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REVIEW

Prevalence of the JP2 genotype of *Aggregatibacter actinomycetemcomitans* in the world population: a systematic review

Nabil Khzam[1,2] · Leticia Algarves Miranda[1] · Omar Kujan[1] · Kate Shearston[1] · Dorte Haubek[3]

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Abstract

Purpose To investigate the global prevalence of the JP2 genotype of *Aggregatibacter actinomycetemcomitans* (*Aa*).

Methods A comprehensive electronic search of databases, PUBMED, MEDLINE, EMBASE, BIOSIS, and SCOPUS, was conducted up to August 2021. All published articles and studies were considered, excluding animal studies, editorials, personal opinions, letters to editor, conference abstracts, posters, and those studies without full text. The primary objective of this systematic review was to determine the presence of the JP2 genotype of *Aa* in the world population.

Results A total of 295 articles were identified, of which 62 were preselected, and 51 were finally included in this review. Due to variable study designs and high heterogeneity, a meta-analysis was not conducted. A total of 9744 subjects were screened for the presence of the JP2 genotype of *Aa* worldwide, and only 621 cases were found positive.

Conclusions A relatively high presence of JP2 genotype of *Aa* was found in subjects from South America, North America, and Africa. There were no studies estimating the presence of the JP2 genotype of *Aa* in the Oceania region. The heterogeneity and quality of the included publications suggest that caution should be exercised when interpreting the data and that there remains an important need for additional evidence.

Clinical relevance. Periodontitis is a highly prevalent inflammatory oral disorder with substantial aesthetic, functional, and psychological implications for patients. The JP2 genotype of *Aa* is implicated in the pathogenesis of periodontitis. To the best of our knowledge, there is a lack of systematic reviews estimating the presence of the JP2 genotype of *Aa* in the global population. We identified a relatively high presence of the JP2 genotype of *Aa* in specific geographic areas of the world, and we propose that cross-sectional and longitudinal studies are lacking in the Oceania region and need to be conducted to estimate the presence of the JP2 genotype of *Aa* in this region.

Keywords *Aggregatibacter actinomycetemcomitans* · Periodontitis · JP2 genotype · Prevalence

Introduction

Periodontitis is characterized by microbially-initiated and/or host-mediated inflammation that results in the loss of periodontal attachment and bone support around teeth [1].

Periodontitis is one of the most prevalent oral diseases in the world and is a leading cause of adult tooth loss. The inflammatory response in periodontitis is initiated by a polymicrobial biofilm formed around the gingival margin of the teeth [2]. *Aa* is a gram-negative, facultative anaerobic oral pathogen identified within the oral biofilm and is implicated in the pathogenesis of periodontitis [3]. Dissemination of *Aa* from the oral cavity can also initiate multiple systemic infections, including soft tissue abscesses, endocarditis, and pneumonia [4–6].

Bacteria and the host immune response play a significant role in the pathogenesis of periodontitis [7]. For a pathogen to successfully colonize the host, it must be able to acquire essential nutrients and regulate gene expression to respond to environmental fluctuations. Among the virulence factors of *Aa*, leukotoxin is suggested to play a central role in the

✉ Nabil Khzam
nokhzam@gmail.com

1 The University of Western Australia, Oral Health Centre of Western Australia, Dental School, Nedlands, WA 6009, Australia

2 NK Perio & Implants, Specialist Private Practice, Suite 41, 11, Preston Street, Como, WA 6152, Australia

3 Section for Paediatric Dentistry, Department of Dentistry and Oral Health, Aarhus University, 8000 Aarhus C, Denmark

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etiology of periodontitis in certain populations. There is also genetic diversity among the different strains of *Aa*, and different strains display variability in their ability to express and release leukotoxin [8]. Of the different strains of *Aa*, the highly leukotoxic JP2 genotype seems to be most strongly associated with periodontitis [3, 9]. *Aa* leukotoxin is the molecule responsible for the leukotoxic effect on human immune cells [10, 11]. Leukotoxin production is reported to be 10–20-fold higher than that for the non-JP2 genotype of *Aa* [12]. *Aa* strains with the 530 base-pair deletion in the leukotoxin operon were found to belong to a genotype JP2 of serotype b, particularly associated with an aggressive form of periodontitis especially in individuals of African origin [11, 13]. Accurate assessment of the presence of *Aa* JP2 genotype in a population is critical to understanding the determinant of periodontitis; however, current understanding of the worldwide prevalence of the Aa JP2 genotype is incomplete.

The primary objective of this systematic review was to estimate, from publically available literature sources, the presence of the JP2 genotype of *Aa* in the world population.

Materials and methods

Study registration and guidelines

The reporting of this systematic review has followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [14]. The protocol of this review was registered in the International Prospective Registry of Systematic Review (PROSPERO) database (CRD42021264375).

Eligibility criteria

Participants

Subjects, who are positive to the JP2 genotype of *Aa* with no age restrictions were included.

Interventions

Studies that investigated the presence of the JP2 genotype of *Aa*.

Outcome

The estimation of the presence of the JP2 genotype of *Aa* in the world population.

Types of study design

All types of the published studies up to August 2021 were included, except editorial, personal opinions, letters to editors, conference abstracts, and posters. All clinical studies in humans were included. Articles other than the English language were excluded due to difficulty to source reliable interpreters.

Search strategy

A developed search strategy was run through the following scientific databases: PubMed, MEDLINE, EMBASE, BIOSIS, and Scopus. The electronic search terms used were as follows: ["*Actinobacillus actinomycetemcomitans*" OR "*aggregatibacter actinomycetemcomitans*"] AND ["periodontitis" OR "aggressive periodontitis" OR "juvenile periodontitis" OR "early onset periodontitis" OR "prepubertal periodontitis" OR "rapidly progressing periodontitis"] AND ["JP2 clone" OR "JP2 genotype"]. Manual searching was also used to screen reference lists of the included studies.

Inclusion criteria

1- Humans' subjects
2- Studies published in English language

Exclusion criteria

1- Animal samples
2- Regarding studies without full text, the corresponding authors were contacted. In the absence of response, these studies were excluded from the final review
3- Excluding editorials, personal opinions, letters to editor, review articles, conference abstracts and posters

Data extraction

Using a standardized form, all relevant information was independently reviewed by two investigators. Any discrepancy was resolved by discussion between the two reviewers (NK and LAM), and if needed, a third reviewer (DH) was consulted. From each study included, the following details were extracted: author/s, publication year, country, study design, ethnicity, origin, gender, age, sample size, inclusion criteria, exclusion criteria, examiner, disease definition/status, periodontal examination, radiographic examination, photographic examination, sampling method, JP2 genotype of *Aa* analysis, source of sample, presence of JP2 genotype

of *Aa*, JP2 genotype/geographic origin, and presence of other bacteria.

Critical appraisal

A stringent critical appraisal process was conducted to report the quality and the risk of bias of the included studies. Assessment of the methodological quality of the included studies was carried out using the Joanna Briggs Institute (JBI) tool [15]. Critical appraisal results were presented as answers (Yes, No, Unclear, or Not Applicable) to nine items. The overall appraisal of the study was "Included," if up to 7 items were fulfilled (low risk of bias). The study was qualified "Exclude," if inappropriateness of the sample or the identification of the condition did not use valid methods (high risk of bias). The study was considered as seeking further information, if at least 2 items were unclear.

Grading the quality of evidence

Quality of evidence and grading the strength of the recommendations across the included studies were completed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [16]. The reviewers evaluated the quality of the evidence and the strength and direction of the recommendations according to the following aspects: study design, risk of bias, the directness of evidence, consistency of results, precision, and magnitude of the effect. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Results of the literature search

The search identified a total of 295 electronic citations. After screening of the titles and abstracts, 62 studies remained for complete-text assessment. Disagreements among reviewers were resolved by discussion. Kappa agreement between the two reviewers (NK and LAM) was 0.84. We excluded four studies, as they reported on the *Aa* isolates and not the subjects [10, 12, 17, 18]. We also excluded two more studies as the *Aa* isolates were collected from human and non-human primates [19], while in the other study the *Aa* isolates were taken from human and captive marmosets [20]. Five more studies were not included, as they used all or some of the microbiological samples from previous studies [21–25]. Finally, 51 studies were deemed eligible and included in this systematic review (Fig. 1).

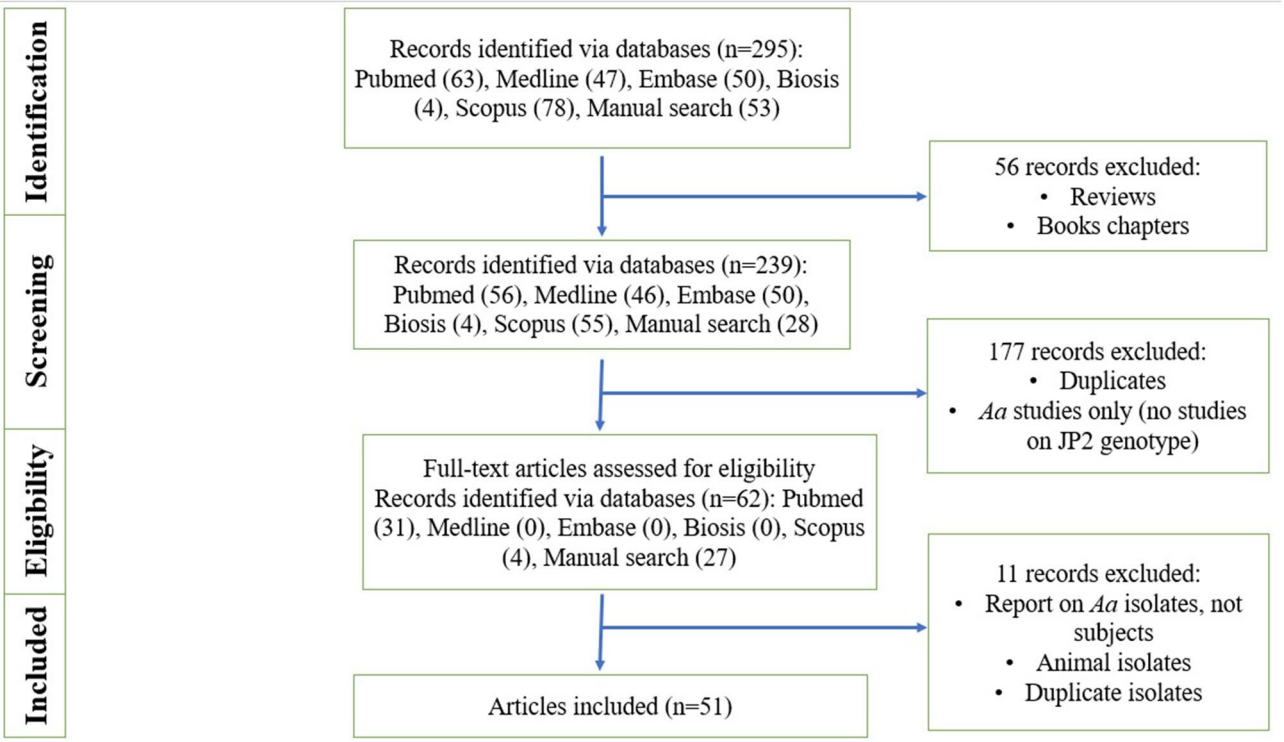

Fig. 1 Flowchart of the study

Description of the included studies

A total of 51 studies reporting on the presence of the *Aa* JP2 genotype were included. The characteristics of these studies are summarized in Table 1 and Fig. 2. The first published report included in this review, collecting biological samples from humans, was conducted in Seoul, Korea, in 1989 [26]. Some of the included studies covered the presence of the *Aa* JP2 genotype in only one continent. Thirteen studies covered the presence of the *Aa* JP2 genotype in Europe [13, 22, 27–37]. Seven studies reported on the presence of the *Aa* JP2 genotype in North America and Jamaica [38–44]. Eight publications tracked the *Aa* JP2 genotype in South America with all of these studies being conducted in Brazil [45–52]. Despite a larger population in Asia, numerous ethnic groups, who live in various landscapes from sea level up to the heights of the Himalayas, only nine studies were conducted to track the presence of the *Aa* JP2 genotype [26, 53–60]. Most of the research tracking the *Aa* JP2 genotype presence was done in the world's oldest continent, Africa, which is considered to be the source of the *Aa* JP2 genotype that emerged from the northern region approximately 2400 years ago and subsequently spread to the rest of the world during the transatlantic slave trade and migration [18]. Nine studies mostly done in Morocco explored the presence of the *Aa* JP2 genotype in Africa [61–69]. Some of the studies covered the presence of *Aa* JP2 genotype in two continents, like in the study conducted by Asikanen et al. in 1997 covering Finland and the USA populations [70]. Kim and co-authors looked for the presence of the *Aa* JP2 genotype in Korea and Germany in 2009 [71]. Haraszthy et al. (2000) tracked the *Aa* JP2 genotype in North and South American populations [72]. Finally, only two studies looked at the distribution of the *Aa* JP2 genotype worldwide, namely Haubek et al. (1997A) and Pinheiro et al. (2011) [73, 74]. Haubek and colleagues looked at the distribution of the *Aa* JP2 genotype in all the world continents, except Oceanic region. Pinheiro and others tracked the *Aa* JP2 genotype in four continents, namely Asia, Africa, Europe, and South America. The included studies covering the presence of the JP2 genotype of *Aa* could be tracked back to the most of the world's continents, but not in Oceania. Nine of the included studies were cross-sectional studies [27, 37, 43, 47, 59–61, 66, 68], three studies were longitudinal follow up papers [39, 58, 62], and one study was cross-sectional with longitudinal follow-up [42]. Furthermore, five studies were case–control studies [44, 46, 52, 63, 64], other three publications were case reports [32, 36, 75], and one was a retrospective study [35]. Twenty-nine of the included studies did not report about their study design.

Seventeen of the included surveys had a sample made up mainly of Caucasian subjects and have been conducted in the European population looking for the prevalence of the *Aa* JP2 genotype in Europe [27, 13, 28, 29, 22, 30, 32, 32–37, 73, 70, 71, 74]. Most of the European studies were conducted in the Scandinavian countries and in Germany. In fifteen of those studies, the age range of the participants included were between 7 and 92 years old, and two of the studies did not report on the age of the included subjects [27, 73]. Female-to-male distribution was reported in ten of the included seventeen studies. There were five hundred twenty-two female and eight hundred eleven male subjects in ten of the included studies. Three hundred and thirty-five male subjects were army recruits from two studies conducted in Germany [28, 29]. Three subjects did not declare their gender status in one study [37]. Total number of subjects included in this European population was 3253.

Eleven studies looked for the distribution of the *Aa* JP2 genotype in Africa [61–69, 73, 74]. Most of the African studies were conducted in Morocco. In seven of those studies, the age of the included subjects ranged between 7 and 55 years. Four studies did not report on the age range of the included participants [62, 66, 73, 74]. Female-to-male distribution was reported in six publications. There were seven hundred ninety-seven female and six hundred sixty-six male subjects included in six publications. The total number of subjects included in the African population was 2498.

Twelve of the included surveys had a sample made up mainly of Asian subjects, and have been conducted in an Asian population looking for the presence of the *Aa* JP2 genotype in Asia [26, 53–60, 71, 73, 74]. In nine of the included studies, the age of the subjects included ranged between 15.8 and 66 years, and the rest of the studies did not report on the age range of the included participants [58, 73, 74]. Female-to-male distribution was reported in six studies [53, 54, 57, 59, 60, 71]. There were three hundred ninety-five female and five hundred thirty-seven male participants included in six publications. The total number of subjects included in this Asian population was 1238.

In North America, most of the publications regarding the presence of the *Aa* JP2 genotype were conducted in the USA, except of one study in Mexico [43]. Ten North American publications explored the presence of the *Aa* JP2 genotype in this region [38–44, 70, 72, 73]. The age of the participates in three of the included studies ranged between 6 and 60 years [41, 42, 44]. Female-to-male distribution was reported in five studies only [41–44, 72]. There were 804 female and 644 male subjects included in five publications. In one study, one patient gender was not clear [41]. The total number of the subjects included in the North American population was 1988.

Finally, in South America most of the publications regarding the presence of the *Aa* JP2 genotype were conducted in Brazil, except for one Chilean study [73]. Ten South American publications explored the presence of the *Aa* JP2 genotype in this region [45–52, 73, 74]. The age of

Table 1 Study characteristics

Author/year	Country	Design	Subject number, origin and JP2-positive subjects
Chung et al. (1989) [26]	South Korea	NR	16 subj. with localized juvenile periodontitis, 8 subj. were + JP2 (50%)
DiRienzo and McKay (1994) [38]	The United State	LS	73 subj. = periodontitis and periodontally healthy in localized juvenile periodontitis family, 30 healthy control, no positive JP2 subj. reported (0%)
Haubek et al. (1995) [27]	Finland	CSS	88 Caucasian subj., no positive JP2 subj. reported (0%)
Haubek et al. (1996) [13]	Denmark, Sweden	NR	17 mixed subj., Cape Verde Islands, Morocco, Algeria, Kuwait, 11 subj. were + JP2 (64.7%)
Haubek et al. (1997A) [73]	29 countries	NR	326 mixed subj. = 47 Asian, 171 European, 32 African, 44 South American, 32 United States, 38 subj. were + JP2 (11.6%)
Asikanen et al. (1997) [70]	Finland, The United State	NR	163 subj. = 112 subj. Finland (54 localized juvenile periodontitis + 58 adult periodontitis), 51 United States (14 early onset periodontitis + 37 adult periodontitis), 3 subj. were + JP2 (1.8%)
Tinoco et al. (1997) [45]	Brazil	NR	36 subj. = 8 periodontally healthy, 19 localized juvenile periodontitis, 9 adult periodontitis, 5 subj. were + JP2 (13.8%)
Bueno et al. (1998) [39]	The United State	LS	58 mixed subj. (24 localized juvenile periodontitis, 34 healthy) African American, Asian, Caucasian, others, 8 subj. were + JP2 (13.7%)
Mombelli et al. (1998) [53]	China	NR	60 Asian subj., no positive JP2 subj. reported (0%)
Macheleidt et al. (1999) [28]	Germany	NR	238 Caucasian army subj. = 201 periodontally healthy + 37 periodontitis, one subj. was + JP2 (0.4%)
Mombelli et al. (1999) [54]	China	NR	185 Chinese subj. = 31 moderate advanced adult periodontitis, 73 workers in factory, 81 rural area, no positive JP2 subj. reported (0%)
He et al. (1999) [55]	Japan	NR	42 Japanese subj. periodontitis, no positive JP2 subj. reported (0%)
Contreras et al. (2000) [40]	The United State & Jamaica	NR	265 mixed subj. = 69 Caucasian, 43 Hispanic, 27 Asian, 26 African American, 100 African-Caribbeans, 12 subj. were + JP2 (4.5%)
Haraszthy et al. (2000) [72]	The United State	NR	146 mixed subj. = 82 African American, 44 Caucasian, 13 Hispanic, 7 Asian American, 41 subj. were + JP2 (28%)
Tan et al. (2001) [56]	Singapore	NR	92 Chinese adult = 42 periodontitis + 50 periodontally healthy, no positive JP2 subj. reported (0%)
Müller et al. (2001) [29]	Germany	NR	97 mixed army subj., 17 healthy had *Aa* in pooled subgingival plaque sample, 17 = 16 Caucasian and 1 female had African American father, no positive JP2 subj. reported (0%)
Haubek et al. (2001) [61]	Morocco	CSS	301 adolescents school students, 19 subj. were + JP2 (6.3%)
Kaplan et al. (2002) [41]	The United State	NR	33 mixed subj. = 20 localized juvenile periodontitis + 4 periodontally healthy (9 reference), 21 African, 8 Caucasian, 1 Hispanic, 1 Asian, 2 NR, 8 subj. were + JP2 (24.2%)
Cortelli et al. (2003) [46]	Brazil	CCS	136 subj., 11 subj. were + JP2 (8%)
Haubek and Westergaard (2004) [75]	Denmark	CR	7 Moroccan migrant family, male dizygotic twins, 4 subj. were + JP2

Table 1 (continued)

Author/year	Country	Design	Subject number, origin and JP2-positive subjects
Cortelli et al. (2005) [47]	Brazil	CSS	203 subj. = 25 localized aggressive periodontitis + 178 chronic periodontitis, 29 subj. were + JP2 (14.2%)
Leung et al. (2005) [57]	China	NR	56 subj. = 9 aggressive periodontitis and 47 dental students control, no positive JP2 subj. reported (0%)
Rosalem Junior et al. (2006) [48]	Brazil	NR	40 subj. = 20 periodontally healthy and 20 chronic periodontitis, 2 subj. were + JP2 (5%)
Orru et al. (2006) [30]	Italy	NR	81 Sardinian subj, 6 subj. were + JP2 (7.4%)
Fine et al. (2007) [42]	The United State	CSS-LS	1,075 mixed school students, 410 African American, 598 Hispanic, 2 Asian, 23 Caucasian non-Hispanic & 28 NR, 7 subj. were + JP2 (0.6%)
Van Der Reijden et al. (2008) [58]	Indonesia	LS	107 Western Java subj., no positive JP2 subj reported (0%)
Haubek et al. (2008) [62]	Morocco	LS	682 periodontally healthy school students, 11 public schools, at re-exam of 428 subj., 50 subj. were + JP2 (7.3%)
Kim et al. (2009) [71]	Germany, South Korea	NR	194 subj. = 96 Germans + 98 Koreans with aggressive periodontitis or severe chronic periodontitis, no positive JP2 subj. reported (0%)
Vieira et al. (2009) [49]	Brazil	NR	86 subj. = 48 native Brazilians gingivitis & 38 chronic periodontitis, Umutima Indian Reservation, no positive JP2 subj. reported (0%)
Sakellari et al. (2011) 31	Greece	NR	228 subj. = 77 non-periodontitis + 151 periodontitis (91 + 46 supportive periodontal therapy), Periodontitis subj. either un-treated or supportive periodontal therapy
Elamin et al. (2011) [63]	Sudan	CCS	34 students, 17 aggressive periodontitis + 17 control, no positive JP2 subj. reported (0%) African Arab: 12 (aggressive periodontitis) + 13 (control), African tribes 4 (aggressive periodontitis) + 4 (control), no positive JP2 subj. reported (0%)
Pinheiro et al. (2011) [74]	Brazil, Sweden, Kenya, Japan	NR	26 mixed subj. = 17 Brazilian (6 chronic periodontitis + 6 aggressive periodontitis + 5 healthy students), 3 Sweden aggressive periodontitis, 4 Kenya mild periodontitis, 2 Japan inactive sites & deep periodontal pockets, two subj. were + JP2 (7.6%)
Claesson et al. (2011) [32]	Sweden	CR	3 Caucasian European subj. = daughter, mother & father, two subj. were + JP2
Bandhaya et al. (2012) [59]	Thailand	CSS	453 plant employees, no positive JP2 subj. reported (0%)
Jentsch et al. (2012) [33]	Germany	NR	99 subj. = Frankfurt 18, Hamburg 18, Jena 27, Leipzig 36 52 aggressive periodontitis, 46 chronic periodontitis, 1 with Papillon–Lefèvre syndrome, Two subj. were + JP2 (2%)
Aberg et al. (2012) [64]	Ghana	CCS	500 adolescents, 44 subj. were + JP2 (8.8%)
Ennibi et al. (2012) [65]	Morocco	NR	70 young periodontitis subj. = 41 localized aggressive periodontitis + 29 generalized aggressive periodontitis, 54 subj. were + JP2 (77%)
Wahasugui et al. (2013) [50]	Brazil	NR	113 subj. = 65 with periodontal pockets, loss of attachment & bone loss confined to molars/incisors and periodontal pocket ≥ 5 mm, 48 healthy, 64 subj. were + JP2 (56.6%)

Table 1 (continued)

Author/year	Country	Design	Subject number, origin and JP2-positive subjects
Martinez-Martinez et al. (2013) [43]	Mexico	CSS	75 Down syndrome subj. = 45 periodontitis + 30 non-periodontitis, no positive JP2 subj. reported (0%)
Silveira et al. (2013) [51]	Brazil	NR	109 subj. = 35 generalized aggressive periodontitis (test), 33 family members, 41 chronic periodontitis (control), 33 family members = 10 aggressive periodontitis, 12 chronic periodontitis, 11 periodontal healthy, Two subj. were + JP2 (1.8%)
Minguez et al. (2014) [34]	Spain	NR	Positive 40 *Aa* periodontitis Caucasian subj., no positive JP2 subj. reported (0%)
Elabdeen et al. (2015) [66]	Sudan	CSS	34 = 19 aggressive periodontitis (10 generalized aggressive periodontitis + 9 localized aggressive periodontitis). 15 healthy employees or school student, One subj. was + JP2 (2.9%)
Minguez et al. (2016) [67]	Morocco	NR	59 periodontitis subj., data available from 45 subj., Two subj. were + JP2 (3.3%)
Jensen et al. (2016) [68]	Morocco	CSS	513 children, 46 subj. were + JP2 (8.9%)
Burgess et al. (2017) [44]	The United State	CCS	180 African American subj. = 60 localized aggressive periodontitis + 60 healthy siblings of localized aggressive periodontitis + 60 healthy control, 90 subj. were + JP2 (50%)
Claesson et al. (2017) [35]	Sweden	RS	1445 subj. = 337 younger (young subj ≤ 35 years), 1108 older (old subj. > 35 years) during 15 years (2000–2014), 17 subj. were + JP2 (1%)
Suprith et al. (2018) [60]	India	CSS	80 subj., no positive JP2 subj. reported (0%)
Amado et al. (2020) [52]	Brazil	CCS	14 African Brazilian, 7 subj. are stage-III, grade-C Molar-Incisor periodontitis, 7 subj. age-gender-race-matched control, One subj. was + JP2 (7%)
Stahli et al. (2020) [36]	Germany	CR	3 non-African, female married to North African male, 17 yrs daughter aggressive periodontitis positive JP2. Both females had chronic periodontitis, two subj. were + JP2
Jensen et al. (2020) [37]	Denmark	CSS	525 subj., 60% of invited subj., No positive JP2 subj. reported (0%)
Haubek et al. (2021) [69]	Kenya	NR	284 Maasai Mara healthy adolescents recruited from schools, Two subj. were + JP2 (0.7%)

NR not reported, *subj* subjects, *LS* longitudinal study, *CSS* cross-sectional study, *CCS* case–control study (CCS), *CR* case report

the participants in six of the included studies ranged between 11 and 96 years. Female-to-male distribution was reported in four studies only [47, 48, 50, 52]. There were 217 female and 99 male subjects included in four publications. The total number of the subjects included in this North American population was 767.

Inclusion and exclusion criteria were stated in 21 and 22 of the included studies, respectively. No systemic antibiotics and no history of periodontal treatment are among the two most mentioned exclusion criteria in the included studies. The definition of periodontitis in the included studies w heterogeneous and inconsistent. Six of the included studies conducted between 1989 and 2001 used Baer's definition of periodontitis [26, 27, 41, 45, 70, 73, 76]. In one study conducted in 2001 by Haubek and co-authors, participants were classified as having periodontitis according to the criteria described by Baer and detailed by Albandar [61, 76, 77]. In another of Haubek's studies, the incidental attachment loss was defined according to Löe and Brown 1991 [78]. One study by Fine and co-workers, conducted in 2007, used Löe and Brown 1991 classification of periodontitis [78]. Eleven of the included studies used the diagnostic criteria presented in the World Workshop of Periodontology 1999 [22, 31, 33, 34, 46, 47, 51, 60, 65–67, 79]. One study by Burgess and others, conducted in 2017, used diagnostic criteria adapted by Armitage in 1999 and Albandar in 2014 [79, 80]. In a case report published in 2020, the authors used a diagnostic criterion adapted from the Centre for Disease Control

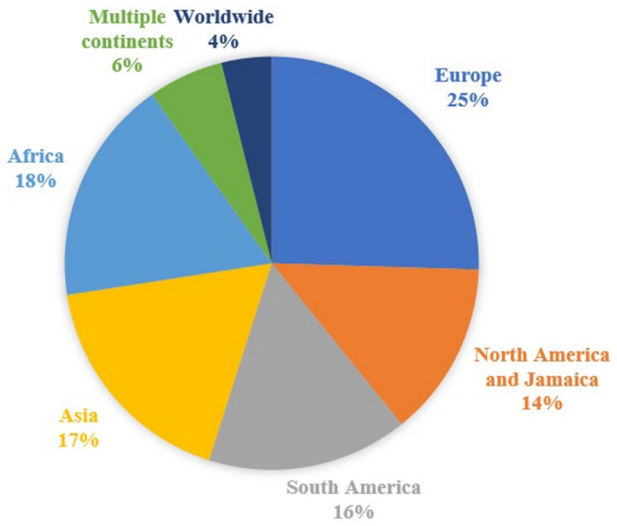

Fig. 2 The frequency of studies per their geographic distribution (pie chart, Excel Microsoft)

and Prevention and the American Academy of Periodontology [79, 81, 82]. Amado, in his research published in the year 2020, used the new staging and grading classification of periodontitis, the 2017 classification of periodontal and peri-implant diseases and conditions [83]. The rest of the included studies did not use a clear definition of periodontitis or used their own diagnostic criteria. Eighteen studies mentioned the number of the examiners, who conducted the periodontal examination and the microbiological sampling [31, 37, 42–45, 48, 51, 52, 56, 59, 61, 62, 64, 66–68, 71]. Twelve studies reported that their examiners were calibrated [31, 37, 42, 43, 48, 51, 59, 61, 64, 66, 68, 71]; in the other studies, it was not clear if there was any calibration process [44, 45, 52, 56, 62, 67]. In two of the included studies, the examiners were periodontists [56, 68]. The gold standard of measuring periodontitis is to measure the clinical attachment levels. Most of the studies examined the clinical attachment levels for some teeth or all fully erupted teeth, including or excluding the wisdom teeth. Some of the studies measured the clinical attachment levels on all surfaces; other studies choose to use four surfaces. A manual periodontal probe was used in most of the studies. Only few studies used automatized or force-controlled periodontal probes, like Brodontics probes (Brodontics Ash/Dentsply, York, UK, 240 N/cm2) and FP32 Florida probes (Florida Probe Corporation, Gainesville, FL, USA). [31, 58]. Only few studies used radiographs as part of their screening and periodontal examination protocols. Few studies used orthopantomogram x-rays [29, 70, 75]. Other studies only included intra-oral x-rays, like periapical and bitewings [44, 62, 65, 66, 68, 70, 75]. In four of the included studies, it was not clear if any x-rays were taken [32, 36, 39, 60]. In another study, only one patient, who was positive to the JP2 genotype of *Aa*, had full-mouth periapical x-rays taken and clinical photographs [28]. Few studies carried out photographic examination of their participants [28, 32, 32, 69]. Table 2 illustrates disease definition and examination protocols employed in the included studies.

Detection of the JP2 genotype of *Aa* was conducted mainly using polymerase chain reaction methodology (PCR) in most of the included studies. In a study by Chung and co-authors carried out in 1989, lactate dehydrogenase release from polymorphonuclear leukocytes exposed to *Aa* was used to detect the JP2 genotype of *Aa* in a Korean population [26]. In another study by DiRienzo and McKay in 1994, isolates were assessed using restriction fragment length polymorphism (RFLP) combined with an anonymous probe cloned from *Aa* [38]. Haubek and colleagues used multilocus enzyme electrophoresis (MEE) to explore subgingival plaque samples for the JP2 genotype of *Aa* [27]. Two of the included studies assessed subgingival plaque samples using loop-mediated isothermal amplification and PCR [43, 63]. In most of the included studies, their samples were collected using sterile curettes, a sterile Gracey curette, a Morse detachable sterile scaler, sterile paper points, sterile cotton swabs, or a wooden tongue depressor. Included studies reported different sources of the samples as follows: subgingival plaque from periodontal pocket (healthy and diseased) or normal gingival crevice, supragingival plaque, endocarditis lesions, mucosal lesions, human blood, actinomycotic or other abscesses, pus, expectorates, periapical granuloma, unstimulated saliva, stimulated saliva, cheek mucosa, tongue dorsum, mucous membrane, tonsils, buccal gingiva, and faeces. Most of the isolated samples were pooled and then submitted for analysis. Few studies looked for the presence of other bacteria than *Aa* [30, 32, 36, 43, 47, 52, 53, 66, 67]. Table 3 illustrates the geographic origin of the JP2 genotype of *Aa* reported in the included studies.

Seventeen surveys using a sample consisting of Caucasian subjects have been conducted in European populations looking for the presence of the *Aa* JP2 genotype in Europe [27, 13, 28, 29, 22, 30, 31, 32, 33, 34, 35, 36 37, 73, 70, 71, 74]. The total number of subjects included in this European population was 3253 subjects. Only 83 (2.5%) participants were positive for the JP2 genotype of *Aa*. Among these, 62 were of African origin (13 from Cape Verde Islands, 17 Moroccan, 4 Algerian, 3 Ghanaian, two African immigrant from Germany, one Gambian, one Ethiopian, 4 African Brazilin and 17 African American). Three of the JP2 genotype-positive subjects were from Asia (one from Israel and two from Iraq). The remaining eighteen were of European origin (six Sardinian, two Germans, seven Swedish, one Croatian and two from Germany with no African origin) (Table 1). Eleven surveys using a sample made up mainly of African subjects have been conducted in African populations looking for the

Table 2 Disease definition and examination protocols of the included studies

Author/year	Disease definition/examiner	Periodontal/X-rays/photographic examination
Chung et al. (1989) [26]	Baer (1971)	Plaque, BoP, gingival crevicular fluid, PPD, CAL
Haubek et al. (1995) [27]	Baer (1971)	NR
Haubek et al. (1996) [13]	NR	NR
Haubek et al. (1997A) [73]	Baer (1971)	NR
Asikanen et al. (1997) [70]	Baer (1971)	Orthopantomograph, periapical x-ray when indicated
Tinoco et al. (1997) [45]	Baer (1971)	NR
Bueno et al. (1998) [39]	NR	Plaque, gingival, eruption, Decayed-Missing-Filled, PPD, CAL, BoP
Mombelli et al. (1998) [53]	NR	Plaque, gingival at 6 surfaces/tooth except third molar
Macheleidt et al. (1999) [28]	NR	PPD, BoP, plaque, calculus, 6 sites, MP
Mombelli et al. (1999) [54]	Community periodontal index	NR
He et al. (1999) [55]	Adult periodontitis based on age of onset, PPD, bone loss	NR
Contreras et al. (2000) [40]	NR	NR
Haraszthy et al. (2000) [72]	NR	NR
Tan et al. (2001) [56]	One periodontist, NR	NR
Müller et al. (2001) [29]	NR	6 sites/tooth. PPD, CAL, BoP, plaque. MP. Orthopantomograph
Haubek et al. (2001) [6(1]	Baer (1971), Albandar (1997), incidental clinical attachment loss by Loe (1991), calibrated periodontist	CAL of mesial/distal sites from both buccal/lingual, MP
Kaplan et al. (2002) [4(1]	Baer (1971)	-
Cortelli et al. (2003) [46]	AAP (1999)	PPD, CAL, plaque, BoP, periapical x-ray
Haubek and Westergaard (2004) [75]	AAP (1999)	PPD, CAL, 6 sites/tooth. Orthopantomograph, bitewing x-ray
Cortelli JR et al. (2005) [47]	AAP (1999)	PPD, CAL/6 sites, plaque/BoP, Michigan MP
Leung et al. (2005) [57]	NR	6 sites PPD, William's 14 W MP, BoP/CAL/plaque
Rosalem Junior et al. (2006) [48]	NR	6 sites/tooth. PPD, CAL, plaque, BoP, pus, North Carolina MP
Orru et al. (2006) [30]	NR	PPD, CAL, BoP, 6 sites/tooth
Fine et al. (2007) [42]	Loe (1991)	6 sites/tooth, bitewing x-ray, Michigan 0 MP
Van Der Reijden et al. (2008) [58]	NR	Plaque, calculus, BoP, force-controlled probe PPD (Brodontics)
Haubek et al. (2008) [62]	NR	CAL, PPD at buccal of mesial/distal surfaces of all teeth, bitewing x-ray
Kim et al. (2009) [71]	NR	Plaque, BoP, PPD, CAL at 4 sites/tooth, MP
Vieira et al. (2009) [49]	NR	PPD, CAL, BoP
Sakellari et al. (2011) [31]	AAP (1999)	PPD, gingival recession, BoP, at 6 sites, FP32 Florida probe & MP
Elamin et al. (2011) [63]	NR	CAL
Claesson et al. (2011) [32]	NR	Photographs
Bandhaya et al. (2012) [59]	NR	PPD, gingival recession, CAL at 6 sites/tooth, MP
Jentsch et al. (2012) [33]	AAP (1999)	CAL, PPD with MP at 6 sites/tooth, BoP, plaque
Aberg et al. (2012) [64]	NR, calibrated periodontist	PPD, gingival recession, MP
Ennibi et al. (2012) [65]	AAP (1999)	Gingival, plaque, CAL, PPD 6 sites MP, periapical x-ray
Martinez-Martinez et al. (2013) [43]	NR, calibrated examiner	PPD, CAL, Michigan MP
Silveira et al. (2013) [51]	AAP (1999), calibrated examiner	MP, plaque, gingival, PPD, CAL 6 sites/tooth
Minguez et al. (2014) [34]	AAP (1999)	CAL, BoP, plaque, PPD, gingival recession, pus

Table 2 (continued)

Author/year	Disease definition/examiner	Periodontal/X-rays/photographic examination
Elabdeen et al. (2015) [66]	AAP (1999, calibrated examiner	Plaque, gingival, BoP, gingival recession, PPD, CAL at 6 sites/tooth, MP
Minguez et al. (2016) [67]	AAP (1999), two examiners	Plaque, BoP, pus, PPD, gingival recession
Jensen et al. (2016) [68]	NR, calibrated periodontist	MP, CAL/4 sites, PPD, calibrated bitewing x-ray, film holder
Burgess et al. (2017) [44]	AAP (1999), Albandar (2014)	6 sites/tooth, PPD, CAL, BoP, plaque MP UNC-15 all data stored in Florida Probe. Bitewing & periapical x-ray
Claesson et al. (2017) [35]	NR	NR
Suprith et al. (2018) [60]	AAP (1999)	Periodontal chart, oral hygiene Index, plaque, gingival, Russell's PD index
Amado et al. (2020) [52]	Tonetti et al. (2018)	BoP, PPD, gingival recession, CAL 6 sites/tooth. North Carolina MP
Stahli et al. (2020) [36]	Centre for Disease Control & Prevention/AAP (1999)	NR
Jensen et al. (2020) [37]	NR, calibrated examiner	6 sites/tooth by Deppeler periodontal probe, plaque, BoP, PPD, CAL
Haubek et al. (2021) [69]	NR	Intraoral photographs

NR not reported, *PPD* periodontal pocket depth, *BoP* bleeding score, *MP* manual probe, *AAP* American Academy of Periodontology, *CDC* Centre for Disease Control & Prevention

prevalence of the JP2 genotype of *Aa* in Africa [61–69, 73, 74] (Table 1). The total number of subjects included in this African population was 2498. Only 228 (9.1%) subjects were positive for the JP2 genotype of *Aa*. Seventy-six percent of these 228 subjects were Moroccan ($n = 174$). The rest of the individuals positive for the JP2 genotype of *Aa* cases were distributed as follows: forty-five Ghanaian, two Algerian, six from Cape Verde Island, and one Sudanese. Twelve surveys using a sample made up mainly of Asian subjects have been conducted in an Asian population looking for the presence of the *Aa* JP2 genotype in Asia [26, 53–60, 71, 73, 74]. The total number of subjects included in this Asian population was 1238. Only 8 (0.6%) Koreans were positive to the JP2 genotype of *Aa* (Table 1). Ten North American publications explored the presence of the *Aa* JP2 genotype in this region [38–44, 70, 72, 73]. The total number of the subjects included in this North American population was 1988. Only 186 (9.3%) of them were positive for the JP2 genotype of *Aa*. Eightone percent of the 186 positive subjective were African American of origin ($n = 164$). The remaining of the positive individuals was as follows: 9 Hispanic (one of them from Israel), 9 Jamaican Afro-Caribbean, 1 Caucasian, one unknown, and two reference positive samples (Table 1). Ten South American publications explored the presence of the JP2 genotype of *Aa* in this region [45–52, 73, 74]. The total number of the subjects included in the South American population was 767. Only 116 (15.1%) of them were positive to the JP2 genotype of *Aa*. All of them (100%) were Brazilians (Table 1).

Publication bias

Every included study was assessed using the JBI tool (Table 4). Thirty-one studies were considered as a low risk of bias research, while the rest of the studies were considered a high risk of bias [29, 31, 33–35, 37, 41–48, 50–52, 54, 59–69, 72].

Grading the quality of evidence

Every included study was assessed according to the GRADE system (Table 5). The strength of recommendation based on the quality of the evidence emerged from this review is estimated to be weak.

Discussion

Early publications suggested that *Aa* was the main microbe behind the initiation of the aggressive form of periodontitis. The association of *Aa* with periodontitis was reinforced by the fact that *Aa* released leukotoxin that killed human immune cells as well as other virulence factors that gave biological plausibility to *Aa* as an etiological agent [44, 84]. However, the role of *Aa* with respect to causation is challenged and although *Aa* is necessary for disease, it needs help from other microbes in the biofilm and some

Table 3 Source, sample numbers and the geographic origin of the JP2 genotype of *Aa* reported in the included studies

Author/year	/Number of samples/source	Presence of JP2 genotype of *Aa*/geographic origin
Chung et al. (1989) [26]	46	10 out of 46 isolates from 13 disease sites in 8 subj. were + JP2
DiRienzo and McKay (1994) [38]	624/subgingival plaque samples	NR
Haubek et al. (1995) [27]	88/subgingival plaque samples	NR
Haubek et al. (1996) [13]	17/subgingival plaque samples	+ JP2 in 11 African decent/6 Cape Verde Islands, 3 Moroccan, 2 Algerian
Haubek et al. (1997A) [73]	326 *Aa* isolates, 225 isolates = subgingival plaque samples subj. with periodontitis, 52 periodontally healthy, 6 endocarditis, 2 mucous membrane, 1 blood, 12 actinomycotic abscesses, 13 pus, 3 expectorates, 1 PA granuloma, 1 saliva, 10 NR	38 isolates were + JP2/1 Israeli, 7 Moroccan, 2 Algerian, 1 Ghanaian, 6 Cape Verde Islanders, 4 African Brazilian, 17 African American
Asikanen et al. (1997) [70]	163/112 *Aa* Finish subgingival plaque sample isolates from 112 subj., 51 *Aa*/United State subj	3 United States + JP2 from 8 and 13 years black subj. and 33 years old of NR race, but United States
Tinoco et al. (1997) [45]	36 *Aa* strains	+ JP2 in 5 isolates from 3 localized juvenile periodontitis and 2 healthy subj., from one family with localized juvenile periodontitis
Bueno et al. (1998) [39]	24 and 34 of localized juvenile periodontitis-susceptible and control children/subgingival plaque samples	8 of 24 localized juvenile periodontitis subj. were positivefor JP2, none of 34 control had JP2/15 subj. in 10 families had JP2/African American origin 2
Mombelli et al. (1998) [53]	60/subgingival plaque samples	NR
Macheleidt et al. (1999) [28]	1005/subgingival plaque samples	Positive for JP2 genotype in one 24-yr old/African Ghanaian, localized juvenile periodontitis
Mombelli et al. (1999) [54]	370/subgingival plaque samples	NR
He et al. (1999) [55]	45 *Aa* isolates (2 references), subgingival plaque samples	NR
Contreras et al. (2000) [40]	NR	12 of 94 + *Aa* subj. had JP2/11 black United States or Jamaica = 2 African Americans + 9 Jamaican Afro-Caribbean, 1 Hispanic
Haraszthy et al. (2000) [72]	636	+ JP2 in subj. with localized juvenile periodontitis or early onset periodontitis. 39 of 71 localized juvenile periodontitis subj. and 2 of 4 early onset periodontitis were + JP2/ + JP2 41 subj. = 33 African American, 1 Caucasian, 7 Hispanic, 0 Asian American
Tan et al. (2001) [56]	92/subgingival plaque samples	-
Müller et al. (2001) [29]	221 from mucosa of oro-pharyngeal cavity + saliva , 477 pooled subgingival plaque sample from mesial surface of first molar, unstimulated saliva, left/right cheek mucosa, dorsum tongue	NR
Haubek et al. (2001) [61]	301/Subgingival plaque samples from 301 adolescents	19 + JP2 in 15 subj. = 4 healthy, 2 early onset periodontitis, 7 generalized juvenile periodontitis, 2 incidental loss of attachment
Kaplan et al. (2002) [41]	33	Of 33 strains, 8 + JP2 = 5 of 20 early onset periodontitis, 1 healthy subj. (2 references)/ all 6 + JP2 African American
Cortelli SC et al. (2003) [46]	136/subgingival plaque samples	+ JP2 in 11 = 7 aggressive periodontitis, 2 chronic periodontitis, 2 gingivitis
Haubek and Westergaard (2004) [75]	7/subgingival plaque samples	+ JP2 in 4 Moroccan kids with periodontitis/Moroccan subj.
Cortelli et al. (2005) [47]	NR	+ JP2 in 29 Brazilian = 14 chronic periodontitis + 15 aggressive periodontitis/Brazilian subj.
Leung et al. (2005) [57]	112, 2 subgingival plaque samples/subj. collected from 9 aggressive periodontitis and control	NR
Rosalem Junior et al. (2006) [48]	Subgingival plaque samples	+ JP2 in 4 diseased sites from 2 chronic periodontitis/Brazilian subj.

Table 3 (continued)

Author/year	/Number of samples/source	Presence of JP2 genotype of *Aa*/geographic origin
Orru et al. (2006) [30]	Subgingival plaque samples, saliva	6 Sardinian subj. were + JP2 = 4 aggressive periodontitis + 2 chronic periodontitis/Sardinian subj.
Fine et al. (2007) [42]	Unstimulated salvia, buccal epithelium cells, epithelial tongue dorsum, subgingival plaque samples from periodontal pocket ≥ 5 mm	7 + JP2 subj./6 African American + one Hispanic
Van Der Reijden et al. (2008) [58]	4 sites/ subj. sampled using 2 PP/site, PP pooled/ subj.	NR
Haubek et al. (2008) [62]	2/subgingival plaque samples, each pooled sample from 4 periodontal pocket sites/ subj	50 subj., + JP2 16 based on incisor/molar subgingival plaque samples
Kim et al. (2009) [71]	Subgingival plaque samples	NR
Vieira et al. (2009) [49]	Supra & subgingival plaque samples	NR
Sakellari et al. (2011) 31	228 subj./each with one pooled subgingival plaque samples	NR
Elamin et al. (2011) [63]	Subgingival plaque samples	NR
Pinheiro et al. (2011) [74]	26	+ JP2 in 2 aggressive periodontitis/Brazilian subj.
Claesson et al. (2011) [32]	Subgingival plaque samples	+ JP2 in 2 of family member, 33 years daughter, 62 yrs mother Germans
Bandhaya et al. (2012) [59]	Subgingival plaque samples	NR
Jentsch et al. (2012) [33]	99/subgingival plaque samples	+ JP2 in 2 African immigrants in Frankfurt
Aberg et al. (2012) [64]	Subgingival plaque samples	44 subj. + JP2
Ennibi et al. (2012) [65]	Subgingival plaque samples	+ JP2 in 34 of localized aggressive periodontitis subj versus 20 of generalized aggressive periodontitis
Wahasugui et al. (2013) [50]	NR	+ JP2 in 64 subj.
Martinez-Martinez et al. (2013 [43]	Subgingival plaque samples	NR
Silveira et al. (2013) [51]	Subgingival plaque samples	+ JP2 in 2 subj., 37 yrs old male with generalized aggressive periodontitis, 31 yrs old female with generalized aggressive periodontitis
Minguez et al. (2014) [34]	Subgingival plaque sample, + 40 *Aa* periodontitis subj, 1–3 isolates/ subj	NR
Elabdeen et al. (2015) [66]	NR	+ JP2 in 1 subj.
Minguez et al. (2016) [67]	Subgingival plaque samples	+ JP2 in 2 females aggressive periodontitis
Jensen et al. (2016) [68]	Subgingival plaque samples	513 = 46 + JP2 subj.
Burgess et al. (2017) [44]	240/subgingival plaque samples	+ JP2 in 90 of 180 subj., 50 localized aggressive periodontitis + JP2 in diseased/healthy site, 16 were healthy sites, 24 healthy control
Claesson et al. (2017) [35]	347 isolates belong to subpopulation of 1,357 subj.	17 + JP2 subj., 13 + JP2 Mediterranean JP2, (7 Sweden, 1 Algerian, 1 Croatia, 2 Iraq, 1 Cape Verde Islands, 3 Morocco, 1 Gambia, 1 Ethiopia)
Suprith et al. (2018) [60]	Subgingival plaque samples	NR
Amado et al. (2020) [52]	Supra and subgingival plaque samples, faces, US	+ JP2 in one, Grade-C/molar-incisor periodontitis subj biofilm/African-descendants
Stahli et al. (2020) [36]	NR	1 female JP2 + and her 17 yrs old daughter/Caucasian
Jensen et al. (2020) [37]	Stimulated saliva, subgingival plaque samples	NR
Haubek et al. (2021) [69]	Subgingival plaque samples	+ JP2 in 2 subj.

NR not reported, *Subj* subjects, + positive result, *SPP/PP* sterile paper point

weaknesses in the host immune system (susceptibility) [84]. The presence of the highly leukotoxic *Aa* strain makes the association of *Aa* with causation likely more relevant. Few longitudinal studies revealed an increased relative risk for the JP2 strain to cause the change from health to disease in African adolescents [42, 62, 84]. While all studies do not support the role of *Aa* in the aggressive form of periodontitis, almost all studies of adolescents of African descent do support this observation. The most likely explanation for these discrepancies can be due to geographic, ethnicity (genetic profile), host immune response, access to dental care, genetic differences in susceptibility, and the microbial composition of the biofilm.

In addition to the JP2 genotype of *Aa*, two other leukotoxin promoter deletions have been reported, one with a 640-bp deletion and one with a 230-bp deletion [85, 86]. Both carriers of these promoter types were suffering from periodontitis and were below the age of 25. Another novel leukotoxin promoter type had a 172-bp duplication [86]. However, probably additional leukotoxin promoter types exist undetected. It is a risk that these putative types pass under the radar and remain undetected. Possibly, the methods used for detection of the JP2 have to be adjusted for a detection of other leukotoxin promoter types in addition to the JP2 type. The JP2 genotype is mainly detected among individuals of African origin [87]. Individuals of non-African origin carrying the JP2 genotype do exist but are not frequently reported [32, 36]. The widespread geographic locations of these observations raise the question of the clonality for the JP2 genotype, which most likely will require further genome sequencing data to elucidate. Previous work on the JP2-genotype strains of *Aa* claims a clonality in the JP2 genotype with a common ancestor from the Mediterranean part of North Africa. The recent findings of JP2 genotype in nearly all parts of the world indicate a substantial transmission. Could that indicate transmission from the ancestor or have new deletions occurred? Further studies of the leukotoxin promoter region are needed.

The current systematic review assessed the presence of the JP2 genotype of *Aa* in the world population. In the 1990s, the highly leukotoxic JP2 genotype of *Aa* was described, and it has been shown to be strongly associated with rapidly progressing forms of periodontitis, particularly in North-West Africans and the Americans [11, 13]. Patients with this aggressive form of periodontitis warrant close monitoring of their periodontal status, as the risk for developing severely progressing periodontitis lesions, tooth mobility, migration, tooth loss, and altered function is very high. The patients are also at risk of psychological issues due to poor aesthetic outcome and low self-esteem. To effectively manage this disease, timely periodontal treatment, including periodontal surgery, supplemented by the use of antibiotics might be needed. More importantly, periodontal attachment loss could be potentially prevented by early detection of the JP2 genotype of *Aa* by microbial sampling and/or other types of testing of *Aa*.

An age predilection for the JP2 genotype of *Aa* infection of only the young appears, however, to be in contrast with the result of this systemic review [88]. The number of positive cases of the JP2 genotype of *Aa* under the age of 18 years old was 196 versus 91 cases above the age of 18. This shows that the infection with the JP2 genotype of *Aa* can affect the adults. However, the age data must be interpretation with great caution, as some of the included studies did not have a clear age of the included subjects. In one Moroccan study, it was investigated if the JP2 genotype of *Aa* was particularly linked to the localized forms versus the generalized forms of aggressive periodontitis [65]. It was found that localized as well as generalized aggressive periodontitis patients were positive for the JP2 genotype of *Aa* (83% versus 69%). Since patients with generalized periodontitis are generally older than patients with localized periodontitis, it appears that adults could be colonized with the JP2 genotype of *Aa* as well as children and adolescents but less frequently, which is in line with the findings of this review. Furthermore, two published case reports showed that some of the family adult members were positive for the JP2 genotype of *Aa* [32, 36]. Thus, the JP2 genotype of *Aa* may be more prevalent among children and adolescents but apparently can also be detected in adults. Most of the studies that looked at the presence of the JP2 genotype of *Aa* in the schoolchildren included a large number of subjects from both primary and high schools in contrast with the studies that included a smaller sample size of adults; this may be responsible for the high prevalence of the JP2 genotype of *Aa* in children and adolescents.

We found that the presence of the JP2 genotype of *Aa* is higher in South America, North America, and Africa compared to Europe and Asia with complete lack of any data coming from Oceania and specifically Australia and New Zealand. This result reflects a specific geographic distribution of the JP2 genotype of *Aa.* There is no consistency in the used definition of periodontitis among the selected studies in this review. To complicate the research process further, the new periodontitis classification removed the term "aggressive periodontitis" with a new staging and grading system [83]. To add more confusion, the name *Aa* has changed over the years; initially, it was called *Lactobacillus* and then *Haemophilus*, and now it is named *Aggregatibacter actinomycetemcomitans*, making the systemic search task more difficult and complicated [89]. However, PCR technology has been consistently used to detect the JP2 genotype of *Aa*.

Table 4 Risk of bias of the included studies

Author/year	1—RS	2—AR	3—SZ	4—D&R	5—DC	6—CI	7—CM	8—SA	9—RR	OA
Chung et al. (1989) [26]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Exclude
DiRienzo and McKay (1994) [38]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Haubek et al. (1995) [27]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Exclude
Haubek et al. (1996) [13]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Haubek et al. (1997A) [73]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Exclude
Asikanen et al. (1997) [70]	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Exclude
Tinoco et al. (1997) [45]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Include
Bueno et al. (1998) [39]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Exclude
Mombelli et al. (1998) [53]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Macheleidt et al. (1999) [28]	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Exclude
Mombelli et al. (1999 [54]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Include
He et al. (1999) [55]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Exclude
Contreras et al. (2000) [40]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Haraszthy et al. (2000) [72]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Tan et al. (2001) [56]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Müller et al. (2001) [29]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Haubek et al. (2001) [61]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Include
Kaplan et al. (2002) [41]	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Include
Cortelli SC et al. (2003) [46]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Include
Haubek and Westergaard (2004) [75]	No	No	No	Yes	No	Yes	Yes	No	No	Exclude
Cortelli JR et al. (2005) [47]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Leung et al. (2005) [57]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Rosalem Junior et al. (2006) [48]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Orru et al. (2006) [30]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Fine et al. (2007) [42]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Van Der Reijden et al. (2008) [58]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Exclude
Haubek et al. (2008) [62]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Include
Kim et al. (2009) [71]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Exclude
Vieira et al. (2009) [49]	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Exclude
Sakellari et al. (2011) 31	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Elamin et al. (2011) [63]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Pinheiro et al. (2011) [74]	Yes	Yes	No	No	Yes	No	Yes	No	Yes	Exclude
Claesson et al. (2011) [32]	No	No	No	Yes	No	No	Yes	No	No	Exclude
Bandhaya et al. (2012) [59]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Jentsch et al. (2012) [33]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Aberg et al. (2012) [64]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Ennibi et al. (2012) [65]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Wahasugui et al. (2013) [50]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Martinez-Martinez et al. (2013) [43]	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Include
Silveira et al. (2013) [51]	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Include
Minguez et al. (2014) [34]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Elabdeen et al. (2015) [66]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Minguez et al. (2016) [67]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Jensen et al. (2016) [68]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Burgess et al. (2017) [44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Claesson et al. (2017) [35]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Include
Suprith et al. (2018) [60]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Include
Amado et al. (2020) [52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
Stahli et al. (2020) [36]	No	No	No	Yes	No	Yes	Yes	No	No	Exclude
Jensen et al. (2020) [37]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Include
Haubek et al. (2021) [69]	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Include

RS representative sample, *AR* appropriate recruitment, *SZ* sample size, *D&R* description and reporting, *DC* data coverage, *CI* condition identification, *CM* condition measured, *SA* statistical analysis, *RR* response rate, *OA* overall appraisal

Table 5 Summary of findings on the body of the estimated evidence profile and appraisal of the strength of the recommendation

Determinants of quality	Presence of JP2 *Aa* genotype
Study design	Mixed
Number of studies	51
Risk of bias (table 4)	Low to high
Consistency	Not consistent
Directness	Generalizable
Precision	Low
Magnitude of the effect	Small
Strength of the recommendation based on the body of evidence	Weak
Direction of recommendation	Weak

Conclusion

A relatively high presence of the JP2 genotype of *Aa* was found in South American, North American, and African continents. There is a complete lack of data in the Oceania region concerning the presence of the JP2 genotype of *Aa*. The heterogeneity and quality of the included publications made it impossible to conduct a meta-analysis. This suggests that caution should be exercised when interpreting the data and that there remains an important need for additional evidence.

Declarations

Ethics approval No ethical clearance was required to conduct this systematic review.

Informed consent No informed consent was required for this systemic review.

Conflict of interest The authors declare no competing interests.

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