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REVIEW ARTICLE

Mutational landscape of gastric adenocarcinoma in Latin America: A genetic approach for precision medicine

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Abstract Latin-America (LATAM) is the second region in gastric cancer incidence; gastric adenocarcinoma (GA) represents 95% of all cases. We provide a mutational landscape of GA highlighting a) germline pathogenic variants associated with hereditary GA, b) germline risk variants associated with sporadic GA, and c) somatic variants present in sporadic GA in LATAM, and analyze how this landscape can be applied for precision medicine. We found that Brazil, Chile, Colombia, Mexico, Peru, and Venezuela are the countries with more published studies from LATAM explicitly related to GA. Our analysis displayed that different germline pathogenic variants for the *CDH1* gene have been identified for hereditary GA in Brazilian, Chilean,

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Colombian, and Mexican populations. An increased risk of developing somatic GA is associated with the following germline risk variants: *IL-4*, *IL-8*, *TNF-α*, *PTGS2*, *NFKB1*, *RAF1*, *KRAS* and *MAPK1* in Brazilian; *IL-10* in Chilean; *IL-10* in Colombian; *EGFR* and *ERRB2* in Mexican, *TCF7L2* and Chr8q24 in Venezuelan population. The path from mutational landscape to precision medicine requires four development levels: 1) Data compilation, 2) Data analysis and integration, 3) Development and approval of clinical approaches, and 4) Population benefits. Generating local genomic information is the initial padlock to overcome to generate and apply precision medicine.

Introduction

Gastric cancer ranks fifth in cancer-related death, with a 5-year survival rate of less than 30% in Western countries.[1,2] Asia is the region with the highest gastric cancer incidence, followed by Latin America (LATAM) and Europe.[3] In LATAM, gastric cancer is in the sixth position in cancer incidence with Chile, Peru, Guatemala, Ecuador, and Costa Rica as the top five countries with the highest gastric cancer incidence and mortality rates.[4] Up to 95% of all cases of gastric cancer are diagnosed as gastric adenocarcinoma (GA), and poor dietary habits,[5,6] tobacco usage,[6,7] Epstein Barr virus infection,[8,9] and occupational exposure such as farming are the main risk factors[10–12] (Fig. 1A). GA is classified into diffuse, intestinal, and mixed type (Fig. 1B) including sporadic and hereditary cases (Fig. 1C).[13] *Helicobacter pylori* (*H. pylori*) infections[14] have been considered one of the leading causes of the high GA incidence in LATAM,[15,16] and 80% of GA cases are sporadic; the remaining cases are attributed to germline variants; however, the known germline pathogenic variants only explain 3% of these cases.[17] Clinical peculiarities of LATAM GA patients could result in unknown interactions between the environment and either germline risk or somatic variants. GA Ecuadorian patients living in high altitude conditions that have higher prevalence and mortality odds than those residing at low-lying regions[18]; Peruvians with strong Native American ancestry that have a higher risk of developing GA[19]; or Hispanics that have more likelihood to be diagnosed with non-cardia GA at a younger age and with diffuse histology than non-Hispanics Caucasians from the United States[20] are examples of the peculiarities which could be explained and probably prevented by elucidating genomic variants in LATAM populations. We aimed to analyze published studies highlighting germline pathogenic variants associated with hereditary GA, germline risk variants associated with sporadic GA, and somatic variants present in sporadic GA to

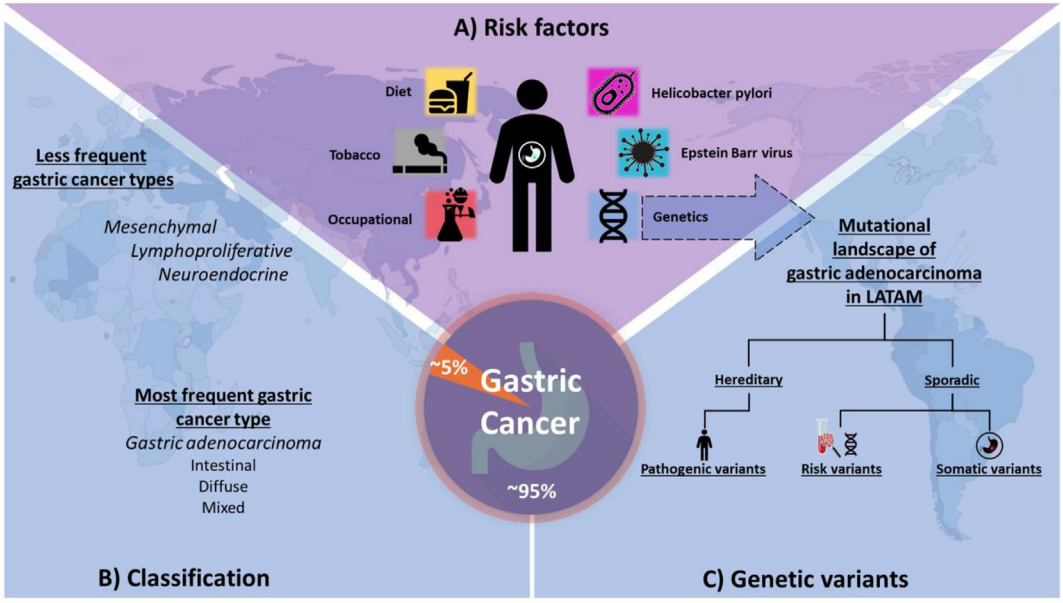

Figure 1 Gastric cancer in Latin America (LATAM) population. **(A)** Risk factors associated to the development of gastric cancer. **(B)** Gastric cancer is classified into four different types, the three less frequent represent ~5% of all cases. The most frequent is gastric adenocarcinoma, represents ~95% of all cases and is classified according to Laurén. **(C)** Genetic variants from diverse origin provide the mutational landscape for gastric adenocarcinoma in LATAM populations.

provide a GA mutational landscape from LATAM populations and an organizational level of the path from landscape to precision medicine achievement.

Comprehensive literature search

The present analysis was performed based on a comprehensive literature search from peer-reviewed studies published until January 2021 in Pubmed, Europe PMC, Springerlink, SciELO, and Redalyc. We included articles from LATAM, Argentina, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, Guatemala, Mexico, Peru, Uruguay, and Venezuela identifying germline pathogenic variants associated with hereditary GA, germline risk variants associated with sporadic GA, or somatic variants present in sporadic GA identified either by protein chain reaction, targeted sequencing, microarray, or whole exome/genome sequencing.

Germline pathogenic variants associated with hereditary GA in LATAM

Less than 3% of all GA cases are linked to germline pathogenic variants. Different hereditary GA syndromes have been described, including familial adenomatous polyposis (FAP), juvenile polyposis, Li-Fraumeni syndrome, Lynch syndrome, *MUTYH*-associated polyposis (MAP), hereditary diffuse gastric cancer (HDGC), familial intestinal gastric cancer (FIGC), and gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). This review is focused on the three last mentioned syndromes: HDGC, FIGC, and GAPPS.[21]

HDGC is the most common hereditary GA syndrome, and is associated with diffuse histology and pathogenic variations in *CDH* and *CTNNA1*. At least 122 *CDH1* germline pathogenic variants have been identified worldwide. However, about 30% are missense alterations found in middle to high GA incidence regions like East Asia or LATAM.[22] In LATAM, only Brazil,[23–27] Chile,[28] Colombia,[29] and Mexico[30–32] have reported germline *CDH1* variants. Also, Brazil is the country with the highest number of germline variants reported (Table 1).

Less than 40% of the patients meet the clinical criteria for HDGC carries a germline *CDH1* variant.[21] A thoughtful clinical scrutiny and high-throughput sequencing techniques should be used to identify the incidence and penetrance of clinically relevant *CDH1* variants because of 1) most of the germline variants present by GA patients are non-missense or variables of uncertain significance[22] and 2) not all the individuals presenting *CDH1* missense variants met the criteria for HDGC.[33]

A total of 7 germline pathogenic variants in *PALB2* (c.1240C > T, c.3201+1G > T, c.1882_1890DelAAGTCCTGC, c.2753C > A) *RAD51C* (c.709C > T) and *BRCA1* (c.3331_3334DelCAAG, c.1674DelA) were identified as germline pathogenic variants in *CDH1* negative HDGC patients from Chile, Colombia, and Mexico.[34] According to the genetic testing registry of the United States, only *CDH1* and *CTNNA1* genes are included in the Hereditary gastric cancer gene panel (GTR000525305.4). Because an increasing body of evidence suggest that germline pathogenic variants in *PALB2* might play an important role in HDGC predisposition,[34,35] they could be considered in gastric cancer genetic testing, but more information is needed to identify the incidence and penetrance of *PALB2* and *RAD51C* germline variants in LATAM and world population.

For FIGC patients, no germline pathogenic variant is known yet. The diagnosis is performed by familial clustering of intestinal GA cases without polyposis.[36] For GAPPS patients, point pathogenic variants in exon 1B of *APC* (c.−191T > C, c.−192A > G, and c.−195A > C) have been found in Caucasian.[37,38] However, we found no reports from LATAM cohorts exposing germline pathogenic variants for these two syndromes.

Germline risk variants associated to sporadic GA in LATAM

IL-8 c.-251A > T, IL-10 c-592C > A, and IL-10 c.-1082 A > G are the most studied germline risk variants, with GA susceptibility studies reported in countries such as Brazil,[39–43] Chile,[44,45] Colombia,[46] Mexico,[47] and Peru[48] (Fig. 2 and Table 2). IL-8 c.-251A > T germline risk variants were associated with a reduction and c.-845T > C with an increment of GA susceptibility in the Brazilian population, without association in Chilean and Peruvian populations where IL-8 germline risk variants did not affect GA susceptibility (Table 2). Increased GA susceptibility with the IL-4 intron 3, 70bp variable number tandem repeat (VNTR), the TLR9 c.-1237T > C and the c.-1486C > T, *NFKB1* promoter, -94 ATTG Ins/Del, *PTGS2* c. -765G > C germline risk variants was found in Brazilian population. Only the IL-10 c.-1082A > G and the IL-10 c.-592C > A germline risk variants were associated to increased GA susceptibility in Colombia and Chile, respectively. None of the studied inflammatory response-related germline risk variants were associated with GA susceptibility in the Mexican population. *IL1RN* VNTR was the only risk variant associated to LATAM population found in a meta-analysis including reports from Brazilian, Costa Rican, Honduran, Mexican, Peruvian and Venezuelan populations.[6] No significant associations were found with *IL-1β*, *TP53*, *TNFA* or *GSTM1* variants, heterogeneity among studies was a big limitation.

No associations were found with mutations in cytochrome P450 enzymes such as CYP2E1 96bp Deletion, CYP19A1 Intro 4, TCT Ins/Del, and uridine glucuronosyltransferase (UGT) UGT1A1 TATA box VNTR in the Brazilian population.[40] However, the authors claimed limitations in terms of sample size and control to risk factors exposure could affect the results.

A reduction of GA susceptibility was associated to the germline risk variant c.-1518 Ins/Del on the *MDM2* gene, whereas the presence of *TP53* 16bp deletion in Brazilian patients shown no association.[40] Moreover, *MAPK1* (c.857−3854A > C and c.119 + 21641G > A), *RAF1* (c.1669-36C > T) and *HRAS* (c.-1115T > C) intronic variants increased GA susceptibility on the Chilean population,[45] even when they were initially reported as variables of uncertain significance in ClinVar. Similar disparities between studies were found in Mexican population, where an increased GA susceptibility was associated with the *EGFR*

Table 1 *CDH1* germline pathogenic variants associated to HDGC in LATAM.

Population	Variants	Exon/Intron	Mutation	Significance	Reference
Brazil	c.48+6C>T	Intron 1	Intronic variant	Non-coding	23
	c.49-59G>T	Intron 1	Intronic variant	Non-coding	23
	c.163+57G>A	Intron 1	Intronic variant	Non-coding	23
	c.163+59G>C	Intron 2	Intronic variant	Non-coding	23
	c.313T>A	Exon 3	Missense	p.S105T	23
	c.324A>G	Exon 3	Synonymous	p.R108R	23
	c.345G>A	Exon 3	Synonymous	p.T115T	23
	c.387G>T	Exon 3	Missense	p.Q129H	23
	c.387+27C>T	Intron 3	Intronic variant	Non-coding	23
	c.388-44G>A	Intron 3	Intronic variant	Non-coding	23
	c.531+10G>C	Intron 4	Intronic variant	Non-coding	23
	c.532-18C>T	Intron 4	Intronic variant	Non-coding	23
	c.833-16C>G	Intron 6	Intronic variant	Non-coding	23
	c.1676G>A	Exon 11	Missense	p.S559N	23
	c.1806C>A	Exon 12	Missense	p.F602L	23
	c.1849G>A	Exon 12	Missense	p.A617T	23,27
	c.1896C>T	Exon 12	Synonymous	p.H632H	23
	c.1937−13T>C	Intron 12	Intronic variant	Non-coding	23
	c.2076T>C	Exon 13	Synonymous	p.A692A	23,27
	c.2164+16InsA	Intron13	Intronic variant	Non-coding	23
	c.2253C>T	Exon 14	Synonymous	p.N751N	23
	c.2439+10C>T	Intron 15	Intronic variant	Non-coding	23
	c.2439+56T>G	Intron 15	Intronic variant	Non-coding	23
	c.2634C>T	Exon 16	Synonymous	p.G878G	23,27
	c.160C>A	Promoter	—	Decreased transcription	24
	c.347GInsGA	Promoter	—	—	24
	c.1763-176DelTG	—	Frameshift	p.V588E fs*2	25
	c.185G>T	Exon 3	Missense	p.G62V	26
	c.1018A>G	Exon 8	Missense	p.T340A	26
	c. 1023T>G	Exon 8	Nonsense	p.Y341*	27
Chile	c.285C>A	Promoter	—	Non-coding	28
	c.197A>C	Promoter	—	Non-coding	28
	c.48+6C>T	Intron1	Splice site	—	28
	c.88C>A	Exon 2	Missense	p.P30T	28
	c.531+10G>C	Intron 4	Splice site	—	28
	c.1272A>T	Exon 9	Synonymous	p.T424T	28
	c.1531C>T	Exon 10	Nonsense	p.Q511*	28
	c.1893A>T	Exon 12	Synonymous	p.T631T	28
	c.2052C>T	Exon 13	Synonymous	p.S684S	28
	c.2076T>C	Exon 13	Synonymous	p.A692A	28
	c.2253C>T	Exon 14	Synonymous	p.N751N	28
Colombia	c.2245C>T	Exon 14	Missense	p.R749W	29
Mexico	c.160C>A	Promoter	—	Decreased transcription	30–32
	c.347GInsGA	Promoter	—	—	31

Abbreviations: Ins: insertions, Del: deletion, fs: frameshift.

promotor region variants c.-216G > T, c.-191C > A[49] (related to augmented expression of EGFR protein), the *ERBB2* intronic variants c.-18 + 1614C > T, c.-18 + 3073G > T and the missense variant c.3418C > G,[50] classified as variables of uncertain significance in ClinVar. Also, a decreased susceptibility was associated with the TGF-β promoter variant c.-509C > T which is associated with higher TGF-β plasmatic concentration.

TCF7L2 transcription factor variant IVS3 C > T and IVS4 G> T variant[51] and to chromosome 8q24 position variation was associated with an increased GA susceptibility in Venezuelan patients.[52] Germline risk variants related to oxidative damage and DNA repair genes, *MTHFR*, *XRCC1* and *TYMS* were studied in Brazilian population but association with GA susceptibility was not found.[40,53] In addition, an analysis of epithelial-to-mesenchymal transition (EMT)-related genes (*CDH1*, *TWIST1*, *SNAIL2*, *ZEB1* and *ZEB2*) in Chilean population found that only *TWIST* (*rs2526614* and *rs6953766*) and *ZEB1* (*rs431073*) germline risk variants were associated with poor prognosis.[54] A similar association was found in inflammatory response related to the germline risk variant IL-8 c.-251T > A, also in Chilean population.[55]

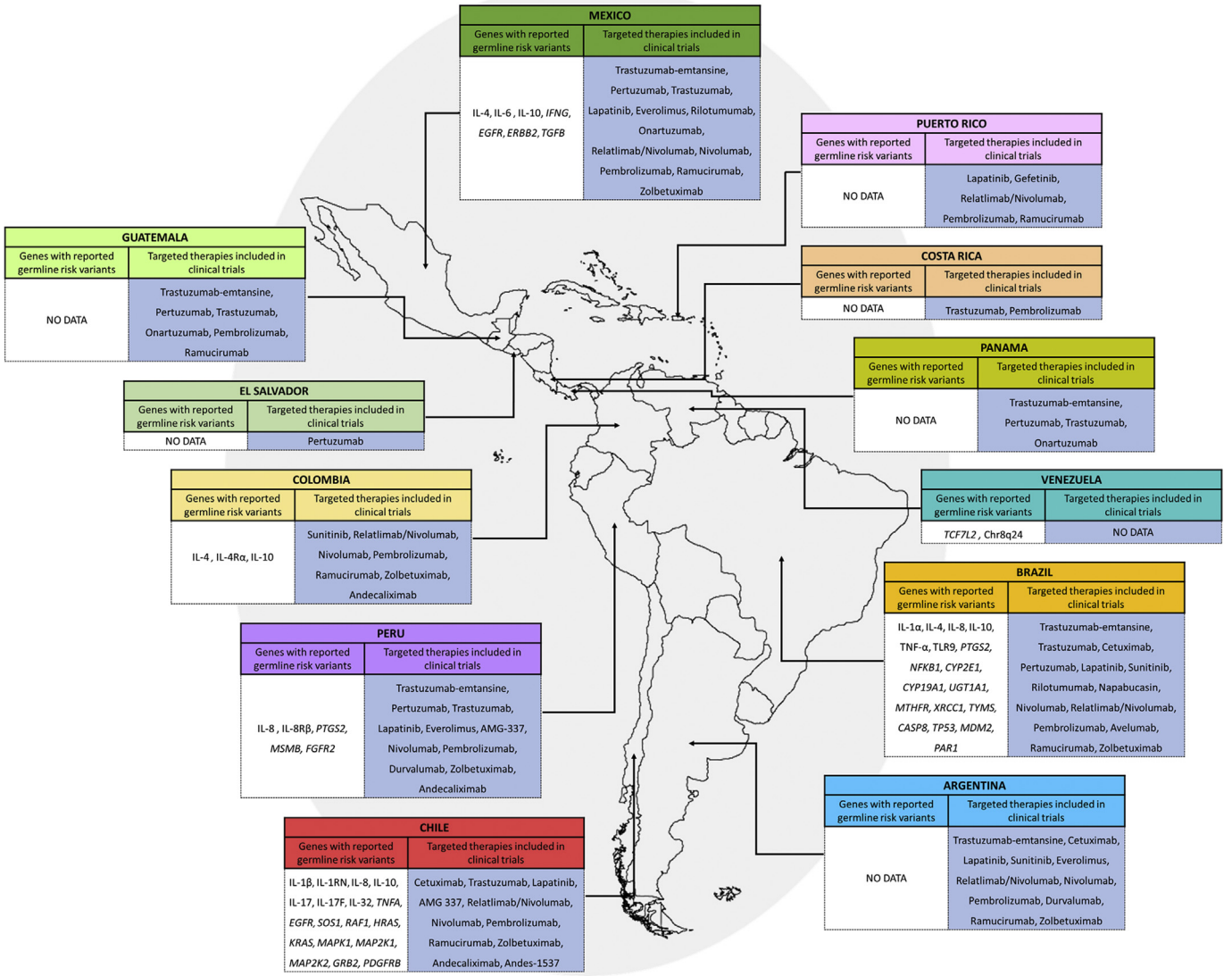

Figure 2 Mutational landscape of gastric adenocarcinoma from LATAM. Genes with described germline risk variants are reported from Mexico, Colombia, Perú, Chile, Venezuela, and Brazil, while data from Guatemala, El Salvador, Puerto Rico, Costa Rica, and Panamá are not available. Clinical trials conducted for targeted therapies in LATAM are available for all mentioned countries. The higher prevalence in mutations could be grouped into five categories of cellular significance: a) apoptosis and oncogenes (*SOS1*, *MSMB*, *MDM2*, *KRAS*, *HRAS*, *ERBB2*, *FGFR*, *CDH1*, *EGFR*, *MAPK1*, *PDGFRB*, *RAF1*, *MAP2K1*, *TCF7L2*, *CASP8*, *TGF-β*, *GRB2*, *TP53*); b) inflammatory response (IL-8, IL-4Rα, IFN-γ, IL-32, IL-1α, IL-17, IL-4, TNF-α, IL-17F,IL-10, IL-6, IL-1β, TLR9, IL-1RN, *PTGS2*, *NFKB1* and IL-8Rβ; c) oxidative damage and DNA repair (XRCC, MTHFR, TYMS); d) detoxifying mechanisms (*CYP19A1*, *CYP2E1* and *UGT1A1*) and e) unknown function (Chr8q24). Currently, EGFR/HER 2 and PD-1/PD-L1 inhibitors are the most common targeted therapies used in clinical trials conducted in LATAM.

Table 2 Germline risk variants associated to somatic GA in LATAM 2014—2020.

Pathway	Genes	Germline risk variants	dbSNP	Population	Risk	Reference
Inflammatory response	*IL-1β*	c.-511C>T	rs16944	Brazil	Not-aff	[39]
		—	—	Chile	Not-aff	[44]
		c.-31C>T	rs1143627	Chile	Not-aff	[44]
		—	—	Brazil	Red	[39]
		c.+3954C>T	rs1143634	Chile	Not-aff	[44]
	IL-1α	4-bp Ins/Del	rs3783553	Brazil	Not-aff	[40]
	IL-1RN	Intron 2, VNTR	rs380092	Chile	Not-aff	[44]
	IL-4	c.-590C>T	rs1800629	Mexico	Not-aff	[47]
				Colombia	Not -aff	[46]
		Intron 3, 70 bp VNTR	rs79071878	Brazil	Inc	[40]
	IL-4Rα	p.Q576R	—	Colombia	Not-aff	[46]
		p.I50V	—	Colombia	Not-aff	[46]
	IL-6	c.-573G>C	rs1800796	Mexico	Not-aff	[47]
	IL-8	c.-251A>T	rs4073	Brazil	Red	[39]
				Perú	Not-aff	[48]
				Chile	Not-aff	[44]
				Brazil	Not-aff	[43]
		c.-845T>C	rs2227532	Brazil	Inc	[43]
	IL-8Rβ	—	rs4674258	Peru	Not-aff	[48]
	IL-10	c.-1082A>G	rs1800896	Mexico	Not-aff	[47]
				Chile	Not-aff	[44]
				Colombia	Inc	[46]
		c.-819C>T	rs1800871	Mexico	Red	[47]
				Colombia	Not-aff	[46]
		c.-592C>A	rs1800872	Mexico	Not-aff	[47]
				Chile	Inc	[44]
				Colombia	Not aff	[46]
				Brazil	Inc	[43]
	IL-17	c.-197G>A	rs2275913	Chile	Not-aff	[44]
	IL-17F	c.482A>G (p.H161R)	rs763780	Chile	Not-aff	[44]
	IL-32	—	rs28372698	Chile	Not-aff	[44]
	TNF-α	c.-308G>A	rs1800629	Chile	Not-aff	[44]
		—	—	Brazil	Not-aff	[43]
		c.-857C>T	rs1799724	Brazil	Inc	[43]
	IFN-γ	c.-1615C>T	rs2069705	Mexico	Not-aff	[47]
	TLR9	c.-1237T>C	rs5743836	Brazil	Inc	[41]
		c.-1486C>T	rs187084	Brazil	Inc	[41]
	PTGS2	c.-1195G>A	rs689466	Perú	Not-aff	[48]
		c.-1290A>G	rs689465	Peru	Not-aff	[48]
		c.-765G>C	rs20417	Brazil	Inc	[42]
	NFKB1	Promoter, -94 ATTG Ins/Del	rs28362491	Brazil	Inc	[40]
Detoxifying mechanisms	*CYP2E1*	96 bp Deletion	—	Brazil	Not-aff	[40]
	CYP19A1	Intro 4, TCT Ins/Del	rs11575899	Brazil	Not-aff	[40]
	UGT1A1	TATA box, VNTR	rs8175347	Brazil	Not-aff	[40]
Oxidative damage and DNA Repair	*MTHFR*	c.677C>T (p.A222V)	rs1801133	Brazil	Not-aff	[53]
	XRCC1	Gene deletion	rs3213239	Brazil	Not-aff	[40]
	TYMS	6bp Ins/Del	rs16430	Brazil	Not-aff	[40]
		—	—	Brazil	Not-aff	[53]
		28bp VNTR	rs45445694	Brazil	Not-aff	[53]
		2nd repeat of 3R allele G> C	rs34743033	Brazil	Not aff	[53]
Apoptosis and Oncogenesis	*CASP8*	−652 6N Ins/Del	rs3834129	Brazil	Not-aff	[40]
	TP53	16 bp Ins/Del	rs17878362	Brazil	Not-aff	[40]
	MDM2	c.-1518 Ins/Del	rs3730485	Brazil	Red	[40]
	EGFR	c.-216G>T	rs712829	Mexico	Inc	[49]
		—	—	Chile	Not-diff	[45]
		c.-191C>A	rs712830	Mexico	Inc	[49]
		IVS1	—	Mexico	Not-aff	[49]

(*continued on next page*)

Table 2 (*continued*)

Pathway	Genes	Germline risk variants	dbSNP	Population	Risk	Reference
		c.1881-600G>A	rs10228436	Chile	Not-aff	[45]
		c.2283+1296C>T	rs11514996	Chile	Not-aff	[45]
		c.88+3321T>C	rs11770506	Chile	Not-aff	[45]
		c.89−58442T>C	rs17172438	Chile	Not-aff	[45]
		c.2470−3426C>T	rs2740761	Chile	Not-aff	[45]
		c.88+37628A>G	rs6593201	Chile	Not-aff	[45]
		c.2469+959G >A	rs7795743	Chile	Not-aff	[45]
	ERBB2	c.-18+1614C >T	rs2643194	Mexico	Inc	[50]
		c.-18+1663C >T	rs2517951	Mexico	Not-aff	[50]
		c.-18+1684A>G	rs2643195	Mexico	Not-aff	[50]
		c.-18+3073G>T	rs2934971	Mexico	Inc	[50]
		c. 3418C>G	rs1058808	Mexico	Inc	[50]
	SOS1	c.1859-1142T>C	rs10184015	Chile	Not-aff	[45]
	RAF1	c.1417+170C>G	rs2290159	Chile	Not-aff	[45]
		c. 1669-36C>T	rs3729931	Chile	Inc	[45]
		c.-26-2203C>T	rs73812837	Chile	Not-aff	[45]
	HRAS	c.-1115T>C	rs45604736	Chile	Not-aff	[45]
	KRAS	c.*633T>C	rs9266	Chile	Inc	[45]
	MAPK1	c.857−3854A>C	rs2283792	Chile	Inc	[45]
		c.119+7040A>G	rs4821401	Chile	Not-aff	[45]
		c.857−1944T>C	rs743409	Chile	Not-aff	[45]
		c.*3186C>T	rs9340	Chile	Not-aff	[45]
		c.119+21641G>A	rs9610417	Chile	Inc	[45]
	MAP2K1	c.81−996C>T	rs1347069	Chile	Not-aff	[45]
		c.569−16806A>G	rs62010232	Chile	Not-aff	[45]
	MAP2K2	c.919+423T>C	rs350912	Chile	Not-aff	[45]
		c.303+1424C>T	rs1823059	Chile	Not-aff	[45]
	GRB2	c.78+20210G>A	rs959260	Chile	Not-aff	[45]
	TGF-β	c.-509C>T	rs1800469	Mexico	Red	[47]
	PAR1	c.-506 Ins/Del	rs11267092	Brazil	Not-aff	[40]
	MSMB	c.-57C>T	rs10993994	Peru	Not-aff	[48]
	FGFR2	—	rs1219648	Peru	Not-aff	[48]
	PDGFRB	c.*805C>T	rs1017375	Chile	Not-aff	[45]
		c.-152-8335A>G	rs10066011	Chile	Not-aff	[45]
		c.-153+4691A>G	rs58746386	Chile	Not-aff	[45]
	TCF7L2	IVS3 C>T	rs7903146	Venezuela	Inc	[51]
		c.483+9017G>T (IVS4 G>T)	rs12255372	Venezuela	Inc	[51]
Unknown function	Chr8q24	—	rs1447295	Venezuela	Not-aff	[52]
	Chr8q24	—	rs4733616	Venezuela	Inc	[52]
	Chr8q24	—	rs6983267	Venezuela	Not-aff	[52]

Abbreviations: dbSNP: National Center for Biotechnology Information single nucleotide polymorphism database, Inc: Increased risk, Red: Reduced risk, Not-aff: Not Affected, VNTR: variable number tandem repeat, IVS: intervening sequence.

Somatic variants present in sporadic GA in LATAM

Single gene approaches report an alteration in different *TP53* exons, frequently exon 5 and 9 in individuals with G> A transitions as the most common nucleotide substitution in Chilean population.[56] A high frequency of *TP53* somatic variation in tumoral samples but failed finding associations between this somatic variant and clinical outcomes such as tumor localization, histological type, and presence of lymph node metastasis were found in the Chilean population.[57] Comparable results were found in *MYC*, *FBXW7*, and *TP53* copy number variation in Brazilian patients, and only high expression of *MYC* detected by immunohistochemistry was associated with intestinal-type GA patients.[58] In other populations *TP53*, *MYC*, and *PIK3CA* are also among the most frequently mutated genes.[59,60]

Tumor suppressor gene somatic mutations of *CDH1* gene were evaluated in diffuse and mixed type GA Mexican patients, and 17 somatic variants were found, but c.-137C > A (located in the promoter region), c.1138-92DelA, c.1138-75InsA (intron 8) and c.1221 Ins C (exon 9) were newly reported and associated to the diffuse histology.[61] Evaluation of *PTEN* in Brazilian patients failed to find somatic variations at all, only 1 out of 48 patients showed the gene mutated.[62]

Somatic variations in c.4479G > A (p.T1493T) *APC* gene were found more prevalent in GA than colorectal cancer in

Colombian patients. *TP53* c.782 + 72C > T and c.782 + 92T > G were also frequent in Colombian GA patients. *KRAS* coding variants, c.35G > A (p.G12D) and c.38G > A (p.G13D), were found in 6.9% of Colombian GA patients and the intronic variants, c.111 + 190A > T and c.111 + 116_111 + 120delAGTTA, in 27.6% and 3.5% of the patients, respectively.[63] Sotorasib[64] (formerly AMG 510) and Adagrasib[65] (formerly MRTX849) are two novel drugs with targeted activity to *KRAS* p.G12D variant in non-small cell lung cancer (NSCLC) and other solid tumors like colorectal cancer, that could be an asset to GA precision medicine. The NSCLC group treated with sotorasib show a 32.2% of objective response rate and a median progression-free survival of 6.3 months.

Another Colombian study identified that some *KRAS* somatic variations could be determinant to precancerous lesion progression to cancerous lesions, especially G>A transitions in position 1 of codon 12.[66] Contrasting results were found in Venezuelan patients with *H. pylori* infection, where *KRAS* somatic variations in codon 12 were common in precancerous lesions but uncommon in cancerous lesions.[67]

DNA copy number alterations affect both protein-coding and non-coding genes present in the affected region. Amplification involving 8q, 20q, and 17q; deletions involving 3p, 6p, and 2q as well as loss of heterogeneity in 16p were present in 50% or more intestinal type GA Brazilian patients.[68] *TP53TG3B*, *TP53TG3* and *ZNF267* were the most frequently affected genes by the previous genetic alterations and were not frequent in genomic sequencing studies from other populations[69] and they could be distinctive for Brazilian population, but more information is needed. Gains in Xq26 (cancer/testis antigen family 45, member A4) and Xp22.31 (microsomal steroid sulfatase, isozyme S) and loss in 11p15.4 (olfactory receptor, family 52, subfamily N, member 5 - *OR52N5* and *OR52N1*) were associated with early-onset intestinal type GA. Further copy number analysis of 17q21 located prohibitin gene in Brazilian patients and found amplification in 34.2% of patients but no association to disease clinicopathological features.[70]

The comparative genomic hybridization in Brazilian patients highlighted the high frequency of chromosomal gains in GA intestinal type, specially 8q chromosomal gains with 8q24 amplification in metastasized intestinal-type GA[71] and a high-frequency chromosome losses in chromosome regions 11q and 18q were found in Brazilian patients with diffuse type GA,[72] and similar alterations were found in Asian and European populations.[73–75]

Tumoral tissue had significantly higher heteroplasmy than paired healthy tissues and gastric tissue of healthy Brazilian patients[76] with an average of 50 heteroplasmic variants with exclusive tumor variants observed in MT-*DLOOP2*, MT-*DLOOP1*, and MT—*ND5* genes. This study also identified Native American ancestry as the group with more variants than European, African, and Asian ancestry groups. The compound Andes-1537 developed in Chile targets the antisense non-coding mitochondrial RNA, inducing apoptosis, decreasing proliferative signaling and inhibiting invasion associated proteins.[77] Andes-1537 is currently in phase I clinical trial tested in patients with advance solid tumors, including gastric cancer.[78]

The Chilean Gastric Cancer Task Force One (FORCE1), using a panel of 143 known cancer-related genes presented the mutational landscape of 224 Chilean GA patients.[79] A high proportion of advanced-stage patients with intestinal-type GA without the presence of signet ring cells were included. *TP53*, *PIK3CA*, *VHL*, *NRAS*, and *KRAS* were the 5 frequently mutated genes. *MYC*, *CCND1* and *CCNE* were the genes with the highest frequency of copy number variations and *EML4-ALK* the most frequent fusion. Alpelisib, a *PIK3CA* inhibitor recently approved for breast cancer treatment[80] has shown antiproliferative effect on gastric cancer cells[81] and could be a therapeutic option for GA patients. Compared with the TCGA results, FORCE1 study found a higher proportion of PD-L1 positive patients and only 13.3% of microsatellite unstable tumors, from which 46% had diffuse type histopathology.[82] KEYNOTE-062 study, which included Chilean patients, probed the noninferiority of the PD-L1 inhibitor, pembrolizumab to convention chemotherapy and presented a new asset for the treatment of this higher proportion of PD-L1 positive GA patients.[83]

The Brazilian initiative Genomics and Epidemiology for gastric cancer adenocarcinomas (GE4GAC) seeks to integrate epidemiological, clinical, molecular, and microbiota data from subjects living in three different regions of Brazil,[84] but no published studies are available yet.

Our team recently explored the association between nutritional indexes, mutational landscape, and survival of Mexican GA patients. The nutritional prognostic index and body mass index were identified as independent prognostic factors in GA. Within the mutational landscape, *NOTCH1*, *GNAS*, *FBXW7* and *IDH2* were the top 5 most mutated genes in a Mexican population. Age-associated signature 1, liver cancer-related signature 23 and mismatch-related signature 6 were the most common mutational signatures found in these patients. Somatic variations in *NOTCH1*, *FBXW7*, *TET2*, or *SDHB* were related to at least one of the nutritional indexes.[85]

From GA mutational landscape to precision medicine in LATAM

Precision medicine is based on two main pillars. First, determining cancer predisposition through germline pathogenic or risk variants identification to provide a prompt diagnose and genetic counseling. Second, to test the tumor itself to decide the best treatment option through somatic variants evaluation. The starting point for precision medicine is the design of epidemiological studies that include sequencing strategies to obtain the mutational landscape of the tumor (Level 1: Data compilation). The subsequent bioinformatic analysis plays a key role in finding functional and clinically relevant mutations and the non-actionable mutation are re-analyzed, providing novel information later (Level 2: Data analysis and integration). Then, the data can be used for early diagnosis and the development of clinical approaches of specific therapeutic targets, which normally is expensive in terms of economic resources and time (Level 3: Development and approval of clinical approaches). If a specific therapy for a novel detected mutation does not exist, conventional therapy is used, but simultaneously

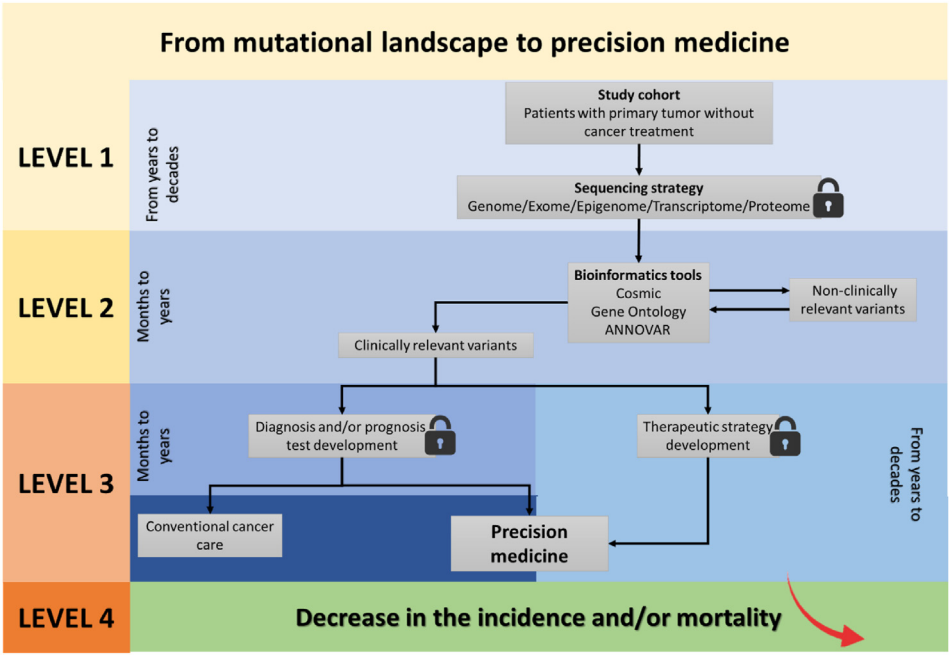

Figure 3 From mutational landscape to precision medicine for gastric adenocarcinoma (GA) in LATAM. The achievement of precision medicine requires several levels. The first level is the design of a proper cohort selection in which patients without previous treatment for GA are included properly for mutational landscape detection through available sequencing strategies (exome/transcriptomic/proteomic). Level 2 requires the data analysis derived from sequencing methods and for this purpose bioinformatic tools delivers functional and clinically relevant data or non-actionable mutations, which can be re-analyzed and deliver information that correlates with epidemiological data and turns into clinically relevant information. Level 3 is reached when the mutational landscape is applied for diagnosis/prognosis and therapeutic development for precision medicine. Finally, level 4 is successfully achieved by significantly decreasing the incidence and/or mortality of the cancer.

Table 3 Clinical trials for targeted therapies for gastric cancer in LATAM.

Agent	Trial name	LATAM participating countries	NCT Identifier (Status)
EGFR/HER 2 inhibitors			
Trastuzumab-emtansine	GATSBY	Argentina, Brazil, Guatemala, Mexico, Panama, Peru	NCT01641939 (Terminated)
Trastuzumab-emtansine	TRAXHER2	Argentina, Brazil	NCT01702558 (Terminated)
Trastuzumab	GASTHER2	Brazil	NCT04168931 (Not yet recruiting)[a]
Cetuximab	EXPAND	Argentina, Brazil, Chile	NCT00678535 (Completed)
Trastuzumab-deruxtecan	DESTINY-Gastric03	Brazil	NCT04379596 (Recruiting)
Pertuzumab	JACOB	Brazil, El Salvador, Guatemala, Mexico, Panama, Peru	NCT01774786 (Completed)
Trastuzumab	ToGA Study	Brazil, Costa Rica, Guatemala, Mexico, Panama, Peru	NCT01041404 (Completed)
Trastuzumab	HELOISE	Brazil, Chile, Mexico, Panama, Peru	NCT01450696 (Terminated)
RTK Inhibitors			
Lapatinib	LOGiC	Argentina, Brazil, Chile, Mexico, Peru, Puerto Rico	NCT00680901 (Active)
Sunitinib		Argentina, Brazil, Colombia	NCT00428220 (Completed)[a]
Lapatinib		Mexico	NCT00526669 (Completed)
Gefetinib		Puerto Rico	NCT00215995 (Completed)
PI3K/AKT/mTOR Inhibitors			
Everolimus	GRANITE-1	Argentina, Mexico, Peru	NCT00879333 (Completed)
MET Inhibitors			

Table 3 (*continued*)

Agent	Trial name	LATAM participating countries	NCT Identifier (Status)
Rilotumumab	RILOMET-1	Brazil, Mexico	NCT01697072 (Terminated)
AMG 337		Chile, Peru	NCT02016534 (Terminated)
Onartuzumab	METGastric	Guatemala, Mexico, Panama	NCT01662869 (Completed)
JAK/STAT Inhibitors			
Napabucasin (BBI608)	BRIGHTER	Brazil	NCT02178956 (Completed)
PD-1/PD-L1 Inhibitors			
Relatlimab/Nivolumab		Argentina, Brazil, Chile, Colombia, Mexico, Puerto Rico	NCT03704077 (Withdrawn)
Nivolumab	CheckMate649	Argentina, Brazil, Chile, Colombia, Mexico, Peru	NCT02872116 (Active)
Relatlimab/Nivolumab		Argentina, Chile, Puerto Rico	NCT03662659 (Active)
Pembrolizumab	MK-3475-859/ KEYNOTE-859	Argentina, Brazil, Chile, Colombia, Costa Rica, Guatemala, Mexico, Peru	NCT03675737 (Recruiting)
Durvalumab		Argentina, Peru	NCT04592913 (Recruiting)
Pembrolizumab	MK-3475-811/ KEYNOTE-811	Brazil, Chile, Guatemala	NCT03615326 (Recruiting)
Pembrolizumab	MK-3475-585/ KEYNOTE-585	Brazil, Chile, Guatemala	NCT03221426 (Recruiting)
Avelumab	JAVELIN Gastric 100	Brazil	NCT02625610 (Active)
Pembrolizumab	MK-7902-005/ E7080-G000-224/LEAP-005	Chile	NCT03797326 (Recruiting)
Pembrolizumab	MK-3475-062/ KEYNOTE-062	Argentina. Brazil, Chile, Colombia, Guatemala, Mexico, Puerto Rico	NCT02494583 (Active)
Angiogenesis inhibitor			
Ramucirumab	REGARD	Argentina, Brazil, Chile, Colombia, Guatemala, Mexico	NCT00917384 (Completed)
Ramucirumab	RAINBOW	Argentina, Brazil, Chile, Mexico	NCT01170663 (Completed)
Ramucirumab	RAINFALL	Argentina, Mexico, Puerto Rico	NCT02314117 (Completed)
Ramucirumab		Argentina	NCT02443883 (Completed)[a]
CLDN18.2 directed antibody			
Zolbetuximab	GLOW	Argentina	NCT03653507 (Recruiting)
Zolbetuximab	SPOTLIGHT	Brazil, Chile, Colombia, Mexico, Peru	NCT03504397 (Recruiting)
MMP9 Inhibitors			
Andecaliximab	GAMMA-1	Colombia, Chile, Peru	NCT02545504 (Completed)
Antisense non-coding mitochondrial RNA Inhibitors			
Andes-1537		Chile	NCT03985072 (Recruiting)[a]

Abbreviations: LATAM: Latin America, BSC, best supportive care; XELOX, Oxaliplatin and capecitabine; FOLFOX, Oxaliplatin, leucovorin and fluorouracil; SOX, Oxaliplatin and tegafur/gimeracil/oteracil potassium; FP, 5-Fluorouracil and cisplatin; FLOT, Flurouroacil, leucovorin, oxaliplatin and docetaxel; ECX, Epirrubicin, cisplatin and capecitabine; SOC, Cisplatin, 5-fluorouracil, capecitabine.

[a] Pharmacokinetic studies.

specific therapy is developed, and clinical trials succeed, followed by the approval of health authorities (Level 3: Development and approval of clinical approaches). The cost for sequencing large cohorts and the high costs of treatments targeting specific mutations are the main padlocks. We consider that precision medicine will succeed until the personalized treatments achieve a significant decrease in the incidence or mortality in the population (Level 4: Population benefits) (Fig. 3).

The United States and Puerto Rico are conducting MATCH (molecular analysis for therapy choice) clinical trial, which falls within the level 3 of the proposed pathway from mutational landscape to precision medicine. This trial is based on genomic screening where patients are allocated to experimental aims depending on the genetic changes found in the tumor, regardless the cancer type.[86,87] Several clinical studies have been conducted in LATAM to prove the efficacy and security of targeted therapies (Table 3) but

non involving genomic screening and a design like the MATCH clinical trial. To date, only HER-2 and PD-1/PD-L1 inhibitors are only targeted therapies available to treat GA patients in LATAM. GA patients with *KRAS*, *PIK3CA*, *ERBB2*, *EGFR*, *CD247*, *CLDN18*, *MET* and *FGFR* pathogenic variants could be benefit from precision medicine clinical trials.

Brazil and Chile are the countries with more tangible scientific efforts done to generate local genetic data and elucidate the GA mutational landscape, this would ease the implementation of precision medicine and gene counseling programs to provide better care to GA patients. Even though the direct impact of this care options has not been measured, a decrease of GA incidence and mortality in these countries has been reported, with up to a 15% reduction in gastric cancer mortality in Brazilian cohorts[88] and a 3.5% annual percentage reduction of mortality from 2012 to 2015 in Chilean cohorts.[89] On the other hand, in most of LATAM countries the shortage on genetic data and founding opportunities hampers the implementation of short-term precision medicine and genetic counseling programs.

Conclusions

Despite LATAM population shares vast ethnic and cultural background, the mutational landscape is dissimilar. Brazilians show increased GA risk associated with variants in interleukins; Mexicans display also increased GA risk associated with growth factor receptors. Chileans and Mexicans present discrepancies in all the top 5 frequently mutated somatic variants. Though some difficulties should be overcome, Brazil, Chile, and Mexico may become the first LATAM countries providing precision medicine fighting GA based on its regional mutational landscape.

Author contributions

Dennis Cerrato-Izaguirre: Conceptualization, Writing-Original draft preparation, Writing-Reviewing and Editing. **Yolanda I. Chirino**: Writing-Original draft preparation, Writing-Reviewing and Editing. **Claudia M García-Cuellar**: Writing-Reviewing and Editing. **Miguel Santibáñez-Andrade**: Conceptualization, Writing-Original draft preparation, Writing-Reviewing and Editing. **Diddier Prada**: Writing-Reviewing **Angélica Hernández-Guerrero**: Writing-Reviewing. **Octavio Alonso Larraga**: Writing-Reviewing. **Javier Camacho**: Writing-Reviewing and Editing. **Yesennia Sánchez-Pérez**: Conceptualization, Writing-Reviewing and Editing.

Conflict of interests

Authors declare that they have no conflicts of interest.

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