Familial Cancer (2015) 14:89–94
DOI 10.1007/s10689-014-9764-x

SHORT COMMUNICATION

Gastric cancer in three relatives of a patient with a biallelic *IL12RB1* mutation

Ingrid P. Vogelaar · Rachel S. van der Post · Esther van de Vosse · J. Han J. M. van Krieken · Nicoline Hoogerbrugge · Marjolijn J. L. Ligtenberg · Encarna Gómez García

Published online: 3 December 2014

Abstract IL-12Rβ1 deficiency, also known as immunodeficiency 30 (IMD30, OMIM 614891), is a rare immunodeficiency syndrome caused by biallelic mutations in *IL12RB1*. Three second-degree relatives of a patient with this syndrome, all women, developed intestinal-type gastric cancer (GC). In the Netherlands the incidence of non-cardia GC in women is only 7 per 100,000 person years. Both relatives that were available for testing proved to be heterozygous for the familial *IL12RB1* mutation, suggesting there might be a causal relation. Testing 29 index patients from families with early onset and/or a familial history of GC for germline mutations in both *IL12RB1* and *IL12RB2,* that encodes the binding partner of IL-12Rβ1, did not reveal other germline mutations in these genes. Therefore heterozygous inactivating mutations in *IL12RB1* and *IL12RB2* are unlikely to be frequently involved in GC predisposition. Additional research in families with *IL12RB1* mutations is required to determine whether carriers of *IL12RB1* mutations have an increased (gastric) cancer risk.

Keywords Gastric cancer · Interleukin-12 receptor · Genetics · *Salmonella* infections · *Mycobacterium* infections

Introduction

IL-12Rβ1 deficiency, also known as immunodeficiency 30 (IMD30, OMIM 614891), is an autosomal recessive disorder caused by biallelic mutations in *IL12RB1*. To date, 156 patients have been described [1, 2]. Interleukin-12 (IL-12) plays an important role in the interaction between the innate and adaptive immunity. Phagocytic cells and dendritic cells produce this cytokine after an encounter with pathogens. IL-12 is involved in the cytotoxic activities of T cells and NK cells and is important for the production of cytokines, especially interferon (IFN) gamma [3, 4]. The receptor for IL-12 on NK- and T-cells is composed of two chains, IL-12 receptor beta-1 (IL-12Rβ1) and IL-12 receptor beta-2 (IL-12Rβ2). IL-12Rβ1 is primarily responsible for binding, while IL-12Rβ2 is essential for signaling through the JAK–STAT pathway [5, 6]. Patients with biallelic inactivation of IL-12Rβ1 are extremely susceptible to severe infections caused by otherwise poorly pathogenic mycobacteria (non-tuberculous mycobacteria or *Mycobacterium bovis* BCG) and *Salmonella* spp. [7, 8].

Three relatives of a patient with IL-12Rβ1 deficiency, caused by a homozygous truncating mutation in *IL12RB1* [8], developed gastric cancer (GC). In the Netherlands, the incidence of non-cardia GC is only 14 per 100,000 person years for men and 7 per 100,000 person years for women [9]. In its early stages GC is often asymptomatic or causes

I. P. Vogelaar · N. Hoogerbrugge · M. J. L. Ligtenberg
Department of Human Genetics, Radboud university medical center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands
e-mail: ingrid.vogelaar@radboudumc.nl

R. S. van der Post · J. H. J. M. van Krieken · M. J. L. Ligtenberg
Department of Pathology, Radboud university medical center, Nijmegen, The Netherlands

E. van de Vosse
Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands

E. Gómez García (✉)
Department of Clinical Genetics, Maastricht University Medical Center, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands
e-mail: encarna.gomezgarcia@mumc.nl

only nonspecific symptoms. By the time symptoms occur, the cancer has often reached an advanced stage, which is one of the main reasons for the low average 5-year survival [9].

According to the Laurén classification, GC can be roughly divided into three histopathological types; diffuse, intestinal and mixed/indeterminate type [10]. Another commonly used classification of GC is the classification of the World Health Organization (WHO), that recognizes five main types of GC, namely tubular, papillary, mucinous, poorly cohesive (including signet-ring cell type) and mixed carcinomas [11]. Gastric cancer is a multifactorial disease, both genetic alterations and environmental factors play a role in GC development. The main environmental factor involved is infection with *Helicobacter pylori* (*H. pylori*) and this pathogen has been recognised as a carcinogen by the WHO in 1994 [12, 13].

Familial aggregation of GC is estimated to occur in 8–30 % of the patients [14–16]. The most important GC susceptibility gene is *CDH1*, which accounts for 1–3 % of all GC [17]. *CDH1*-associated GC is mainly of the diffuse-type. The criteria to test patients/families with GC for mutations in this gene include: (1) 2 or more GC cases in family, one DGC <50 years; (2) 3 or more DGC cases in 1st- or 2nd- degree relatives, regardless of age; (3) DGC <40 years and (4) personal or family history of DGC and lobular breast cancer, one diagnosed <50 years [18]. *CDH1* mutations have been encountered in up to 50 % of strictly selected families [19–21]. The remaining families are still genetically unexplained and may carry mutations in other, still to be identified, GC susceptibility genes.

To date, there is no literature on subjects with heterozygous and/or homozygous mutations in *IL12RB1* and *IL12RB2* and gastric cancer. A few studies have been reported about mutations in these genes in esophageal cancer. Cardenes et al. reported a subject with a homozygous splice site mutation in *IL12RB1* who developed esophageal squamous cell carcinoma at the age of 25, which is extremely young for this type of cancer. Therefore, the authors speculate on the possible role of a defective IL-12Rβ1 protein underlying this malignancy [22]. This case is also mentioned in an extensive study of 141 patients with IL-12Rβ1 deficiency, in which this patient is the only patient who developed cancer. However, it is unclear whether systematic analysis for the occurrence of tumors was performed [2, 22]. Tao et al. [23] also reported an association between *IL12RB1* and esophageal cancer. In their study, they found that the CC genotype of a single nucleotide polymorphism (SNP) in *IL12RB1* (rs401502, indicated in the article as 378 C/G) was associated with increased IL-12p40 levels and protection from esophageal cancer susceptibility. Airoldi et al. [24] describe the consequence of lack of Il-12 signaling in mice, they observed that *Il12rb2* homozygous knock-out mice are prone to develop tumors of the lung epithelia.

Table 1 Characteristics of patients screened for mutations in *IL12RB1* and *IL12RB2*

Number of patients	29
Mean age at diagnosis (SD)	54.2 (16.4)
Gastric cancer classification according to WHO[a]	
Tubular	8
Poorly cohesive (incl. signet-ring cell carcinoma)	16
Mixed histology	1
No histology available	4
Tumor classification according to Laurén[b]	
Intestinal type	8
Diffuse	16
Mixed	1
No histology available	4
Helicobacter pylori in pathology specimen	
Yes	5
No	20
Unknown	4
Chronic gastritis	
Yes	15
No	9
Unknown	5
Helicobacter pylori infection in medical history	
Yes	1
No	0
Unknown	28
Family history of gastric cancer	
Yes	21
No	4
Unknown	4

SD standard deviation

[a] Bosman et al. [11]

[b] Lauren [10]

To determine whether *IL12RB1* and *IL12RB2* can be considered candidate genes for GC susceptibility, we analyzed whether the GC patients in the family with IL-12Rβ1 deficiency were carriers of this mutation and tested 29 GC patients that were suspected for a genetic predisposition based on their personal and/or familial GC history for germline mutations in these genes.

Materials and methods

Patient samples

DNA was isolated from peripheral blood samples and formalin-fixed paraffin-embedded tumor material of two

GC patients from the family with IL-12Rβ1 deficiency to test for the familial mutation at the department of Infectious Diseases of the Leiden University Medical Center, Leiden, the Netherlands.

For mutation analysis of *IL12RB1* and *IL12RB2*, DNA was isolated from peripheral blood samples from GC patients who were tested negative for *CDH1* mutations at the department of Human Genetics of the Radboud university medical center, Nijmegen after genetic counseling at the Radboud university medical center or the Maastricht University Medical Center, Maastricht, both in the Netherlands. Because of the relatively high age of the GC patients in the *IL12RB1* family, no further selection was made based on age and/or family history. Patient characteristics, including *H. pylori* status, can be found in Table 1.

LOH analysis by pyrosequencing

To isolate DNA from formalin-fixed paraffin-embedded tissue, thin sections were treated by initial xylol extraction to remove paraffin. The extracted tissue was incubated overnight at 37 °C in 600 µl nuclei lysis solution (Promega) supplemented with 400 µg pronase, followed by addition of protein precipitation solution (Promega), incubation for 5 min on ice, and centrifugation to remove proteins. Supernatant was incubated on ice with an equal volume of isopropanol to precipitate the DNA, the pellet was dissolved in TE and further purified with a QIAquick gel extraction kit (Qiagen). PCR and pyrosequencing was essentially performed according to the protocol described previously [25], primers used for the PCR are ps-F: 5′-CTCCCCTCTCCTTCCAGAAC and ps-R: biotine labeled 5′-TTCCAGGCCATTACCCATT. Pyrosequencing primer ps-seq: 5′-TGGCSGCCTGTGGT.

Mutation analysis of *IL12RB1* and *IL12RB2*

The full coding sequence of *IL12RB1* (transcript numbers NM_005535.1 and NM_153701.1) and *IL12RB2* (transcript number NM_001559.2) including splice junctions was amplified using polymerase chain reaction (PCR) and screened for mutations using Big-Dye terminator sequencing (BigDye Terminators (v 1.1) Applied Biosystems, USA) and analysis on an ABI 3730 DNA Analyzer (Applied Biosystems). Subsequently, data was analyzed for variants using the Sequence Pilot software (JSI Medical Systems, Germany).

Missense variants were analyzed using the Alamut 2.0 software package (Interactive Biosoftware, Rouen, France), which incorporates SIFT [26], PolyPhen-2 [27], Align GVGD [28] and dbSNP (build 135). We used the Exome Variant Server of the University of Washington [29], which contains sequencing data of approximately 6,500 individuals of European and African descent, and the database of the GoNL project [30] to assess whether variants were present in individuals without GC.

Results

Gastric cancer patients from the family with the truncating mutation in *IL12RB1*

A 73-year old patient (patient A), recently diagnosed with GC, was referred because of a family history of GC. One of her sisters had been diagnosed with GC at age 72 (patient B) and their mother had died of GC at age 70. Her 62-year old sister was healthy and had a medical history of a few rectal polyps (three tubular adenomas with low grade dysplasia and two hyperplastic). Her niece (daughter of the 62-year old sister) was known to have a biallelic mutation (c.1126C>T, p.(Q376*)) in *IL12RB1*, inducing a rare inheritable immune disorder (described as Patient 2 in the paper by De Jong et al. [8]). The pedigree of this family is shown in Fig. 1. No information is available for the fathers' family of the niece with the immune disorder. Germline *CDH1* mutation analysis of the index patient as well as analysis of her tumor for microsatellite instability were negative.

To elucidate whether an *IL12RB1* mutation could underlie the pathogenesis of GC in this family, we tested both sisters that developed GC. Both were heterozygous for the *IL12RB1* mutation. No material from their mother was available for testing.

Histopathological characteristics of gastric tumors

Material of both sisters with GC was available for histological re-evaluation. In the total gastrectomy specimen of the patient A an ulcerating tumor in the gastric body was seen with a diameter of 5.4 cm. The tumor invaded the subserosal tissue and was staged as pT3N0. Review showed a poorly differentiated intestinal-type adenocarcinoma. The surrounding mucosa showed extensive intestinal metaplasia and chronic active gastritis. No quantitative difference indicating loss of the wild type *IL12RB1* allele was observed in the tumor by quantitative analysis of both alleles by pyrosequencing from blood as well as normal and tumor tissue sections (data not shown). Her sister had a 12 cm large polypoid tumor with central ulceration in the transitional zone of the stomach. Review of the histology showed an intestinal-type adenocarcinoma, poorly differentiated with focally a few poorly formed glands. According to the seventh edition of the TNM classification the tumor is staged as pT4aN3a. The surrounding mucosa

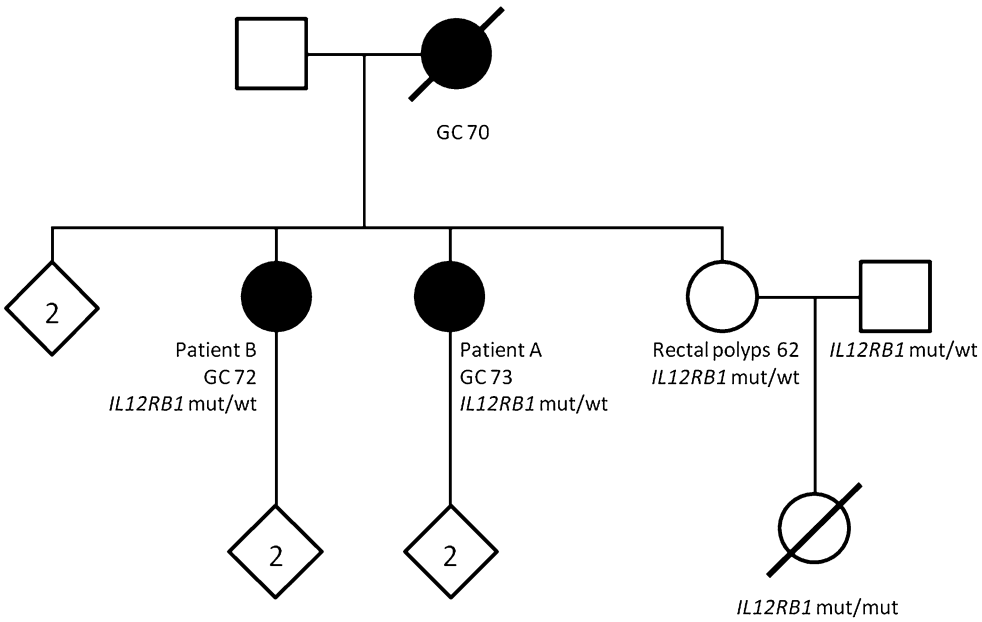

Fig. 1 Pedigree of the family with an IL-12Rβ1 deficiency and gastric cancer

Table 2 Rare variants of unknown significance identified in *IL12RB1* and *IL12RB2*

Gene	Variant identified	Grantham score	SIFT prediction	PolyPhen score	Align GVGD score	Putative splicing effect?	dbSNP id (minor allele frequency in %)	Minor allele frequency in ESP database (%)	Frequency in The Netherlands
IL12RB1	c.102G>A (p.(=))	NA	NA	NA	NA	No	rs146978336 (T = 0.8)	EA T = 1.2	15/990
IL12RB1	c.848G>A (p.(Arg283Gln))	43	Tolerated	Benign	Class C0	No	rs117511121 (T = 0.6)	EA T = 0.8	7/996
IL12RB1	c.1161G>A (p.(=))	NA	NA	NA	NA	No	rs144192488 (unknown)	EA T = 0.0	0/∼996
IL12RB1	c.1619-6C>T (p.(?))	NA	NA	NA	NA	No	–	–	1/996

EA European American allele frequency in EVS database, *NA* not applicable

showed intestinal metaplasia and chronic atrophic inflammation. Loss of heterozygosity analysis could not be performed due to insufficient quality of the material. *Helicobacter pylori* was not identified in the resection specimens of both patients.

Mutation analysis of *IL12RB1* and *IL12RB2* in 29 patients with gastric cancer

Twenty-nine patients with GC, that were suspected for genetic predisposition, were screened for mutations in the two genes encoding the IL-12 receptor chains, *IL12RB1* and *IL12RB2*. The histological characteristics of GC patients in our cohort, including *H. pylori* status, are shown in Table 1. Several common polymorphisms in both genes (data not shown) and four rare heterozygous variants of unknown significance (VUS) in *IL12RB1* were identified (c.102G>A, c.848G>A, c.1161G>A, c.1619-6C>T), but none of them appear to be pathogenic according to various in silico prediction programs (Table 2). The variants were all identified only once and in different patients. We conclude that no clear deleterious mutations were found.

Discussion

In the current study we describe cosegregation of a heterozygous germline defect in *IL12RB1* and GC development in a family with IL-12Rβ1 deficiency. This heterozygosity might lead to impaired response of T- and NK-cells to pathogens that increase the risk of GC development. Therefore the gene would not act as a tumor suppressor gene for which loss of the wild-type allele would drive tumorigenesis. Indeed, the wild-type allele was still present in the tumor of one of the patients.

The truncating mutation found in the family, (c.1126C>T, p.(Q376*)), probably does not render a stable protein. However, if a stable truncated protein would be formed, part of the FNIII extracellular domains, which are necessary for the IL-12Rβ1-IL-12Rβ2 dimerization would be missing, as well as the transmembrane domain required for expression of the protein on the cell surface [31]. Although IL-12 can bind with low affinity to IL-12Rβ1 and IL-12Rβ2 separately, presence of a heterodimer is necessary for high affinity binding [31].

To determine whether germline mutations in the IL-12 receptor chains are a common event in GC patients, we sequenced these genes in a cohort of GC patients who were suspected for genetic predisposition. Although we identified several rare heterozygous variants in *IL12RB1*, none appeared to be deleterious using in silico prediction programs. The variants we identified were found in patients with both intestinal-type (n = 2) and diffuse-type GC (n = 1) according to the Laurén classification. For one patient in whom we detected a variant the histological subtype is unknown. One of these variants, c.848G>A, results in an amino acid substitution of an arginine to a glutamine in the FNIII domain of the IL-12Rβ1 protein. This is the domain required for IL-12Rβ1-IL-12Rβ2 dimerization. Although this substitution is predicted not to affect the function of the protein only experimental evidence, such as obtained with *IL12RB1* expression constructs [32], can determine whether this is indeed the case.

The results of our study suggest that germline mutations in *IL12RB1* and *IL12RB2* do not play a frequent role in GC predisposition. However, in contrast to the two heterozygous carriers with GC of the index family, the majority of patients in our cohort have been diagnosed with diffuse-type GC and therefore mutations in *IL12RB1* and *IL12RB2* may still play a more prominent role in intestinal-type GC predisposition.

Taken together, we found a heterozygous *IL12RB1* mutation to segregate with intestinal-type GC in one family. No additional mutations were found in 29 families with GC. Since only little is known about cancer risks in families with *IL12RB1* mutations, the observation in the current study may warrant additional research in other families with this deficiency to determine whether they are at increased risk for developing (gastric) cancer.

Acknowledgments The authors would like to thank Heleen Diepstra for excellent assistance with the data analysis.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ouederni M, Sanal O, Ikinciogullari A, Tezcan I, Dogu F, Sologuren I, Pedraza-Sanchez S, Keser M, Tanir G, Nieuwhof C, Colino E, Kumararatne D, Levy J, Kutukculer N, Aytekin C, Herrera-Ramos E, Bhatti M, Karaca N, Barbouche R, Broides A, Goudouris E, Franco JL, Parvaneh N, Reisli I, Strickler A, Shcherbina A, Somer A, Segal A, Angel-Moreno A, Lezana-Fernandez JL, Bejaoui M, Bobadilla-Del Valle M, Kachboura S, Sentongo T, Ben-Mustapha I, Bustamante J, Picard C, Puel A, Boisson-Dupuis S, Abel L, Casanova JL, Rodriguez-Gallego C (2014) Clinical features of candidiasis in patients with inherited interleukin 12 receptor beta1 deficiency. Clin Infect Dis 58(2):204–213. doi:10.1093/cid/cit722
2. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, Al-Muhsen S, Janniere L, Rose Y, de Suremain M, Kong XF, Filipe-Santos O, Chapgier A, Picard C, Fischer A, Dogu F, Ikinciogullari A, Tanir G, Al-Hajjar S, Al-Jumaah S, Frayha HH, AlSum Z, Al-Ajaji S, Alangari A, Al-Ghonaium A, Adimi P, Mansouri D, Ben-Mustapha I, Yancoski J, Garty BZ, Rodriguez-Gallego C, Caragol I, Kutukculer N, Kumararatne DS, Patel S, Doffinger R, Exley A, Jeppsson O, Reichenbach J, Nadal D, Boyko Y, Pietrucha B, Anderson S, Levin M, Schandene L, Schepers K, Efira A, Mascart F, Matsuoka M, Sakai T, Siegrist CA, Frecerova K, Bluetters-Sawatzki R, Bernhoft J, Freihorst J, Baumann U, Richter D, Haerynck F, De Baets F, Novelli V, Lammas D, Vermylen C, Tuerlinckx D, Nieuwhof C, Pac M, Haas WH, Muller-Fleckenstein I, Fleckenstein B, Levy J, Raj R, Cohen AC, Lewis DB, Holland SM, Yang KD, Wang X, Wang X, Jiang L, Yang X, Zhu C, Xie Y, Lee PP, Chan KW, Chen TX, Castro G, Natera I, Codoceo A, King A, Bezrodnik L, Di Giovani D, Gaillard MI, de Moraes-Vasconcelos D, Grumach AS, da Silva Duarte AJ, Aldana R, Espinosa-Rosales FJ, Bejaoui M, Bousfiha AA, Baghdadi JE, Ozbek N, Aksu G, Keser M, Somer A, Hatipoglu N, Aydogmus C, Asilsoy S, Camcioglu Y, Gulle S, Ozgur TT, Ozen M, Oleastro M, Bernasconi A, Mamishi S, Parvaneh N, Rosenzweig S, Barbouche R, Pedraza S, Lau YL, Ehlayel MS, Fieschi C, Abel L, Sanal O, Casanova JL (2010) Revisiting human IL-12Rbeta1 deficiency: a survey of 141 patients from 30 countries. Medicine 89(6):381–402. doi:10.1097/MD.0b013e3181fdd832
3. Colombo MP, Trinchieri G (2002) Interleukin-12 in anti-tumor immunity and immunotherapy. Cytokine Growth Factor Rev 13(2):155–168
4. Trinchieri G (1995) Interleukin-12: a proinflammatory cytokine with immunoregulatory functions that bridge innate resistance and antigen-specific adaptive immunity. Annu Rev Immunol 13:251–276. doi:10.1146/annurev.iy.13.040195.001343
5. Presky DH, Yang H, Minetti LJ, Chua AO, Nabavi N, Wu CY, Gately MK, Gubler U (1996) A functional interleukin 12 receptor complex is composed of two beta-type cytokine receptor subunits. Proc Natl Acad Sci USA 93(24):14002–14007
6. Trinchieri G (2003) Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nat Rev Immunol 3(2):133–146. doi:10.1038/nri1001
7. Altare F, Durandy A, Lammas D, Emile JF, Lamhamedi S, Le Deist F, Drysdale P, Jouanguy E, Doffinger R, Bernaudin F, Jeppsson O, Gollob JA, Meinl E, Segal AW, Fischer A, Kumararatne D, Casanova JL (1998) Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 280(5368):1432–1435
8. de Jong R, Altare F, Haagen IA, Elferink DG, Boer T, van Breda Vriesman PJ, Kabel PJ, Draaisma JM, van Dissel JT, Kroon FP, Casanova JL, Ottenhoff TH (1998) Severe mycobacterial and *Salmonella* infections in interleukin-12 receptor-deficient patients. Science 280(5368):1435–1438
9. Dassen AE, Dikken JL, Bosscha K, Wouters MW, Cats A, van de Velde CJ, Coebergh JW, Lemmens VE (2014) Gastric cancer: decreasing incidence but stable survival in the Netherlands. Acta Oncol 53(1):138–142. doi:10.3109/0284186X.2013.789139

10. Lauren P (1965) The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 64:31–49
11. Bosman FT, Carneiro F, Hruban RH, Theise ND (2010) WHO classification of tumours of the digestive system, 4th edn. IARC, Lyon, France
12. Infection with *Helicobacter pylori* (1994). IARC Monogr Eval Carcinog Risks Hum 61:177–240
13. Suerbaum S, Michetti P (2002) *Helicobacter pylori* infection. N Engl J Med 347(15):1175–1186. doi:10.1056/NEJMra020542
14. Bernini M, Barbi S, Roviello F, Scarpa A, Moore P, Pedrazzani C, Beghelli S, Marrelli D, de Manzoni G (2006) Family history of gastric cancer: a correlation between epidemiologic findings and clinical data. Gastric Cancer 9(1):9–13. doi:10.1007/s10120-005-0350-7
15. La Vecchia C, Negri E, Franceschi S, Gentile A (1992) Family history and the risk of stomach and colorectal cancer. Cancer 70(1):50–55
16. Roviello F, Corso G, Pedrazzani C, Marrelli D, De Falco G, Suriano G, Vindigni C, Berardi A, Garosi L, De Stefano A, Leoncini L, Seruca R, Pinto E (2007) High incidence of familial gastric cancer in Tuscany, a region in Italy. Oncology 72(3–4):243–247. doi:10.1159/000113015
17. Stone J, Bevan S, Cunningham D, Hill A, Rahman N, Peto J, Marossy A, Houlston RS (1999) Low frequency of germline E-cadherin mutations in familial and nonfamilial gastric cancer. Br J Cancer 79(11–12):1935–1937. doi:10.1038/sj.bjc.6690308
18. Fitzgerald RC, Hardwick R, Huntsman D, Carneiro F, Guilford P, Blair V, Chung DC, Norton J, Ragunath K, van Krieken JH, Dwerryhouse S, Caldas C (2010) Hereditary diffuse gastric cancer: updated consensus guidelines for clinical management and directions for future research. J Med Genet 47(7):436–444
19. Oliveira C, Seruca R, Carneiro F (2006) Genetics, pathology, and clinics of familial gastric cancer. Int J Surg Pathol 14(1):21–33
20. Kaurah P, MacMillan A, Boyd N, Senz J, De Luca A, Chun N, Suriano G, Zaor S, Van Manen L, Gilpin C, Nikkel S, Connolly-Wilson M, Weissman S, Rubinstein WS, Sebold C, Greenstein R, Stroop J, Yim D, Panzini B, McKinnon W, Greenblatt M, Wirtzfeld D, Fontaine D, Coit D, Yoon S, Chung D, Lauwers G, Pizzuti A, Vaccaro C, Redal MA, Oliveira C, Tischkowitz M, Olschwang S, Gallinger S, Lynch H, Green J, Ford J, Pharoah P, Fernandez B, Huntsman D (2007) Founder and recurrent CDH1 mutations in families with hereditary diffuse gastric cancer. JAMA 297(21):2360–2372. doi:10.1001/jama.297.21.2360
21. Oliveira C, Senz J, Kaurah P, Pinheiro H, Sanges R, Haegert A, Corso G, Schouten J, Fitzgerald R, Vogelsang H, Keller G, Dwerryhouse S, Grimmer D, Chin SF, Yang HK, Jackson CE, Seruca R, Roviello F, Stupka E, Caldas C, Huntsman D (2009) Germline CDH1 deletions in hereditary diffuse gastric cancer families. Hum Mol Genet 18(9):1545–1555. doi:10.1093/hmg/ddp046
22. Cardenes M, Angel-Moreno A, Fieschi C, Sologuren I, Colino E, Molines A, Garcia-Laorden MI, Campos-Herrero MI, Andujar-Sanchez M, Casanova JL, Rodriguez-Gallego C (2010) Oesophageal squamous cell carcinoma in a young adult with IL-12R beta 1 deficiency. J Med Genet 47(9):635–637. doi:10.1136/jmg.2009.071910
23. Tao YP, Wang WL, Li SY, Zhang J, Shi QZ, Zhao F, Zhao BS (2012) Associations between polymorphisms in IL-12A, IL-12B, IL-12Rbeta1, IL-27 gene and serum levels of IL-12p40, IL-27p28 with esophageal cancer. J Cancer Res Clin Oncol 138(11):1891–1900. doi:10.1007/s00432-012-1269-0
24. Airoldi I, Di Carlo E, Cocco C, Sorrentino C, Fais F, Cilli M, D'Antuono T, Colombo MP, Pistoia V (2005) Lack of Il12rb2 signaling predisposes to spontaneous autoimmunity and malignancy. Blood 106(12):3846–3853. doi:10.1182/blood-2005-05-2034
25. Roos A, Dieltjes P, Vossen RH, Daha MR, de Knijff P (2006) Detection of three single nucleotide polymorphisms in the gene encoding mannose-binding lectin in a single pyrosequencing reaction. J Immunol Methods 309(1–2):108–114. doi:10.1016/j.jim.2005.11.017
26. Kumar P, Henikoff S, Ng PC (2009) Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. Nat Protoc 4(7):1073–1082. doi:10.1038/nprot.2009.86
27. Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, Sunyaev SR (2010) A method and server for predicting damaging missense mutations. Nat Methods 7(4):248–249. doi:10.1038/nmeth0410-248
28. Tavtigian SV, Deffenbaugh AM, Yin L, Judkins T, Scholl T, Samollow PB, de Silva D, Zharkikh A, Thomas A (2006) Comprehensive statistical study of 452 BRCA1 missense substitutions with classification of eight recurrent substitutions as neutral. J Med Genet 43(4):295–305. doi:10.1136/jmg.2005.033878
29. Exome Variant Server, NHLBI Exome Sequencing Project (ESP), Seattle, WA. http://evs.gs.washington.edu/EVS/
30. GoNL database. http://www.nlgenome.nl/search/
31. van de Vosse E, Haverkamp MH, Ramirez-Alejo N, Martinez-Gallo M, Blancas-Galicia L, Metin A, Garty BZ, Sun-Tan C, Broides A, de Paus RA, Keskin O, Cagdas D, Tezcan I, Lopez-Ruzafa E, Arostegui JI, Levy J, Espinosa-Rosales FJ, Sanal O, Santos-Argumedo L, Casanova JL, Boisson-Dupuis S, van Dissel JT, Bustamante J (2013) IL-12Rbeta1 deficiency: mutation update and description of the IL12RB1 variation database. Hum Mutat 34(10):1329–1339. doi:10.1002/humu.22380
32. van de Vosse E, de Paus RA, van Dissel JT, Ottenhoff TH (2005) Molecular complementation of IL-12Rbeta1 deficiency reveals functional differences between IL-12Rbeta1 alleles including partial IL-12Rbeta1 deficiency. Hum Mol Genet 14(24):3847–3855. doi:10.1093/hmg/ddi409