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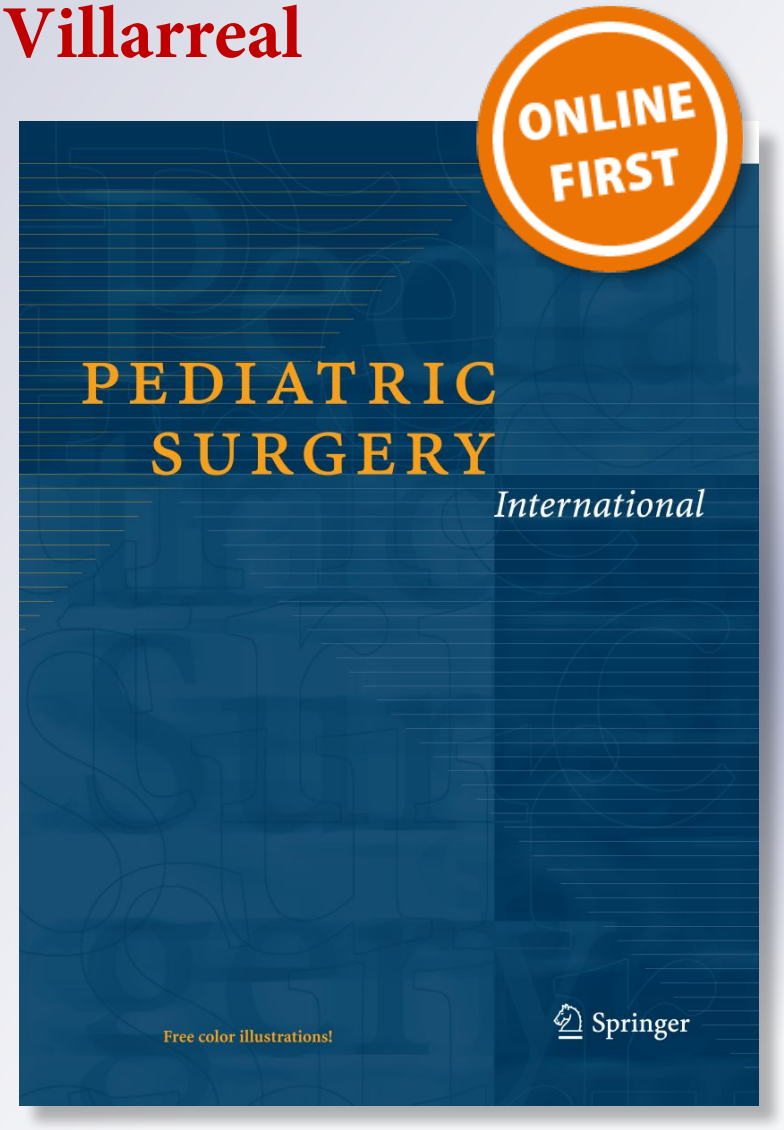

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ORIGINAL ARTICLE

A clinical-pathogenetic approach on associated anomalies and chromosomal defects supports novel candidate critical regions and genes for gastroschisis

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Abstract

Background Gastroschisis has been assumed to have a low rate of syndromic and primary malformations. We aimed to systematically review and explore the frequency and type of malformations/chromosomal syndromes and to identify significant biological/genetic roles in gastroschisis.

Methods Population-based, gastroschisis-associated anomalies/chromosomal defects published 1950–2018 (PubMed/MEDLINE) were independently searched by two reviewers. Associated anomalies/chromosomal defects and selected clinical characteristics were subdivided and pooled by race, system/region, isolated, and associated cases (descriptive analysis and chi-square test were performed). Critical regions/genes from representative chromosomal syndromes including an enrichment analysis using Gene Ontology Consortium/Panther Classification System databases were explored. Fisher's exact test with False Discovery Rate multiple test correction was performed.

Results Sixty-eight articles and 18525 cases as a base were identified (prevalence of 17.9 and 3% for associated anomalies/chromosomal defects, respectively). There were 3596 associated anomalies, prevailing those cardiovascular (23.3%) and digestive (20.3%). Co-occurring anomalies were associated with male, female, American Indian, Caucasian, prenatally diagnosed, chromosomal defects, and mortality ($P < 0.00001$). Gene clusters on 21q22.11 and 21q22.3 (*KRTAP*), 18q21.33 (*SERPINB*), 18q22.1 (*CDH7, CDH19*), 13q12.3 (*FLT1*), 13q22.1 (*KLF5*), 13q22.3 (*EDNRB*), and 13q34 (*COL4A1, COL4A2, F7, F10*) were significantly related to biological processes: blood pressure regulation and/or vessel integrity, angiogenesis, coagulation, cell–cell and/or cell-matrix adhesion, dermis integrity, and wound healing ($P < 0.05$).

Conclusions Our findings suggest that gastroschisis may result from the interaction of several chromosomal regions in an additive manner as a pool of candidate genes were identified from critical regions supporting a role for vascular disruption, thrombosis, and mesodermal deficiency in the pathogenesis of gastroschisis.

Keywords Chromosomes · Gastroschisis · Genes · Genetics · Population based

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Introduction

Gastroschisis, an anterior abdominal wall defect, is perhaps unique among major congenital anomalies with a prevalence rate that varies from 0.5 up to 9 per 10,000 live births affecting all human populations. Along with this trend, the fetus of young women is disproportionately affected whereas its pathogenesis remains elusive [1, 2]. Furthermore, associated anomalies in gastroschisis range widely in addition to diverse proposed explanations for these clinical scenarios (e.g., inclusion/exclusion criteria, classification/type of concurrent anomalies, miscoding/collecting method, others) [3–5]. Indeed, the reported frequency of associated

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anomalies ranges from as low as 5% to over 50%, in contrast, its association with major chromosomal or genetic syndrome has been described as not significant [3]. Although gastroschisis has been assumed to have a low rate of concurrent primary malformations and even more so in chromosomal syndromes, exploring these influences may be useful to identify additional genetic or environmental causative factors in gastroschisis [6–8]. To date, most studies assessing gastroschisis clinical and syndromic spectra have been limited by the small case counts, that may have prevented the recognition of social, demographic, and clinical factors and its differences from other populations. Moreover, few studies provide a specific analysis by type and frequency of the associated anomalies and chromosomal syndromes using a large population-based data. Therefore, we examine the literature to pool data from a large, population-based, and representative sample of gastroschisis cases over the course of six decades with a twofold purpose; to explore the frequency and type of malformations and chromosomal syndromes associated with gastroschisis and to identify significant biological/genetic roles of these influences in gastroschisis.

Materials and methods

Search strategy, selection criteria, and data extraction

We conducted a literature survey within a date range from January 1, 1950 to May 31, 2018, to identify population-based studies that examined the frequency and type of malformations and chromosomal syndromes associated with gastroschisis. Articles were identified using the Medline search engine (by means of PubMed); search terms used were as follows: ⟨{[(gastroschisis) AND abnormalities] OR anomalies} AND chromosomal⟩ AND syndrome).

Observational studies with quantitative data that examined the frequency and type of malformations and chromosomal syndromes associated with gastroschisis were considered. The inclusion criteria were: (1) articles written in English; (2) any population-based study that investigated the frequency and type of malformations or chromosomal syndromes associated with gastroschisis; (3) any case report that included associated anomalies and chromosome analysis by karyotype or array-based comparative genomic hybridization; and (4) included only human subjects. Two independent reviewers (V.M.S.T. and R.A.S.T.) analyzed and determined if the articles met the inclusion criteria by looking through all titles and abstracts of the identified studies.

Summary data for the frequency and type of malformations and chromosomal syndromes associated with gastroschisis were extracted independently by two reviewers (V.M.S.T. and R.A.S.T.) using a standardized form. Data extracted from each paper included: the first author's name, year of publication, recruitment or period of study of participants, sample size, race (American Indian, Caucasian, African American, Hawaiian/Pacific Islander, Hispanic, White or Black), frequency and type of malformations and chromosomal or genetic syndromes, frequency of prenatal diagnosis by ultrasound examination, sex of studied participants, mortality, and geographical location where the study was done. These data were computerized separately by each reviewer. Then, both data were compared and validated to identify disagreements. Meetings between the two reviewers (V.M.S.T. and R.A.S.T.) and a third party (R.M.C.F.) were then setup to discuss and solve disagreements.

Data synthesis and statistical analysis

Published data on associated anomalies and chromosomal defects in gastroschisis were subdivided into three main categories: data among population-based American Indian race, data among population-based Caucasian race, and data within case reports (Multiracial). Also, associated anomalies, multiple-anomaly patterns, and chromosomal defects were pooled and classified by system or region. Descriptions referring to major anomalies (concurrent primary malformations) as well as chromosomal defects and those cases with multiple-anomaly patterns with potentially different mechanisms (e.g., limb-body wall defect) were retained for analysis. The latter cases were included to avoid biasing and did not significantly alter percentages of gastroschisis cases with associated anomalies. Several anomalies interpreted as minor (e.g., epicanthal folds), or designated as secondary malformations (e.g., intestinal malrotation) were excluded for analysis.

For all categories or system/region, frequencies of associated anomalies and chromosomal defects were deducted from the reported data and presented in numbers and percentages. For studies providing cytogenetic data, we calculated separate rates of chromosomal defects among isolated (if available) and associated anomalies cases of gastroschisis. If studies were reported from retrospective registry data without information about the presence or absence of associated anomalies, we assumed that chromosomal analysis had been performed in associated cases only. Where possible, prevalence data as well as other sociodemographic and clinical characteristics were also subdivided according to isolated and associated cases.

Among the most representative chromosomal syndromes associated with gastroschisis, we explore each critical region and their genes [9] emphasizing, when possible, on abdominal wall defects and the most common concurrent primary malformations resulting from our analysis. Then, an enrichment analysis of the identified genes using the Gene Ontology Consortium and Panther Classification System

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databases was performed [10], to identify the significant biological process as well as the possible candidate critical regions/genes. These databases include the Fisher's exact test with False Discovery Rate (FDR) multiple test correction (*P* values less than 0.05).

Descriptive statistical analysis and a contingency table (chi square) test for selected sociodemographic and clinical characteristics of gastroschisis cases stratified by isolated and associated anomalies were performed with SPSS version 24 (IBM, Armonk, NY, USA). A *P* value less than 0.05 was considered significant.

Results

A total of 14,463 studies were located from Medline by means of PubMed (1950–2018). After 2226 studies were removed, the literature search yielded 12,237 citations. Initial screening by title identified 101 potentially relevant abstracts, subsequently, 33 of these studies were excluded due to the established criteria or duplicate data. Thus, a total of 68 studies meeting the inclusion criteria were examined including 3323 gastroschisis cases with associated anomalies from 18,525 gastroschisis cases, for a prevalence of 17.9%. Regarding chromosomal defects, we identified 116 chromosomal defects associated with gastroschisis among 3782 gastroschisis cases for a prevalence of 3%. Prenatal diagnosis by ultrasound examination within the included studies yielded a range from 28 to 99% (mostly before 24 weeks of gestation).

Studies among population-based American Indian race

Table 1 shows the associated anomalies and chromosomal defects distribution in gastroschisis among American Indian race. A total of 31 studies were identified [4, 11–40] over the period 1960–2014 (median 1987), including 2636 gastroschisis cases with associated anomalies from 13,369 gastroschisis cases and 54 chromosomal defects from 2647 gastroschisis cases for a prevalence of 19.7 and 2%, respectively.

Studies among population-based Caucasian race

Table 2 shows the associated anomalies and chromosomal defects distribution in gastroschisis among Caucasian race. A total of 21 studies were identified [41–61] over the period 1965–2013 (median 1989), including 651 gastroschisis cases with associated anomalies from 5084 gastroschisis cases and 58 chromosomal defects from 1102 gastroschisis cases for a prevalence of 12.8 and 5.2%, respectively.

Studies within case reports (multiracial)

Table 3 shows the associated anomalies and chromosomal defects distribution in gastroschisis within case reports (Multiracial). There were 14 case reports and 2 case series [62–77] including 36 gastroschisis cases with associated anomalies from 72 gastroschisis cases and 4 chromosomal defects from 33 gastroschisis cases for a prevalence of 50 and 12.1%, respectively.

Spectra of associated anomalies in gastroschisis

There were 3596 associated anomalies for gastroschisis. Overall, concurrent primary malformations accounted for 92.3%, whereas recognized syndromes with gastroschisis (multiple-anomaly pattern and chromosomal) were identified in 7.7%. More frequent by system or region were those of the cardiovascular (23.3%), digestive (20.3%), genitourinary (9%), CNS (7.2%), musculoskeletal (6.2%), limbs (5.7%), renal (5.4%), craniofacial (4.9%), multiple-anomaly patterns (4.5%), axial/trunk and pulmonary (3.7%, respectively), chromosomal defects (3.2%), miscellaneous (3.1%), and endocrine (0.1%). About 50% of these associated anomalies were distributed in those of the cardiovascular and digestive systems prevailing ASD, VSD, and PDA, and intestinal atresias, respectively. Facial minor anomalies as well as digestive-secondary (e.g., intestinal malrotation) were not included as primary anomalies but are listed along with the spectra of associated anomalies in Table 4.

Selected sociodemographic and clinical characteristics stratified by isolated and associated anomalies

Comparison of selected sociodemographic and clinical characteristics about the presence ($n = 3323$) or absence ($n = 15{,}202$) of any type of associated anomalies is showed in Table 5. The presence of co-occurring anomalies were associated with the following: male and female sex (OR = 2.15 and 1.30, $P < 0.00001$, respectively), American Indian and Caucasian race (OR = 1.59 and 0.59, $P < 0.00001$, respectively), prenatally diagnosed (OR = 1.25, $P = 0.0001$), chromosomal defects (OR = 36.25, $P < 0.00001$), and mortality (OR = 10.76, $P < 0.00001$).

Possible candidate critical regions and genes from chromosomal syndromes

Trisomy 18, 13, and 21 were the most representative chromosomal syndromes associated with gastroschisis. Investigation of chromosomal regions included both short (p) and long (q) arms for chromosome 18 and the long (q) arm for chromosome 13 (given its extremely variability and

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Table 1 Summary of published data among population-based American Indian race on associated anomalies and chromosomal defects in gastroschisis

Author, year	Time period	Associated anomalies % (*n*)	Chromosomal defects % (*n*)
Mahour, 1973	1960–1970	13.0 (3/23)	0.0 (0/3)[a]
Colombani, 1977	1962–1976	20.0 (4/20)	–
Mayer, 1980	1971–1979	23.4 (11/47)	0.0 (0/11)[a]
Klein, 1981	1976–1980	27.7 (5/18)	–
Baird, 1981	1964–1978	48.0 (14/29)	–
Hoyme, 1981	1970–1980	38.4 (10/26)	–
Kaplan, 1986	1974–1984	17.8 (5/28)	–
Reid, 1986	1954–1984	5.3 (12/225)[b]	–
Bair, 1986	1977–1985	50.0 (4/8)	0.0 (0/2)[a]
Gauderer, 1987	1976–1986	100.0 (3/3)	0.0 (0/1)[a]
Fogel, 1991	1985–1988	17.6 (3/17)	6.2 (1/16)[a]
Aliotta, 1992	1980–1985	25.0 (3/12)	–
Yang, 1992	1980–1987	16.0 (13/81)	–
Loder, 1993	1975–1990	34.4 (20/58)	–
Levard, 1997	1980–1992	40.0 (4/10)	–
Snyder, 1999	1969–1999	3.2 (6/185)	16.6 (1/6)[a]
Reiss, 2000	1996–1997	33.3 (4/12)	0.0 (0/1)[a]
Salihu, 2003	1992–1999	–	0.0 (0/308)[a]
Hwang, 2004	1982–1999	23.9 (29/121)	0.0 (0/37)[a]
Goldkrand, 2004	1994–2002	17.6 (6/34)	0.0 (0/3)[a]
Curry, 2005	1985–2001	1.5 (1/63)[c]	–
Kunz, 2005	1992–1997	11.1 (69/621)	–
Eggink, 2006	1983–2003	41.6 (30/72)	–
Abdullah, 2007	1988–2003	23.1 (1005/4344)	0.3 (4/1005)[a]
Heinrich, 2007	2005–2006	–	0.0 (0/6)[d]
Forrester, 2008	1986–2001	59.3 (57/96)	–
Akhtar, 2012	2006–2010	8.8 (47/529)	4.3 (1/23)[a]
Corey, 2014	1997–2012	7.7 (390/4687)	0.3 (16/390)[a]
Benjamin, 2015	1999–2008	42.2 (774/1831)	3.6 (28/774)[a]
Corona-Rivera, 2016	2009–2014	48.1 (52/108)	–
Feldkamp, 2016	1997–2011	15.4 (52/336)	5.8 (3/51)[a]
Total: 31 studies	Median: 1987	19.7 (2636/13,369)	2.0 (54/2647)

Studies may involve cases of gastroschisis among Black/African American or Hawaiian/Pacific Islander or Hispanic races

[a]Chromosome analysis included karyotype

[b]Cases of amyoplasia

[c]Cases of schizencephaly

[d]Chromosome analysis included karyotype and array-based comparative genomic hybridization

no clear consensus), whereas locus 21q22.11 to 21q22.3 were explored for chromosome 21 [78]. Overall, from the pooled genes in chromosome 18, two candidate critical regions were identified: 18q21.33 (*SERPINB2, B3, B4, B5, B7, B11, B12*, and *B13*) involved in negative regulation of endopeptidase activity (*P* 3.06E-11, FDR 4.79E-07), and 18q22.1 (*CDH7* and *CDH19*) involved in calcium-dependent cell–cell adhesion via plasma membrane cell adhesion molecules (*P* 1.50E-06, FDR 2.34E-02). Among chromosome 13 pooled genes, four candidate critical regions were identified: 13q12.3 (*FLT1*) involved in vascular endothelial growth factor receptor-1 signaling pathway (*P* 2.23E−02, FDR 3.15E−00), 13q22.1 (*KLF5*) involved in cell–cell signaling via exosome (*P* 2.23E−02, FDR 3.23E−00), 13q22.3 (*EDNRB*) involved in endothelin receptor signaling pathway (*P* 3.33E−02, FDR 2.48E−00), and 13q34 (*COL4A1* and *COL4A2* involved in collagen-activated tyrosine kinase receptor signaling pathway, and *F7* and *F10* involved in blood coagulation fibrin clot formation) (*P* 7.70E−03, FDR 4.46E−00 and *P* 3.92E−02, FDR 2.57E−00, respectively).

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Table 2 Summary of published data among population-based Caucasian race on associated anomalies and chromosomal defects in gastroschisis

Author, year	Time period	Associated anomalies % (*n*)	Chromosomal defects % (*n*)
Lindham, 1981	1965–1976	4.9 (3/61)	–
Nicolaides, 1992	1983–1991	30.7 (8/26)	0.0 (0/26)[a]
Claussen, 1994	1985–1992	12.5 (1/8)	12.5 (1/8)[a]
Calzolari, 1995	1980–1990	20.8 (57/274)	3.2 (9/274)[a]
Heydanus, 1996	1981–1993	36.3 (4/11)	0.0 (0/4)[a]
Nicholls, 1996	1983–1992	33.3 (7/21)	6.6 (1/15)[a]
Tan, 1996	1987–1993	5.0 (27/539)	–
Rankin, 1999	1986–1996	5.2 (7/133)	14.2 (1/7)[a]
Axt, 1999	1989–1997	27.7 (5/18)	0.0 (0/18)[a]
Kitchanan, 2000	1988–1997	23.8 (5/21)	–
Barisic, 2001	1996–1998	21.6 (23/106)	1.8 (2/106)[a]
Hsu, 2002	1990–2000	35.3 (23/65)	0.0 (0/23)[a]
Saxena, 2002	1984–1998	31.4 (22/70)	–
Brantberg, 2004	1988–2000	6.2 (6/64)	0.0 (0/6)[a]
Lee, 2006	1980–2004	2.2 (1/45)[b]	–
Mastroiacovo, 2007[c]	1974–2004	12.2 (404/3322)	8.7 (41/469)[a]
Tan, 2008	1993–2002	52.3 (11/21)	9.0 (1/11)[a]
Stoll, 2008	1979–2003	16.6 (10/60)	10.0 (1/10)[a]
Fillingham, 2008	1997–2006	6.9 (10/143)	20.0 (1/5)[a]
Ruano, 2011	1998–2006	12.9 (14/108)	0.0 (0/108)[a]
Ekin, 2015	2007–2013	25.0 (3/12)	0.0 (0/12)[a]
Total: 21 studies	Median: 1989	12.8 (651/5084)	5.2 (58/1102)

Studies may involve cases of gastroschisis among Black or White races

[a]Chromosome analysis included karyotype

[b]Cases of situs inversus

[c]Multiracial cases of gastroschisis (mostly Caucasian)

Regarding chromosome 21 pooled genes, two candidate critical regions were identified: 21q22.11 (*KRTAP6-1, 6-3, 8-1, 11-1, 13-1, 13-2, 13-3, 13-4, 15-1, 19-1, 19-3, 19-7, 19-8, 21-2, 21-3, 23-1, 24-1, 25-1, 26-1*, and *27-1*) and 21q22.3 (*KRTAP10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-7, 10-8, 10-9, 10-10, 10-11, 10-12, 12-1, 12-2*, and *12-4*) both involved in keratinization biological process (*P* 8.25E-26, FDR 1.29E-21 and *P* 5.47E-15, FDR 8.57E-11, respectively).

Discussion

The present work is the first study exploring the evidence regarding syndromic and primary malformations in gastroschisis from 1950 to 2018. Our findings confirmed the high frequency of isolated occurrence (82.1%) as well as the presence of more frequent digestive and cardiovascular anomalies previously reported from population-based studies [34, 37, 38, 40, 56]. Nevertheless, a considerably higher frequency of the aforementioned primary anomalies, along with significant differences in sex, race, prenatal diagnosis, chromosomal defects, and mortality when stratified among the presence or absence of any associated anomalies are novel findings. Moreover, our systematic review of the literature assessed the available evidence regarding chromosomal syndromes associated with gastroschisis. Overall, we observed an increased frequency of these disorders (up to 3%, namely trisomy 18, 13, and 21), thereby providing possible candidate critical regions/genes for gastroschisis (18q21.33, 18q22.1, 13q12.3, 13q22.1, 13q22.3, 13q34, 21q22.11, 21q22.3).

We demonstrated that the prevalence of associated structural and chromosomal defects varies widely among all categories (races) and system/region (type and distribution of associated anomalies), as displayed in Tables 1, 2, 3 and 4. Thus, the present study gives researchers the possibility to have several observations. In this regard, associated anomalies in gastroschisis range from as low as 3.2% to over 59.3% [26, 36]. Interestingly, population-based studies among American Indian race showed increased frequencies of associated anomalies (OR = 1.59, $P < 0.00001$), conversely, Caucasian race showed decreased frequencies of

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Table 3 Summary of published data within case reports on associated anomalies and chromosomal defects in gastroschisis

Author, year	Study design	Associated anomalies % (*n*)	Chromosomal defects % (*n*)
Willert, 1978	Case report	100.0 (1/1)	0.0 (0/1)[a]
Verhagen, 1981	Case report	100.0 (1/1)	0.0 (0/1)[a]
Short, 1985	Case report	100.0 (1/1)	0.0 (0/1)[a]
Nicolaides, 1986	Case series	100.0 (3/3)	0.0 (0/3)[a]
Lewinsky, 1990	Case report	100.0 (1/1)	100.0 (1/1)[a]
Robertson, 1992	Case report	100.0 (1/1)	0.0 (0/1)[a]
Spencer, 1996	Case series	11.1 (2/18)[b]	–
Ramsey, 1998	Case report	100.0 (1/1)	100.0 (1/1)[a]
Koivusalo, 1998	Case series	44.4 (16/36)	0.0 (0/16)[a]
Kiliç, 2001	Case report	100.0 (1/1)	0.0 (0/1)[a]
Orpen, 2004	Case report	100.0 (1/1)	0.0 (0/1)[a]
Guler, 2007	Case report	100.0 (1/1)	100.0 (1/1)[a]
Khalil, 2007	Case report	100.0 (3/3)	0.0 (0/2)[a]
Brockmann, 2009	Case report	100.0 (1/1)	0.0 (0/1)[c]
Shi, 2012	Case report	100.0 (1/1)	0.0 (0/1)[a]
Inoue, 2016	Case report	100.0 (1/1)	100.0 (1/1)[a]
Total	16 studies	50.0 (36/72)	12.1 (4/33)

Studies involving multiracial cases of gastroschisis

[a]Chromosome analysis included karyotype

[b]Cases of ischiopagus twins

[c]Chromosome analysis included karyotype and array-based comparative genomic hybridization

associated anomalies (OR = 0.59, $P < 0.00001$) and a high frequency of chromosomal syndromes which diverges from American Indian race (5.2 and 2%, respectively). Moreover, chromosomal defects were almost always seen in association with additional anomalies (OR = 36.25, $P < 0.00001$) and hence, the presence of associated anomalies on prenatal ultrasound examination could be a significant predictor of underlying chromosomal defects in fetuses with gastroschisis (OR = 1.25, $P = 0.0001$); notwithstanding that the impact in the mortality among these fetuses/infants is also significant (OR = 10.76, $P < 0.00001$).

There may be several factors in play for these findings, for instance, the rising trend and prevalence of gastroschisis along with its epidemiologic patterns indicate that populations of the American continent show a higher prevalence than those of European or Asian continents [1, 2]. Another critical factor resides in the fact that these data could be hindered due or related to different neonatal survival rates among countries, which may also include an inaccurate coding/recording of gastroschisis and its congenital anomalies associated to surveillance databases [2, 34, 37, 38, 40, 56]. Furthermore, we believe that a significant source for the identified variability of associated anomalies in gastroschisis is due to its definition. Despite several explanations for these

Table 4 Distribution by system or region of associated anomalies with gastroschisis in the included studies

System/region	% (*n*)
CNS	**7.2 (260)***
Hydrocephaly	1.91 (69)
Holoprosencephaly	0.13 (5)
Porencephaly	0.02 (1)
Schizencephaly	0.05 (2)
Meningomyelocele/spina bifida	1.33 (48)
Encephalocele	0.36 (13)
Anencephaly	1.36 (49)
Dandy Walker malformation	0.11 (4)
Septum pellucidum atresia	0.05 (2)
Absent corpus callosum	0.05 (2)
Craniofacial	**4.9 (177)***
Facial minor[†‡]	4.64 (167)
Cleft lip/palate	1.89 (68)
Microcephaly	0.38 (14)
Macrocephaly	0.25 (9)
Anophthalmia/microphthalmia	0.13 (5)
Anotia/microtia	0.08 (3)
Craniosynostosis	0.08 (3)
Choanal stenosis	0.08 (3)
Axial/trunk	**3.7 (135)***
Vertebral anomalies	0.33 (12)
Scoliosis	0.38 (14)
Sacrococcygeal teratoma	0.05 (2)
Hypoplastic/abnormal thorax	0.30 (11)
Rib anomalies	0.58 (21)
Sternal defects	0.69 (25)
Diaphragmatic hernia	0.55 (20)
Diaphragmatic eventrion	0.11 (4)
Limbs	**5.7 (205)***
Upper malformed/hypoplasia	1.14 (41)
Upper amelia (unilateral)	0.13 (5)
Upper meromelia (unilateral)	0.30 (11)
Lower malformed/hypoplasia	1.02 (37)
Lower amelia (unilateral)	0.19 (7)
Lower meromelia (unilateral)	0.22 (8)
Polydactyly	0.75 (27)
Syndactyly	0.52 (19)
Sirenomelia	0.05 (2)
Musculoskeletal	**6.2 (226)***
Arthrogryposis/amyoplasia	1.86 (67)
Hip dysplasia/dislocation	1.52 (55)
Club foot	1.33 (48)
Pectoral hypoplasia	0.33 (12)
Endocrine	**0.08 (3)**
Thyroid	0.02 (1)
Adrenal	0.02 (1)
Pituitary	0.02 (1)
Cardiovascular	**23.3 (841)***

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Table 4 (continued)

System/region	% (*n*)
ASD	7.61 (274)
VSD	4.25 (153)
PDA	7.06 (254)
Hypoplastic left heart	0.02 (1)
Transposition of great vessels	0.05 (2)
Common arterial truncus	0.05 (2)
Dextrocardia	0.08 (3)
Coarctation of the aorta	0.69 (25)
Ebstein anomaly	0.05 (2)
Tetralogy of Fallot	0.08 (3)
Ectopia cordis	0.30 (11)
Pulmonary	**3.7 (136)***
Lung hypoplasia	0.97 (35)
Tracheoesophageal fistula	0.25 (9)
Bronchopulmonary dysplasia	1.69 (61)
Peripheral pulmonary stenosis	0.72 (26)
Digestive-primary	**20.3 (730)***
Intestinal atresias	14.0 (506)
Meckel diverticulum	1.11 (40)
Biliary/gall bladder anomalies	0.41 (15)
Anal atresia	1.36 (49)
Enteric duplication	2.03 (73)
Cloaca exstrophy	0.36 (13)
Hirschsprung	0.08 (3)
Digestive-secondary	**6.2 (223)*‡**
Intestinal malrotation	1.80 (65)
Hepatosplenomegaly	1.19 (43)
Pyloric stenosis	0.50 (18)
Ladd's bands	0.41 (15)
Renal	**5.4 (196)***
Hydronephrosis	2.80 (101)
Renal agenesis	0.77 (28)
Cystic kidneys	0.61 (22)
Genitourinary	**9.0 (324)***
Cryptorchidism	4.86 (175)
Hypospadia	1.05 (38)
Ambiguous genitalia	1.14 (41)
Uterine/vaginal anomalies	0.25 (9)
Exstrophy of urinary bladder	0.58 (21)
Extraabdominal ectopic testis	0.08 (3)
Multiple-anomaly pattern	**4.5 (162)***
Amniotic band sequence	1.08 (39)
Limb-body wall complex	1.02 (37)
Prune belly	0.11 (4)
Situs inversus	0.08 (3)
OIES	0.11 (4)
Oromandibular limb hypoplasia	0.05 (2)
Pentalogy of Cantrell	0.11 (4)
Moebius syndrome	0.11 (4)
Poland syndrome	0.11 (4)
Hurler syndrome	0.02 (1)
Pena-Shokeir syndrome	0.02 (1)
Kallman syndrome	0.02 (1)
Chromosomal defects	**3.2 (116)***
Trisomy 18	0.97 (35)
Trisomy 13	0.83 (30)
Trisomy 21	0.27 (10)
Triploidy	0.13 (5)
45,X0	0.05 (2)
47,XXY	0.02 (1)
Monosomy 22 mosaicism	0.02 (1)
Trisomy 16	0.02 (1)
inv(5)(q33.3-q35.3)	0.02 (1)
inv(9)	0.02 (1)
Miscellaneous	**3.1 (115)***
Cystic hygroma	1.33 (48)
Hemangioma	0.94 (34)

Total associated anomalies 3596 for gastroschisis; totals for each category are bolded

*Frequencies may not add to total due to non-specific data or described as a system/region affected

†Facial minor include: eyes widely spaced, deep-set eyes, epicanthal folds, low-set or posteriorly rotated ears, ear with tag-dimple-crease, nasal bridge depressed or broad, anteverted nares, small or beaked nose, high palate, flat or long philtrum, down-turned corners of mouth, micrognathia

‡Anomalies not included in the totals

variations have been proposed [3–5], clinical scenarios in the present study are comparable to the proportion previously reported from population-based studies (e.g., gastroschisis-amyoplasia association) including the fact that no definitive pattern of malformations emerged [34, 37, 38, 40, 56].

We have showed that those critical regions with genes on 18q21.33 (*SERPINB2, B3, B4, B5, B7, B11, B12*, and *B13*), 18q22.1 (*CDH7* and *CDH19*), 13q12.3 (*FLT1*), 13q22.1 (*KLF5*), 13q22.3 (*EDNRB*), 13q34 (*COL4A1, COL4A2, F7*, and *F10*), 21q22.11 (*KRTAP6-1, 6-3, 8-1, 11-1, 13-1, 13-2, 13-3, 13-4, 15-1, 19-1, 19-3, 19-7, 19-8, 21-2, 21-3, 23-1, 24-1, 25-1, 26-1*, and *27-1*), and 21q22.3 (*KRTAP10-1, 10-2, 10-3, 10-4, 10-5, 10-6, 10-7, 10-8, 10-9, 10-10, 10-11, 10-12, 12-1, 12-2*, and *12-4*) could be potential candidates for future studies. Even though we were able to find possible candidate regions from the most representative chromosomal syndromes associated with gastroschisis, it is not clear whether those genes are causing directly the defect or contain regulatory elements for different regions on the investigated chromosomal influences or on other chromosomes (e.g., long distance regulation or chromosomal heterogeneity). However, the genes identified from critical

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Table 5 Selected sociodemographic and clinical characteristics of gastroschisis cases stratified by isolated and associated anomalies in the included studies

Variables	Gastroschisis cases ($n = 18{,}525$)		OR	*P* value
	Associated anomalies ($n = 3323$) % (n)	Without associated anomalies ($n = 15{,}202$) % (n)		
Male	49.9 (1661)	30.2 (4598)	2.15	< 0.00001
Female	37.9 (1262)	31.8 (4848)	1.30	< 0.00001
American Indian[a]	79.3 (2636)	70.6 (10,733)	1.59	< 0.00001
Caucasian[b]	19.5 (651)	29.1 (4433)	0.59	< 0.00001
Prenatally diagnosed	12.6 (421)	10.3 (1574)	1.25	0.0001
Chromosomal defects	2.5 (85)	0.07 (11)	36.25	< 0.00001
Mortality	19.8 (660)	2.2 (342)	10.76	< 0.00001

Frequencies may not add to total due to missing or non-specific data

[a]Studies may involve cases of gastroschisis among Black/African American or Hawaiian/Pacific Islander or Hispanic races

[b]Studies may involve cases of gastroschisis among Black or White races

regions in the present study have been linked to disorders such essential hypertension, diabetes, cardiovascular and cerebrovascular disease, thromboembolism, Hirschsprung disease, palmoplantar keratosis, and a variety of cancers [79–85]. The aforementioned highlights several physiological processes such as blood pressure regulation and/or vessel integrity, angiogenesis, coagulation, cell–cell and/or cell-matrix adhesion, dermis integrity, and wound healing, and intervene in biologic mechanisms by which a genetic predisposition within these pathogenetic grouping might be associated with gastroschisis.

We observed local gene clusters in several chromosomal regions with a significance judged at *P* values < 0.05 in all cases. In this context, gene clusters identified on chromosome 21q22.11 and 21q22.3 (*KAP*/*KRTAP*, keratin-associated protein genes) are involved in major biological processes such as developmental biology and keratinization. *KAP* and subfamily *KRTAP* gene products presumably play a significant role in epidermal and follicular keratinocyte differentiation by inducing alignment and lateral crosslinking of keratin intermediate filaments [86, 87]. Experimental transgenic animal models (LZ-GC13/GC13 mutant mice) have shown that *Hoxc13* in GC13 mutant skin is overexpressed in differentiating epidermal and follicular keratinocytes, regions known to be hair-specific keratin genes such as *KAP*/*KRTAP*-encoding genes, and resulting in alopecia and a skin phenotype that resembles ichthyosis [88, 89]. Of note, *Hox* genes harbor several transcription factors and signaling molecules whose products act as master switches in development as well as cytodifferentiation, correlating with our findings in the proposed critical regions and genes.

Gene clusters identified on chromosome 18q21.33 (*SERPINB*, Serpin clade B genes) are involved in the negative regulation of endopeptidase activity biological process, with significant roles on epidermal barrier hemostasis, mucous production (mainly expressed in epithelial tissues) and inflammation/immune system function [79]. In line with this, *SERPINB2* is involved in physiological processes such as hemostasis, fibrinolysis, and wound healing. Experiments on human neonatal keratinocyte cultures have indicated that PAI-2 (plasminogen activator inhibitor 2, *SERPINB2*) has an intracellular function related to keratinocyte terminal differentiation and formation of the cornified envelope [90]. *SERPINB3*/*B4* are involved in physiological processes related to regulation of proteolysis, cell migration, and proliferation. Recently, *Serpinb3a* deficiency in an experimental murine model of atopic dermatitis has elucidated an attenuation of epidermal barrier dysfunction/disruption including an early inflammatory response, supporting a role for *SERPINB3*/*B4* in the initiation of acute inflammatory response and barrier function in the epidermis [91, 92]. *SERPINB5*/*B7* are involved in physiological processes such as extracellular matrix organization, regulation of epithelial cell proliferation, platelet-derived growth factor production, and collagen biosynthetic process. Maspin (*SERPINB5)* is widespread through several organs in which it localizes to epithelia, specifically, associated with secretory vesicles and present at the cell surface. Experiments on cultured mammary epithelial cells have shown that this protein mediates and/or regulates motility, proliferation, and cell adhesion of these cells [93, 94], whereas loss-of-function mutations in *SERPINB7* (present in the cytoplasm of the stratum granulosum and corneum of the epidermis) cause Nagashima-type palmoplantar keratosis [80]. *SERPINB11*/*B12*/*B13* are involved in physiological processes related to regulation of proteolysis and keratinocyte differentiation. These intracellular serine protease inhibitors have shown a critical role in barrier function by providing protection to epithelial cells and blocking the invasion, migration, and tube formation of endothelial cells, including a reduced angiogenic capacity mediated by interleukin 8 and vascular endothelial growth factor (VEGF) on experimental murine models [95, 96].

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Gene clusters identified on chromosome 18q22.1 (*CDH7* and *CDH19*, type II cadherins) are transmembrane proteins that mediate calcium-dependent adhesive interactions through homophilic interactions by their extracellular domains and hence, classical cell–cell adhesion molecules. Overexpression of cadherin-7 contributes to early delamination of neural crest cells from neuroepithelial cells of chicken embryos (especially for melanocyte precursors), whereas cell lines from primary melanomas resulted in delamination of these cells from keratinocytes suggesting that cadherin-7 play a role in tumor development of melanoma [81, 97]. Furthermore, three candidate genes (*CDH7, CDH19*, and *ZNF407*) were identified at chromosome 18q22.1–18q22.3 by employing multipoint linkage analysis in a Pakistani consanguineous family who exhibited anomalies of the hair, nails, and teeth, resembling ectodermal dysplasia [98]; in addition, a maternally inherited deletion of 2.7 Mb in size at chromosome 18q22.1 involving the genes *CDH19, DSEL, TXNDC10*, and *CCDC102B* has been associated with a late-presenting, right-sided diaphragmatic hernia and microphthalmia in a single patient [99]. Such influences recall the possible role of genes related to neural crest cell development enhanced by cardiovascular and digestive anomalies in the pathogenesis of Fryns syndrome [100, 101] as were observed in our analysis.

On the other hand, identification of *FLT1* on chromosome 13q12.3 and *KLF5* on chromosome 13q22.1 is involved in biological processes such as vascular endothelial growth factor receptor-1 (VEGFR-1) signaling pathway and cell–cell signaling via exosome, respectively. Such genes are also related to essential physiological processes including angiogenesis, cell migration and differentiation, and embryonic morphogenesis. In this context, experiments on human microvascular endothelial cells from neonatal dermis have shown that hypoxia down-regulates soluble *Flt-1* expression increasing VEGF in these cells and contributing to hypoxia-induced angiogenesis [102]; additionally, expression of VEGFR-1 was detected in murine keratinocytes during wound repair and in normal human epidermal keratinocytes, alternatively, by neutralizing VEGFR-1 antibodies delayed re-epithelialization suggesting that VEGF play a critical role in cutaneous wound repair [103]. Moreover, knockout of *Klf5* was downregulated during an epithelial-mesenchymal transition model (transforming growth factor and epidermal growth factor-treated epithelial cells) indicating that *Klf5* maintains epithelial morphology in mouse prostates even in the absence of the aforementioned growth factors [104]. Regarding chromosome 13q22.3, *EDNRB* was identified to be involved in endothelin receptor signaling pathway, such gene is also related to regulation of blood pressure, epithelial cell proliferation, and neural crest cell migration. Recent experiments on *EdnrB* knockout mice have shown a significant improvement in brain, heart, and kidney tissue perfusion under various levels of hypoxia suggesting that *EDNRB* plays a crucial role in hypoxia tolerance [105], whereas an increased expression of ET-1 along with ET_AR and ET_BR is associated with increased VEGF and higher vascularity of breast carcinoma [82]. Interestingly, the T-allele of the 561C/T polymorphism in *EDNRB* has been identified in patients with Hirschsprung disease and co-existing Down syndrome [83]. Taken together, these data raise the possibility of an aberrant neural crest cell migration, however, it is clear that neural crest involvement may be one of many factors in the pathogenesis of gastroschisis. In this sense, it must be noted that *Klf5* and *Flt-1* regulated interactions between human umbilical vein endothelial cells and VEGF indicating a deficient angiogenesis after *Klf5* knockout and *Flt-1* mutants whereas endothelin receptor type B appears to have a significant contraction in the human umbilical vessels [84, 106, 107].

Gene clusters identified on chromosome 13q34 (*COL4A1, COL4A2*, and *F7, F10*) are involved in biological processes such as collagen-activated tyrosine kinase receptor signaling pathway and blood coagulation, respectively. Such genes are also related to physiological processes including angiogenesis, extracellular matrix organization, and epithelial/endodermal cell migration and differentiation. *COL4A1* and *COL4A2* heterotrimers are a major structural element of all basement membranes and their mutations are pleiotropic with consequences on several syndromic and non-syndromic phenotypes [85]. Experimental models in type IV collagens have identified biologically active proteins (arresten, the 229 amino acid NC1 domain of *COL4A1* and canstatin, the 227 amino acid NC1 domain of *COL4A2*) with potent endogenous angiogenesis, anti-angiogenesis, and tumor growth characteristics [108, 109]. On the other hand, experimental studies on cell-surface proteases (Factor VIIa/tissue factor/factorXa) support the evidence of physiological cell growth, chemotaxis, blood coagulation, and fibrinolysis triggered by trauma or vascular injury, in which epidermal growth factor domains are critical for the formation of this complex [110, 111]. Yet, radiolabeled factor VIIa binding in non-stimulated human umbilical vein endothelial cells was specific and independent of tissue factor [112].

Overall, the gene clusters identified on chromosome 13q12.3, 13q22.1, 13q22.3, and 13q34 highlights the hypothesis that gastroschisis may have an underlying pathogenesis with a vascular disruption or thrombosis [16, 113, 114] associated with genes related to blood pressure regulation and/or vessel integrity, angiogenesis, coagulation, dermis integrity, and wound healing. While those on chromosome 21q22.11, 21q22.3, 18q21.33, and 18q22.1 with a mesodermal deficiency [115] associated with genes related to cell–cell and/or cell-matrix adhesion (balance of cell–cell and cell-matrix adhesion interaction) as well as dermis integrity and wound healing. Accordingly, our results

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support the hypothesis that single candidate critical regions/genes are likely to be responsible for the defect in an additive manner, in contrast, a unique critical region/gene for gastroschisis seems unlikely to exist. Indeed, our findings suggest that this phenotype may result from the interaction of several chromosomal regions (chromosomal heterogeneity).

The present study has considerable strengths, mainly, the size and breadth of the sample. Our analysis of associated anomalies and chromosomal defects in gastroschisis is the largest one so far, including 18,525 gastroschisis cases as a base, and comprising a systematic approach on the worldwide population-based reported data over the course of six decades (1950–2018). Thereby, providing a more representative basis on associated anomalies and chromosomal defects as well as novel candidate critical regions/genes for gastroschisis. However, interpretation of our findings should consider several limitations. The most considerable issue was the non-uniform definition of associated anomalies whereas case ascertainment and classification from retrospective registries may also affect our findings. Although we found many differences in the characteristics and designs between reviewed studies (which partly explains the wide variety of associated anomalies, Table 4), pooled clinical scenarios were comparable to the proportion from previous studies [34, 37, 38, 40, 56]. The latter stress the need of an accurate categorization in associated cases given that in both secondary and primary concurrent anomalies the role of other genetic or environmental causative factors may be in play, as were observed in our analysis. As an approximation to this, when considering the attribution of sex or race among the gene clusters identified in the present study, epidemiological, heritability, and genetic susceptibility among American Indian race, particularly Hispanic population, has an increased risk of gastroschisis [2, 6–8]. Unfortunately, scant genetic studies of gastroschisis among these populations are available, which limits our ability to explore the gene-gastroschisis association by race; nevertheless, further investigations on this topic are warranted. On the other hand, as the proportion of gastroschisis is rising worldwide previous prenatal studies may not have provided representative samples of current prenatal gastroschisis, notwithstanding that some prenatal cases experienced termination of pregnancy. In line with this, the reviewed studies also varied considerably in their cytogenetic data (Tables 1, 2, 3). Even though most studies provided extensive information regarding their associated anomalies, in about half of them, lacking cytogenetic analysis was identified or did not give any specific data at all. As consequence, rates on chromosomal defects could not always be completed and explains why a predominant proportion of chromosomal defects were associated with additional anomalies (Table 5). It should be noted that in the majority of these studies, cytogenetic results were not obtained in all gastroschisis cases and hence, the inclusion of cases with undetected chromosomal defects cannot be ruled out. Moreover, an overwhelming proportion of studies were lacking further cytogenetic and molecular techniques. In this regard, our methodological design gave us a unique perspective to identify novel features regarding candidate critical regions/genes for gastroschisis emphasizing several underlying biological processes, which allow us to provide further insights into the pathogenesis of gastroschisis.

Conclusion

In brief, cardiovascular and digestive malformations are common associated anomalies in gastroschisis and should be particularly sought among prenatally diagnosed patients. Detailed follow-up studies are needed to gain more insight into associated cases and singularly among chromosomal defects identified after birth, which could aid in a more optimal counseling and timely treatment of affected children. We observed evidence for putative critical regions/genes related to blood pressure regulation and/or vessel integrity, angiogenesis, coagulation, cell–cell and/or cell-matrix adhesion, dermis integrity, and wound healing, which support a significant role of vascular disruption, thrombosis, and mesodermal deficiency in the pathogenesis of gastroschisis. In addition, this study provides tools and insights for further analysis of biological process and identifies a pool of candidate genes for gastroschisis, which suggests that this phenotype may result from the interaction of several chromosomal regions (chromosomal heterogeneity). The continued study of this knowledge along with the investigation using next generation or microarray technologies (SNP-arrays and array-CGH) will help clarify our findings. Finally, given the bewildering origin of gastroschisis, the elucidation of genes/regulatory proteins will be a major challenge in the near future, but further research, particularly from familial recurrences, may broaden our understanding of ventral wall development and ultimately, gastroschisis.

Compliance with ethical standards

Conflict of interest The authors declared no potential conflicts of interest and received no financial support with respect to the research, authorship, and/or publication of this article.

Ethical approval and informed consent This article does not contain any studies with human participants or animals performed by any of the authors and did not require formal ethical approval, similarly, no form of informed consent was required.

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