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Isoniazid Resistance and the Future of Drug-Resistant Tuberculosis

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ABSTRACT

Bacterial chromosomal mutations that confer antibiotic resistance often have deleterious effects that impose costs on reproductive fitness. This observation has led to the generalization that in the absence of the selection pressure exerted through treatment, the frequency of resistance will decrease. This model implies that the prudent use of antibiotics will eventually result in a decline in the prevalence of drug resistance. Recent work, however, suggests that some resistance-conferring mutations may not significantly impair fitness and that others may be accompanied by compensatory mutations that restore the organisms' reproductive potential. Thus drug resistance, once introduced, may persist unless specific measures are implemented to target prevalent drug-resistant cases. Here we present ecological evidence to support the hypothesis that mutations at the 315 position of *katG* confer isoniazid resistance for *Mycobacterium tuberculosis* without diminishing virulence or transmissibility.

INTRODUCTION

RECENT GLOBAL SURVEYS reveal that drug-resistant tuberculosis exists in virtually every location examined.[7] Antibiotic resistance in tuberculosis is ultimately a "man-made" phenomenon, and the burden of drug resistance is primarily due to inappropriate treatment of initially drug-sensitive disease. However, in places where recommended treatment strategies are employed, but where drug-resistant strains are nonetheless prevalent, the transmission of drug-resistant strains may cause the persistence or propagation of drug-resistant disease. While some have claimed that "the frequency of resistance will wane at a rate proportional to the fitness costs associated with resistance,"[17] others have shown that these fitness costs may not be fixed.[3] Understanding the relationship between antibiotic resistance and the transmissibility and virulence of tuberculosis is essential for predicting the future burden of drug-resistant disease. If resistance is associated with fitness deficits, the effect of this transmitted resistance may be negligible; however, if resistance does not incur a cost, transmission of resistant strains may undermine current control strategies.

Isoniazid (INH) is an agent with bactericidal activity against dividing bacilli and plays an essential role in short-course treatment regimens. INH is a prodrug that must be metabolized by mycobacterial catalase-peroxidase to exert its antibacterial activity. Most INH resistance in clinical isolates results from blocking prodrug activation through mutations in the gene *katG* that alter or eliminate mycobacterial catalase-peroxidase activity.[25] Loss of catalase-peroxidase activity has been associated with loss of virulence in a mouse model.[18] Although *katG* insertions, deletions, and frameshifts do occur occasionally and induce complete loss of the functional gene product and correspondingly high levels of INH resistance, the majority of the mutations identified in clinical isolates are single point mutations that result in intermediate levels of resistance.[23] The INH resistance mutation that has been most commonly found in clinical isolates is a Ser315Thr point mutation in *katG* (Fig. 1). The mutant gene product manifests a reduced capacity for prodrug activation while retaining much of the catalase-peroxidase activity of the wild-type enzyme.[24] These observations have led researchers to propose that these S315T *katG* mutations lead to clinically significant INH resistance without exacting a significant fitness cost. This hypothesis is consistent with both animal models of virulence and molecular epidemiological cluster studies.[30]

We speculate that in geographic areas with a high incidence of tuberculosis infection, a relatively high proportion of INH resistance is due to transmitted disease. If this is indeed the

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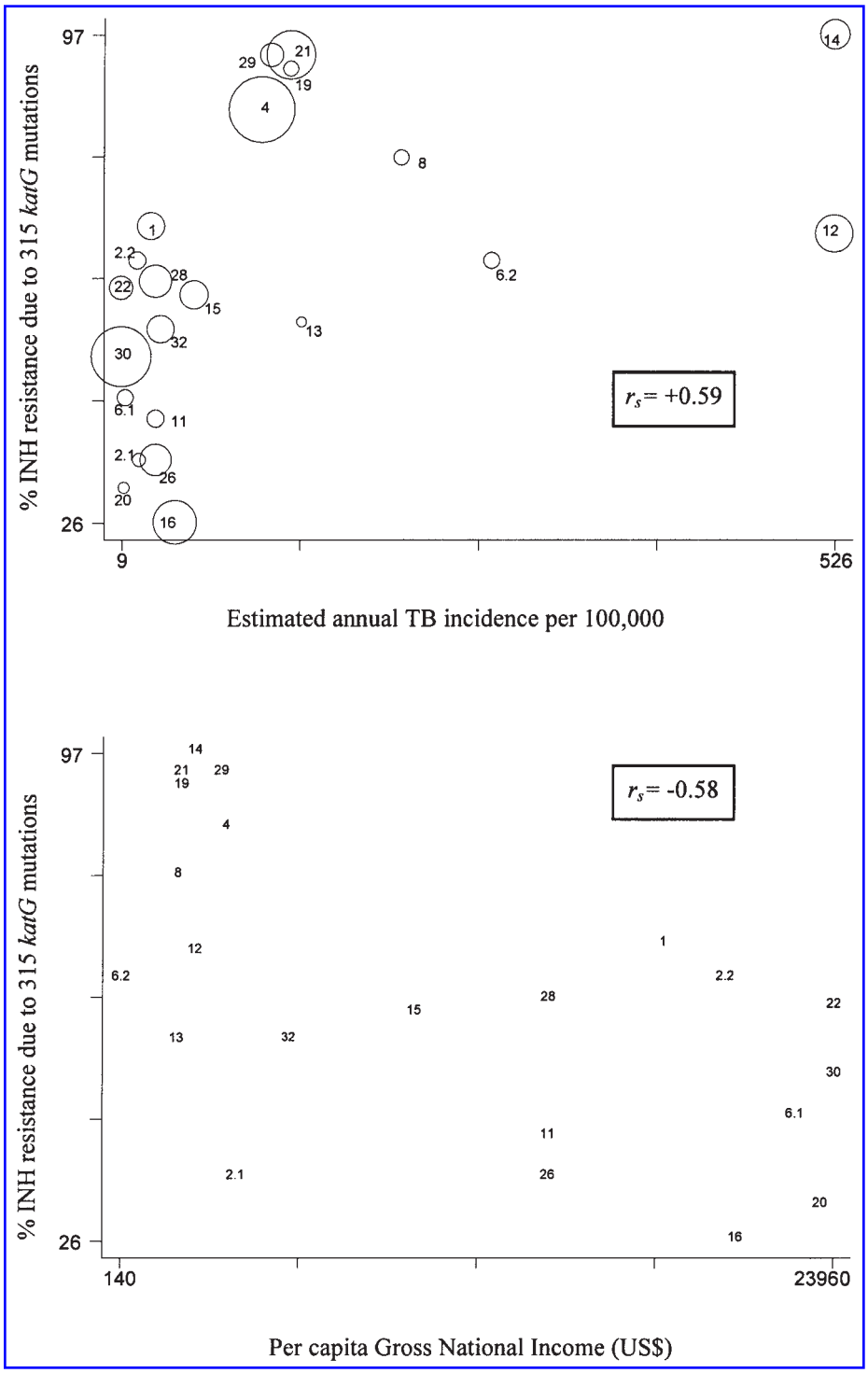

FIG. 1. (*Top*) INH resistance due to 315 *katG* mutations and estimated incidence of tuberculosis by country. The areas of the circles are proportional to the sample size. Spearman correlation coefficients (r_s) are given. (*Bottom*) INH resistance due to 315 *katG* mutations and estimated per capita Gross National Income by country. Data are provided in Table 1. Reference numbers, 1, Kuwait; 2.1, Lebanon; 2.2, UAE; 4, Lithuania; 6.1, Germany; 6.2, Sierra Leone; 8, Peru; 11, Spain; 12, South Africa; 13, Thailand; 14, South Africa; 15, South Korea; 16, Singapore; 19, Russian Federation; 20, Finland; 21, Russian Federation; 22, Netherlands; 26, Spain; 28, Spain; 29, Latvia; 30, Netherlands; 32, Mexico. Samples cited as 2.1 and 2.2 are from reference 2; samples cited as 6.1 and 6.2 are from reference 6.

case, the INH-resistant isolates most commonly observed should be those in which the mutations causing resistance have the least negative impact on the transmissibility of the strain. Conversely, in areas in which incidence of infection is low, there should be little transmission of resistant strains. In that case, a higher proportion of resistance may be due to mutations that have a deleterious effect on transmissibility but that have not been selected against, having not yet passed through the selective bottleneck of a transmission event. Assuming that tuberculosis notification rates are proxies for the incidence of infection, we conjectured that the proportion of INH-resistant strains that are due to S315T will be higher in those areas with higher case notification rates.

Because tuberculosis notification rates represent both recently acquired tuberculosis and the reactivation of remote infections, we consider these rates to be coarse indicators of actual transmission. We further postulate that the prevalence of S315T mutations among INH-resistant strains may be associated with socioeconomic indicators, which may serve as an additional proxy for high transmission rates. The inverse association between social and economic well being and the risk of tuberculosis transmission has long been recognized and has been confirmed in multiple recent epidemiologic studies.[5,10] If certain drug-resistant mutants are indeed transmissible, they should be found in areas in which poverty favors both their emergence and their further spread.

METHODS

We reviewed the literature for all published surveys that attempted to quantify the amount of clinical INH resistance that was due to 315 point mutations in *katG* in different parts of the world. We conducted this search using the keywords "katG," "mutation," "resistance," "isoniazid," and "tuberculosis" and included studies that were written in English, provided data on origin of patients whose isolates were typed, and included a minimum of 10 strains per location.

We next evaluated the relationship between the proportion of INH resistance caused by these specific *katG* mutations and two indicators: (1) country-specific estimates of tuberculosis incidence, *i.e.,* case notification rates and (2) a general measure of wealth, the World Bank Atlas estimate of per capita Gross National Income in 2002. For those countries for which there was more than one study of the proportion of INH resistance due to *katG* mutations, we tested the equality of the proportions using large-sample statistics.

Using the Shapiro-Wilk test for normality, we determined that neither incidence nor per capita income were distributed normally. Therefore, we analyzed these data using two different approaches. First, we used the nonparametric Spearman rank correlation coefficient (r_s) to quantify these associations. To test for the presence of influential points, we recalculated r_s after removing each observation individually and examined the distribution of the correlations for outliers; this distribution was normal, suggesting that there were no influential points. Next, using a Box-Cox transformation to normalize incidence and per capita income, we calculated Pearson correlation coefficients weighted by study sample size. Since some studies did not differentiate between S315T mutations and other mutations at the 315 locus in *katG*, we repeated these analyses including only those studies for which detailed sequence data were available.

RESULTS

Table 1 summarizes the available studies that report the proportion of INH-resistant strains that are due to mutations at codon 315 in *katG.* The table distinguishes studies that specifically identified these mutations from those which did not. Table 1 also indicates the sample size for each of the studies as well as the estimated tuberculosis incidence rate and gross per capita income from the country in which each study was performed. The prevalence of these mutants among INH-resistant strains increases as the estimated incidence of tuberculosis rises and as the estimated per capita gross income falls (Fig. 1). The crude Spearman correlation coefficients for these associations were 0.59 for incidence and −0.58 for income. Although we found that the two proportions of INH-resistant strains due to the 315 mutation from South Africa were statistically different ($p = 0.0001$), removing each of these studies had no significant effect on the correlation coefficient. Higher coefficients were observed as the criteria for including the data selected for analysis became increasingly refined (Table 2).

DISCUSSION

This analysis shows a strong correlation between the proportion of INH resistance-conferring mutations due to S315T measured in clinical isolates and several different indicators of tuberculosis transmission intensity, supporting the hypothesis that mutations at the 315 position of *katG* confer INH resistance for *Mycobacterium tuberculosis* without diminishing virulence or transmissibility. Our study has several important limitations. First, we used data from published reports in which clinical INH-resistant isolates were characterized by resistance-conferring mutations. Because methods of detecting mutations at the 315 locus varied, not all 315 mutations were confirmed to be S315T substitutions. Other mutations observed at this site have led to Ser-Asn, Ser-Ile, Ser-Arg, and Ser-Leu substitutions, although these have been observed less frequently than S315T.[4,6,12,15,22,26,28] Because these mutations are relatively rare, they may indeed be less fit than their Ser-Thr counterpart. If this is the case, their inclusion would most likely diminish any association detected between 315 mutations and transmissibility.

In addition, the strategies by which isolates were selected differed significantly between studies reviewed and thus our conclusions may be based on nonrepresentative "convenience" samples. Although many of the studies included isolates from specific local regions within countries, we used country-level estimates of tuberculosis incidence published by the World Health Organization to ensure uniformity of data collection techniques. These country-level estimates may not be an accurate measure of the relevant local disease burden. The observed relationship between the 315 mutations and estimates of per capita income is also subject to the ecologic fallacy because we cannot attribute national averages to the individuals included in

TABLE 1. NUMBER OF DRUG-RESISTANT ISOLATES IN SAMPLE, PERCENTAGE OF RESISTANCE DUE TO *katG* CODON 315 MUTATIONS, ESTIMATED INCIDENCE OF TUBERCULOSIS/100,000, AND ESTIMATED PER CAPITA GROSS NATIONAL INCOME BY LOCATION

Location	*Reference number*	*Number of drug-resistant isolates*	*% INH resistance due to 315* katG *mutations*	*Estimated TB incidence per 100,000 (ref. 7)*	*World Bank estimated per capita GNI in US$, 2002 (ref. 27)*
Finland[a]	20	13	31	11	23510
Germany[a]	6.1	25	44	12	22670
Kuwait	1	67	69	31	18270
Latvia[a]	29	51	94	118	3480
Lebanon	2.1[c]	17	35	22	3990
Lithuania[a]	4	364	86	111	3660
Mexico	32	67	54	38	5910
Netherlands[a]	22	51	60	9	23960
Netherlands	30	295	50		
Peru[a]	8	24	79	212	2050
Russian Fed[a]	19	24	92	132	2140
Russian Fed	21	204	94		
Sierra Leone[a]	6.2	25	64	278	140
Singapore[a]	16	160	26	48	20690
South Africa[a]	12	124	68	526	2600
South Africa[a]	14	79	97		
South Korea[a]	15	71	59	62	9930
Spain[a]	26	95	32	34	14430
Spain[a]	11	29	41		
Spain[a]	28	94	61		
Thailand	13	11	55	140	1990
United Arab Emirates	2.2	28	64	21	20340[b]

[a]Information on SNPs available.
[b]1997 estimate; 2002 estimate not available.
[c]Samples cited as 2.1 and 2.2 are from reference 2; samples cited as 6.1 and 6.2 are from reference 6.

these surveys. Finally, although mutations that lead to drug resistance may alter the reproductive fitness of *M. tuberculosis* strains, there may be other genetic polymorphisms that are associated with the differential fitness of strains. For example, several recent studies have suggested that members of the Beijing family of strains display marked differences in pathogenicity and in the rate of intracellular growth compared to other clinical isolates.[31] Although an ideal study of the fitness of drug-resistant mutants would use strains that were isogenic in all other respects, such a study cannot be conducted in the human populations in which tuberculosis transmission takes place.

Despite these limitations, we have shown that the correlation between the proportion of the resistant isolates that are due to 315 mutations and tuberculosis transmission is robust in several sensitivity analyses. The observational data derived from field studies support the hypothesis that the S315T mutation does not impair the fitness of *M. tuberculosis* isolates circulating in human populations. Further testing with studies designed to evaluate the relative likelihood of specific resistant strains spreading within communities is needed. Molecular epidemiological studies, in which strains are characterized by DNA fingerprint pattern and classified as clustered (*i.e.,* part of a recent transmission chain) or unique (*i.e.,* most likely the result of the reactivation of a latent infection), will further our understanding of the impact of specific mutations on fitness. In the Netherlands, van Soolingen *et al.* found that strains with mutations in

TABLE 2. CORRELATION COEFFICIENTS FOR THE ASSOCIATION BETWEEN PREVALENCE OF *katG* CODON 315 MUTANTS AND MEASURES OF TB INCIDENCE AND INCOME

Test	*Correlation with incidence*	*Correlation with income*
Spearman	0.59	−0.58
Spearman[a]	0.72	−0.78
Pearson (weighted by sample size)	0.61	−0.78
Pearson[a] (weighted by sample size)	0.58	−0.83

[a]Including only studies which included information on SNPs.

katG resulting in amino acid substitutions at the 315 position were more likely to be clustered than those with other INH resistance-conferring mutations and equally likely to be clustered as the susceptible strains.[30] Similar cluster analyses conducted in high-incidence countries would be invaluable for discerning the impact of the 315 mutant phenotype on the emergence of drug resistance in locations where the threat of uncontrolled epidemics of drug-resistant tuberculosis is most severe. Additionally, prospective studies among the contacts of those with active tuberculosis could be conducted to compare the distributions of drug-resistance mutations among resistant cases that do not result in secondary cases and those that do.

Given the prolonged course of tuberculosis epidemics, tracking of trends in drug resistance over the course of several decades is necessary to understand the long-term effects of policies aiming to control the emergence of drug resistance. We predict that, in the absence of policies directed at providing effective treatment for those with drug-resistant disease, highly fit resistant strains may have a major impact on the future course of tuberculosis epidemics. Mathematical models that incorporate differential levels of reproductive fitness will be essential for estimating the future burden of drug-resistant disease and identifying effective strategies for its control.

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REFERENCES

1. **Abal, A.T., S. Ahmad, and E. Mokaddas.** 2002. Variations in the occurrence of the S315T mutation within the *katG* gene in isoniazid-resistant clinical *Mycobacterium tuberculosis* isolates from Kuwait. Microb. Drug Resist. **8:**99–105.
2. **Ahmad, S., E. Fares, G.F. Araj, T.D. Chugh, and A.S. Mustafa.** 2002. Prevalence of S315T mutation within the katG gene in isoniazid-resistant clinical *Mycobacterium tuberculosis* isolates from Dubai and Beirut. Int. J. Tuberc. Lung Dis. **6:**920–926.
3. **Andersson, D.I., and B.R. Levin.** 1999. The biological cost of antibiotic resistance. Curr. Opin. Microbiol. **2:**489–493.
4. **Bakonyte, D., A. Baranauskaite, J. Cicenaite, A. Sosnovskaja, and P. Stakenas.** 2003. Molecular characterization of isoniazid-resistant Mycobacterium tuberculosis clinical isolates in Lithuania. Antimicrob. Agents Chemother. **47:**2009–2011.
5. **Barr, R.G., A.V. Diez-Roux, C.A. Knirsch, and A. Pablos-Mendez.** 2001. Neighborhood poverty and the resurgence of tuberculosis in New York City, 1984–1992. Am. J. Public Health **91:**1487–1493.
6. **Dobner, P., S. Rusch-Gerdes, G. Bretzel, K. Feldmann, M. Rifai, T. Loscher, and H. Rinder.** 1997. Usefulness of Mycobacterium tuberculosis genomic mutations in the genes katG and inhA for the prediction of isoniazid resistance. Int. J. Tuberc. Lung Dis. **1:**365–369.
7. **Dye, C., S. Scheele, P. Dolin, V. Pathania, and M.C. Raviglione.** 1999. Consensus statement: Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. J. Am. Med. Assn. **282:**677–686.
8. **Escalante, P., S. Ramaswamy, H. Sanabria, H. Soini, X. Pan, O. Valiente-Castillo, and J.M. Musser.** 1998. Genotypic characterization of drug-resistant *Mycobacterium tuberculosis* isolates from Peru. Tuber. Lung Dis. **79:**111–118.
9. **Espinal, M.A., A. Laszlo, L. Simonsen, F. Boulahbal, S.J. Kim, A. Reniero, S. Hoffner, H.L. Rieder, N. Binkin, C. Dye, R. Williams, and M.C. Raviglione.** 2001. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N. Engl. J. Med. **344:**1294–1303.
10. **Frieden T.R., P.I. Fujiwara, R.M. Washko, and M.A. Hamburg.** 1995. Tuberculosis in New York City—turning the tide. N. Engl. J. Med. **333:**229–233.
11. **Gonzalez, N., M.J. Torres, J. Aznar, and J.C. Palomares.** 1999. Molecular analysis of rifampin and isoniazid resistance of *Mycobacterium tuberculosis* clinical isolates in Seville, Spain. Tuber. Lung Dis. **79:**187–190.
12. **Haas, W.H., K. Schilke, J. Brand, B. Amthor, K. Weyer, P.B. Fourie, G. Bretzel, V. Sticht-Groh, and H.J. Bremer.** 1997. Molecular analysis of katG gene mutations in strains of *Mycobacterium tuberculosis* complex from Africa. Antimicrob. Agents Chemother. **41:**1601–1603.
13. **Imwidthaya, P., K. Mieskes, and S. Rienthong.** 2001. Evaluation of katG codon 315 mutations among isoniazid sensitive and resistant *Mycobacterium tuberculosis* isolates from Thailand. J. Med. Assoc. Thai. **84:**864–869.
14. **Kiepiela, P., K.S. Bishop, A.N. Smith, L. Roux, and D.F. York.** 2000. Genomic mutations in the katG, inhA and aphC genes are useful for the prediction of isoniazid resistance in *Mycobacterium tuberculosis* isolates from Kwazulu Natal, South Africa. Tuber. Lung Dis. **80:**47–56.
15. **Kim S.Y., Y.J. Park, W.I. Kim, S.H. Lee, C. Ludgerus Chang, S.J. Kang, and C.S. Kang.** 2003. Molecular analysis of isoniazid resistance in Mycobacterium tuberculosis isolates recovered from South Korea. Diagn. Microbiol. Infect. Dis. **47:**497–502.
16. **Lee, A.S., I.H. Lim, L.L. Tang, A. Telenti, and S.Y. Wong.** 1999. Contribution of kasA analysis to detection of isoniazid-resistant *Mycobacterium tuberculosis* in Singapore. Antimicrob. Agents Chemother. **43:**2087–2089.
17. **Levin, B.R.** 2002. Models for the spread of resistant pathogens. Neth. J. Med. **60**(7 Suppl):58–64; discussion 64–66.
18. **Li, Z., C. Kelley, F. Collins, D. Rouse, and S. Morris.** 1998. Expression of katG in *Mycobacterium tuberculosis* is associated with its growth and persistence in mice and guinea pigs. J. Infect. Dis. **177:**1030–1035.
19. **Marttila, H.J., H. Soini, E. Eerola, E. Vyshnevskaya, B.I. Vyshnevskiy, T.F. Otten, A.V. Vasilyef, and M.K. Viljanen.** 1998. A Ser315Thr substitution in KatG is predominant in genetically heterogeneous multidrug-resistant *Mycobacterium tuberculosis* isolates originating from the St. Petersburg area in Russia. Antimicrob. Agents Chemother. **42:**2443–2445.
20. **Marttila, H.J., H. Soini, P. Huovinen, and M.K. Viljanen.** 1996. katG mutations in isoniazid-resistant *Mycobacterium tuberculosis* isolates recovered from Finnish patients. Antimicrob. Agents Chemother. **40:**2187–2189.
21. **Mokrousov, I., O. Narvskaya, T. Otten, E. Limeschenko, L. Steklova, and B. Vyshnevskiy.** 2002. High prevalence of KatG Ser315Thr substitution among isoniazid-resistant *Mycobacterium tuberculosis* clinical isolates from northwestern Russia, 1996 to 2001. Antimicrob. Agents Chemother. **46:**1417–1424.

22. **Musser, J.M., V. Kapur, D.L. Williams, B.N. Kreiswirth, D. van Soolingen, and J.D. van Embden.** 1996. Characterization of the catalase-peroxidase gene (katG) and inhA locus in isoniazid-resistant and -susceptible strains of *Mycobacterium tuberculosis* by automated DNA sequencing: restricted array of mutations associated with drug resistance. J. Infect. Dis. **173:**196–202.
23. **Pym, A.S., B. Saint-Joanis, and S.T. Cole.** 2002. Effect of katG mutations on the virulence of *Mycobacterium tuberculosis* and the implication for transmission in humans. Infect. Immun. **70:** 4955–4960.
24. **Rouse, D.A., J.A. DeVito, Z. Li, H. Byer, and S.L. Morris.** 1996. Site-directed mutagenesis of the katG gene of *Mycobacterium tuberculosis*: effects on catalase-peroxidase activities and isoniazid resistance. Mol. Microbiol. **22:**583–592.
25. **Slayden, R.A., and C.E. Barry 3rd.** 2000. The genetics and biochemistry of isoniazid resistance in *Mycobacterium tuberculosis*. Microbes Infect. **2:**659–669.
26. **Telenti, A., N. Honore, C. Bernasconi, J. March, A. Ortega, B. Heym, H.E. Takiff, and S.T. Cole.** 1997. Genotypic assessment of isoniazid and rifampin resistance in *Mycobacterium tuberculosis*: a blind study at reference laboratory level. J. Clin. Microbiol. **35:**719–723.
27. **The World Bank Group.** http://www.worldbank.org/dat/countrydata/countrydata.html.
28. **Torres, M.J., A. Criado, N. Gonzalez, J.C. Palomares, and J. Aznar.** 2002. Rifampin and isoniazid resistance associated mutations in *Mycobacterium tuberculosis* clinical isolates in Seville, Spain. Int. J. Tuberc. Lung Dis. **6:**160–163.
29. **Tracevska, T., I. Jansone, L. Broka, O. Marga, and V. Baumanis.** 2002. Mutations in the rpoB and katG genes leading to drug resistance in *Mycobacterium tuberculosis* in Latvia. J. Clin. Microbiol. **40:**3789–3792.
30. **van Soolingen, D., P.E. de Haas, H.R. van Doorn, E. Kuijper, H. Rinder, and M.W. Borgdorff.** 2000. Mutations at amino acid position 315 of the katG gene are associated with high-level resistance to isoniazid, other drug resistance, and successful transmission of *Mycobacterium tuberculosis* in the Netherlands. J. Infect. Dis. **182:**1788–1790.
31. **van Helden, P., R. Warren, T. Victor, G. van der Spuy, M. Richardson, and H. van Helden.** 2002. Strain families of *Mycobacterium tuberculosis*. Trends Microbiol. **10:**167–168.
32. **Viader-Salvado, J.M., C.M. Luna-Aguirre, J.M. Reyes-Ruiz, R. Valdez-Leal, L. del Bosque-Moncayo Mde, R. Tijerina-Menchaca, and M. Guerrero-Olazaran.** 2003. Frequency of mutations in rpoB and codons 315 and 463 of katG in rifampin- and/or isoniazid-resistant Mycobacterium tuberculosis isolates from northeast Mexico. Microb. Drug Resist. **9:**33–38.

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2. Dinesh S. Reddy, Manasa Kongot, Sandeep P. Netalkar, Mahantesh M. Kurjogi, Rakesh Kumar, Fernando Avecilla, Amit Kumar. 2018. Synthesis and evaluation of novel coumarin-oxime ethers as potential anti-tubercular agents: Their DNA cleavage ability and BSA interaction study. *European Journal of Medicinal Chemistry* **150**, 864-875. [Crossref]
3. Ariadna Rando-Segura, María Luisa Aznar, María Milagros Moreno, Mateu Espasa, Elena Sulleiro, Cristina Bocanegra, Eva Gil, Arlete N.E. Eugénio, Carlos Escartin, Adriano Zacarias, Josep Vegue, Domingos Katimba, María Carmen Vivas, Estevao Gabriel, María Concepción Marina, Jacobo Mendioroz, María Teresa López, Tomas Pumarola, Israel Molina, María Teresa Tórtola. 2018. Drug Resistance of Mycobacterium tuberculosis Complex in a Rural Setting, Angola. *Emerging Infectious Diseases* **24**:3, 569-572. [Crossref]
4. Alemayehu Godana Birhanu, Solomon Abebe Yimer, Carol Holm-Hansen, Gunnstein Norheim, Abraham Aseffa, Markos Abebe, Tone Tønjum. 2017. N ε - and O-Acetylation in Mycobacterium tuberculosis Lineage 7 and Lineage 4 Strains: Proteins Involved in Bioenergetics, Virulence, and Antimicrobial Resistance Are Acetylated. *Journal of Proteome Research* **16**:11, 4045-4059. [Crossref]
5. Ted Cohen, Caroline Colijn, Megan Murray. Mathematical Modeling of Tuberculosis Transmission Dynamics 227-243. [Crossref]
6. Helena I. Boshoff, Ramandeep Singh, Clifton E. Barry. Virulence and Persistence Mechanisms of Mycobacterium tuberculosis 151-191. [Crossref]
7. Noton K. Dutta, Petros C. Karakousis. Mechanisms of Action and Resistance of the Antimycobacterial Agents 359-383. [Crossref]
8. Ameeruddin Nusrath Unissa, Selvakumar Subbian, Luke Elizabeth Hanna, Nagamiah Selvakumar. 2016. Overview on mechanisms of isoniazid action and resistance in Mycobacterium tuberculosis. *Infection, Genetics and Evolution* **45**, 474-492. [Crossref]
9. Willy Ssengooba, Conor J. Meehan, Deus Lukoye, George William Kasule, Kenneth Musisi, Moses L. Joloba, Frank G. Cobelens, Bouke C. de Jong. 2016. Whole genome sequencing to complement tuberculosis drug resistance surveys in Uganda. *Infection, Genetics and Evolution* **40**, 8-16. [Crossref]
10. Gargi Datta, Luisa M. Nieto, Rebecca M. Davidson, Carolina Mehaffy, Caroline Pederson, Karen M. Dobos, Michael Strong. 2016. Longitudinal whole genome analysis of pre and post drug treatment Mycobacterium tuberculosis isolates reveals progressive steps to drug resistance. *Tuberculosis* **98**, 50-55. [Crossref]
11. S. N. Zhdanova, O. B. Ogarkov, G. I. Alexeeva, M. K. Vinokurova, V. V. Sinkov, V. A. Astaf'ev, E. D. Savilov, A. F. Kravchenko. 2016. Genetic diversity of Mycobacterium tuberculosis isolates in the Republic of Sakha (Yakutia), Russia. *Molecular Genetics, Microbiology and Virology* **31**:2, 51-57. [Crossref]
12. S. N. Zhdanova, O. B. Ogarkov, G. I. Alekseeva, M. K. Vinokurova, V. V. Sinkov, V. A. Astaf'ev, E. D. Savilov, A. F. Kravchenko. 2016. Genetic diversity of the mycobacterium tuberculosis isolates in the Republic Sakha (Yakutia), Russia. *Molecular Genetics Microbiology and Virology (Russian version)* **34**:2, 43. [Crossref]
13. Marva Seifert, Donald Catanzaro, Antonino Catanzaro, Timothy C. Rodwell. 2015. Genetic Mutations Associated with Isoniazid Resistance in Mycobacterium tuberculosis: A Systematic Review. *PLOS ONE* **10**:3, e0119628. [Crossref]
14. A. Nusrath Unissa, N. Selvakumar, Sujatha Narayanan, C. Suganthi, L. E. Hanna. 2015. Investigation of Ser315 Substitutions within katG Gene in Isoniazid-Resistant Clinical Isolates of Mycobacterium tuberculosis from South India. *BioMed Research International* **2015**, 1-5. [Crossref]
15. Nusrath Unissa Ameeruddin, Hanna Luke Elizabeth. 2014. Impact of isoniazid resistance on virulence of global and south Indian clinical isolates of Mycobacterium tuberculosis. *Tuberculosis* **94**:6, 557-563. [Crossref]
16. Manu Vanaerschot, Saskia Decuypere, Maya Berg, Syamal Roy, Jean-Claude Dujardin. 2013. Drug-resistant microorganisms with a higher fitness – can medicines boost pathogens?. *Critical Reviews in Microbiology* **39**:4, 384-394. [Crossref]
17. Ameeta S. Kalokhe, James C. Lee, Susan M. Ray, Albert M. Anderson, Minh Ly T. Nguyen, Yun F. Wang, Majid Shafiq, Beverly Metchock. 2013. Multidrug-Resistant Tuberculosis Drug Susceptibility and Molecular Diagnostic Testing. *The American Journal of the Medical Sciences* **345**:2, 143-148. [Crossref]
18. Payam Tabarsi, Masoud Mardani. 2012. Extensively Drug-Resistant Tuberculosis: A Review Article. *Archives of Clinical Infectious Diseases* **7**:3, 81-4. [Crossref]

19. Lorena Cristina Santos. 2012. Review: The Molecular Basis of Resistance in Mycobaterium tuberculosis. *Open Journal of Medical Microbiology* **02**:01, 24-36. [Crossref]
20. S. Borrell, S. Gagneux. 2011. Strain diversity, epistasis and the evolution of drug resistance in Mycobacterium tuberculosis. *Clinical Microbiology and Infection* **17**:6, 815-820. [Crossref]
21. Caroline Colijn, Ted Cohen, Ayalvadi Ganesh, Megan Murray. 2011. Spontaneous Emergence of Multiple Drug Resistance in Tuberculosis before and during Therapy. *PLoS ONE* **6**:3, e18327. [Crossref]
22. Lorena Cristina Santos, Hesther de Macedo Bousquet, Alyne Melo Pereira, Ana Paula Junqueira-Kipnis, André Kipnis. 2010. A high prevalence of resistance in new tuberculosis cases of midwestern Brazil. *Infection, Genetics and Evolution* **10**:7, 1052-1057. [Crossref]
23. Dan I. Andersson, Diarmaid Hughes. 2010. Antibiotic resistance and its cost: is it possible to reverse resistance?. *Nature Reviews Microbiology* **8**:4, 260-271. [Crossref]
24. Adithya Cattamanchi, Raymund B. Dantes, John Z. Metcalfe, Leah G. Jarlsberg, Jennifer Grinsdale, L. Masae Kawamura, Dennis Osmond, Philip C. Hopewell, Payam Nahid. 2009. Clinical Characteristics and Treatment Outcomes of Patients with Isoniazid-Monoresistant Tuberculosis. *Clinical Infectious Diseases* **48**:2, 179-185. [Crossref]
25. Mandeep Jassal, William R Bishai. 2009. Extensively drug-resistant tuberculosis. *The Lancet Infectious Diseases* **9**:1, 19-30. [Crossref]
26. Petros C. Karakousis. Mechanisms of Action and Resistance of Antimycobacterial Agents 271-291. [Crossref]
27. Kathryn M. Orzech, Mark Nichter. 2008. From Resilience to Resistance: Political Ecological Lessons from Antibiotic and Pesticide Resistance. *Annual Review of Anthropology* **37**:1, 267-282. [Crossref]
28. Wing-Wai YEW. 2008. Management of multidrug-resistant tuberculosis in the Asia-Pacific region. *Respirology* **13**, S108-S115. [Crossref]
29. Kouassi Raymond N'Guessan, Mireille Dosso, Euloge Ekaza, Jacquemin Kouakou, Vincent Jarlier. 2008. Molecular characterisation of isoniazid-resistant Mycobacterium tuberculosis isolated from new cases in Lagunes region (Côte d'Ivoire). *International Journal of Antimicrobial Agents* **31**:5, 498-500. [Crossref]
30. Wing Wai YEW, Chi Chiu LEUNG. 2007. Management of multidrug-resistant tuberculosis: Update 2007. *Respirology*, ahead of print071031182005003-???. [Crossref]
31. Yves L. Janin. 2007. Antituberculosis drugs: Ten years of research. *Bioorganic & Medicinal Chemistry* **15**:7, 2479-2513. [Crossref]
32. Dan I Andersson. 2006. The biological cost of mutational antibiotic resistance: any practical conclusions?. *Current Opinion in Microbiology* **9**:5, 461-465. [Crossref]