinase impaired. Our findings further implicate increased RAS signaling in pathological cardiomyocyte hypertrophy.

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Clementi M, Causin R, Marzocchi C, Mantovani A, Tenconi R. **A study of the impact of agricultural pesticide use on the prevalence of birth defects in northeast Italy.** *Reprod Toxicol.* 2007 Jul;24(1):1-8. Epub 2007 May 3.

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Pesticides are probably the most frequently deliberately released toxic chemicals into the environment. However, although the results of experimental studies indicate developmental toxicity hazards for several groups of chemicals used, the studies in humans are contradictory. There are specific regulations in the European Union (EU) regarding the use of pesticides and there is also considerable awareness about possible related health problems. In order to investigate whether, in the current EU situation, the use of certain pesticides could be associated with adverse health effects in the outcome of pregnancies, we have performed a 6-year study in an agricultural area in the Veneto Region of, northeastern Italy, where we have been able to define the exact quantity and type of pesticides as well as the exposed population, in order to quantify the risk of congenital malformations related to the use of pesticides. Data on congenital malformations were obtained from the northeast Italy Congenital malformation Registry, using several sources of ascertainment, while pesticide use were obtained through interviews with users and sellers. The municipalities of three contiguous provinces were divided into those with a high, low or intermediate use of pesticides. In the study period there was a total of 146,239 consecutive pregnancies terminating in birth or induced abortion because of congenital malformation. **No significant differences in the prevalence of congenital malformations were observed between the three different areas (high, low, intermediate risk).** Our study confirms that **in countries such as Italy, where there is close control of the use of pesticides, there is no epidemiological evidence that pesticides have any effect on the prevalence of congenital malformations.**

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Clementi M, Di Gianantonio E, Fabris L, Forabosco P, Strazzabosco M, Tenconi R, Okolicsanyi L. **Inheritance of hyperbilirubinemia: evidence for a major autosomal recessive gene.** *Dig Liver Dis.* 2007 Apr;39(4):351-5.

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**BACKGROUND AND AIM:** To clarify the precise mode of inheritance of Gilbert syndrome, an unconjugated familial hyperbilirubinemia, where impaired bilirubin conjugation is caused by reduced UGT1A1 activity determined by a defective function of the A(TA)<sub>6</sub>TAA promoter region of the UGT1A1 gene.

**SUBJECTS AND METHODS:** Serum bilirubin levels were measured in a large, homogeneous resident population from North-Eastern Italy, consisting of 1.639 males (age 44.5±13.9, range 18-89 years), and 1.420 females (age 45.1±15.0, range 18-85). In 112 nuclear families from hyperbilirubinemic probands living in the same area a complex segregation analysis was then performed. In both samples we carefully excluded potentially confounding factors of bilirubin levels (alcohol abuse, excessive cigarette smoking, drug consumption, overt haemolysis and liver disease).

**RESULTS:** Mean serum bilirubin concentrations are higher in males than in females, showing fluctuations through the different age periods in males. Complex segregation results demonstrate that unconjugated hyperbilirubinemia exhibits a precise mode of inheritance in which a major recessive gene with a frequency of 0.45 is responsible for higher serum bilirubin values.

**CONCLUSIONS:** This major recessive gene accounts only for a part of the serum bilirubin concentration, thus implying additional, environmental factors for the clinical appearance of GS.

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Salviati L, Trevisson E, Baldoin MC, Toldo I, Sartori S, Calderone M, Tenconi R, Laverda A. **A novel deletion in the GJA12 gene causes Pelizaeus-Merzbacher-like disease.** Neurogenetics. 2007 Jan;8(1):57-60.

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Pelizaeus-Merzbacher disease (PMD) and Pelizaeus-Merzbacher-like disease (PMLD) are hypomyelinating disorders of the central nervous system with a very similar phenotype. PMD is an X-linked disorder caused by mutations in PLP1. PMLD is an autosomal recessive condition caused by mutations in GJA12. We report a 5-year-old girl with a complex neurological syndrome and severe hypomyelination on brain magnetic resonance imaging. She harbored a homozygous 34-bp deletion in the coding region of GJA12. There are no distinctive features for the differential diagnosis of PMD/PMLD. GJA12 should be analyzed in all patients without PLP1 mutations but should also be considered the initial genetic test in women and in patients with consanguineous parents.