rabbit genetics

Genetic coevolution between rabbits and myxoma virus

[1]Zsolt A. Grabán, [2]Tudor Păpuc

[1] National Association of Pigeon and Small Animal Breeders of Hungary, Budapest, Hungary; [2] Faculty of Animal Science and Biotechnologies, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Cluj-Napoca, Romania. Corresponding author: Z. A. Grabán, grabanzsolt@gmail.com

Abstract. The introduction of myxoma virus (MYXV) into European rabbit (*Oryctolagus cuniculus*) populations in the mid-20th century represents one of the most extensively documented natural experiments in host–pathogen coevolution. This mini-review synthesizes current knowledge on the genetic and evolutionary dynamics underpinning this interaction, emphasizing reciprocal adaptation between host resistance and viral virulence. Following the initial release of highly virulent MYXV strains, which caused mortality rates exceeding 99%, rapid evolutionary responses were observed on both sides: rabbits evolved heritable, polygenic resistance primarily through enhanced innate and cellular immune mechanisms, while the virus diversified through multiple genetic pathways affecting virulence, immune evasion, and transmission efficiency. Comparative genomic studies reveal parallel evolution of resistance alleles across continents and highlight the remarkable plasticity of the MYXV genome, characterized by high mutation rates, gene loss, duplication, and recombination. Notably, recent viral lineages exhibit novel disease phenotypes, including immune collapse and amyxomatous forms, reflecting ongoing adaptation to resistant host populations. The molecular interplay between host immune pathways—particularly interferon-mediated responses—and viral immunomodulatory proteins illustrates a complex, network-level coevolutionary process rather than a simple one gene–one gene arms race. Ecologically, this interaction has reshaped rabbit population dynamics and continues to influence emerging disease systems. Overall, the rabbit–MYXV system remains a foundational model for understanding the genetic architecture and evolutionary trajectories of host–pathogen coadaptation in natural environments.

Key Words: evolutionary arms race, genetic resistance, host–pathogen coevolution, innate immunity, interferon response, myxomatosis, *Oryctolagus cuniculus*, polygenic adaptation, viral evolution, viral virulence.

Introduction. The deliberate release of myxoma virus (MYXV) into European rabbit populations in Australia and Europe in the 1950s created a uniquely well documented natural experiment in host–pathogen coevolution (Proorocu et al 2020). Over decades, rabbits evolved genetic resistance, while the virus diversified along multiple evolutionary pathways in virulence, tissue tropism and immune evasion (Kerr 2012; Kerr et al 2013; Kerr et al 2015). This interaction is now a textbook model for understanding genetic arms races between hosts and pathogens (Kerr & Best 1998; Kerr 2012; Miller & Metcalf 2019; see also genetic arms races between prey and predator in Păsărin et al 2025; Petrescu-Mag & Păsărin 2025).

The aim of this mini-review is to synthesize current evidence on the genetic and evolutionary mechanisms underlying the coevolution between European rabbits and myxoma virus, with a focus on the reciprocal adaptations shaping host resistance, viral virulence, and their molecular and ecological interactions over time.

Historical and Evolutionary Context of the Arms Race. MYXV is a leporipoxvirus that causes benign cutaneous fibromas in its native American hosts, but produces lethal disseminated myxomatosis in European rabbits (*Oryctolagus cuniculus*) (Kerr 2012; Kerr et al 2015). When highly virulent laboratory strains were released as biocontrol agents in Australia (1950) and later in France (1952), case fatality initially exceeded 99% (Kerr 2012; Kerr et al 2015). Within a few years, attenuated viral strains arose that killed more slowly, but were transmitted more effectively by insect vectors, and wild rabbits with partial genetic resistance were strongly favored, producing a classic pattern of coevolution in which virulence declined, while host resistance increased (Fenner & Marshall 1957; Kerr & Best 1998; Kerr 2012; Kerr et al 2013).

Comparative evolutionary analyses of virus genomes sampled over nearly 50 years in Australia and Europe show rapid mutation and one of the highest nucleotide substitution rates measured for a double stranded DNA virus, reflecting both an inherently high mutation rate and intense, changing selection imposed by resistant rabbit populations and vector ecology (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015). Notably, similar phenotypic outcomes—intermediate virulence maximizing transmission—evolved independently on both continents, but without a single conserved genetic route, demonstrating that multiple genotypic solutions can converge on comparable virulence and transmission profiles (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015).

More recent decades have revealed a new phase of the arms race. Under strong selection from increasingly resistant rabbits, some MYXV lineages have evolved novel disease syndromes, including acute immune collapse with septic shock-like pathology, and amyxomatous forms with minimal skin lesions, but profound systemic effects (Kerr et al 2017). In parallel, MYXV has shown a capacity for further host range evolution, jumping into Iberian hares (*Lepus granatensis*) with novel recombinant genomic inserts, again highlighting its adaptive plasticity in response to new leporid hosts (Águeda-Pinto et al 2019; Dalton et al 2019).

Genetic Basis of Rabbit Resistance. Early experimental infections showed that wild rabbits from Australia and Britain had evolved heritable resistance to myxomatosis, expressed as increased survival or ability to recover, especially against moderately virulent strains (Ross & Sanders 1984; Williams et al 1990; Kerr & Best 1998; Best et al 2000). Rabbits from warmer, arid regions of Australia survived highly virulent strains significantly longer than those from cooler regions, suggesting regional divergence in resistance driven by local epizootic history and environment (Williams et al 1990). By the mid-1980s, genetic resistance was widespread in Britain, with some populations showing significant survival even against fully virulent virus (Ross & Sanders 1984).

Quantitative syntheses of challenge trials in Australia indicate that resistance rose rapidly in the first years after MYXV release, then plateaued for about a decade before increasing again, particularly after the introduction of rabbit fleas as efficient vectors, which altered transmission dynamics and selection pressures (Cooke et al 2023). In the UK, where fleas were already endemic, resistance evolved more slowly, illustrating how vector biology shapes the tempo of host adaptation (Cooke et al 2023).

Mechanistic work comparing resistant wild rabbits and susceptible laboratory animals shows that resistance is not due to reduced permissivity of individual cells or superior neutralizing antibody responses; *in vitro*, virus replication in fibroblasts or lymphocytes is similar across genotypes, and both resistant and susceptible rabbits generate neutralizing antibodies (Best et al 2000). Instead, resistant rabbits limit systemic spread: they control virus replication in draining lymph nodes far more effectively, resulting in 10–100-fold lower viral titers and restricted dissemination to distant tissues, consistent with an enhanced innate and cellular immune response (Best et al 2000).

Genome wide analyses have now provided direct evidence that resistance is polygenic and rooted in standing genetic variation present before MYXV release. By comparing exomes of rabbits sampled before the pandemic with those collected decades later from Australia, France and the UK, researchers identified a strong pattern of parallel evolution: the same alleles at multiple loci increased in frequency independently on different continents (Alves et al 2019; Miller & Metcalf 2019). Many of the selected variants lie in immunity related genes, including components of interferon pathways; experimental validation showed that changes in a particular interferon protein increase its antiviral activity against MYXV, directly linking host genetic evolution to functional enhancement of antiviral defenses (Alves et al 2019; Miller & Metcalf 2019). This pattern of repeated, parallel selection across continents underscores how similar pathogen pressures can drive convergent polygenic adaptation in the host (Alves et al 2019; Miller & Metcalf 2019) (Table 1).

Table 1

Temporal trends in resistance and virulence across continents (summarized by Consensus, 2026)

Aspect	*Australia*	*Europe/UK*	*Citations*
Initial MYXV impact	>99% mortality; rapid emergence of attenuated strains	Similar initial lethality; attenuated strains appeared within a few years	Fenner & Marshall 1957; Kerr 2012
Rabbit resistance trajectory	Fast early increase, decade-long plateau, then renewed rise after flea introduction	Slower, more gradual increase; fleas pre-existing	Ross & Sanders 1984; Kerr & Best 1998; Cooke et al 2023
Evidence of parallel host evolution	Shared allelic shifts in immune genes across continents	Same alleles favored in multiple countries	Alves et al 2019; Miller & Metcalf 2019

Viral Genetic Adaptation and Diversification. From the viral side, MYXV has undergone striking genomic diversification under selection from resistant rabbits and ecological conditions. Sequencing of dozens of strains from Australia and Britain between the 1950s and late 1990s reveals rapid, clock-like evolution with extensive point mutations, gene disruptions and gene duplications, yet no single mutation or set of mutations uniquely defines attenuated or highly virulent strains (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015). Instead, multiple genetic routes—often involving loss of function in virulence associated genes through insertions or deletions—can yield similar virulence grades, indicating high functional redundancy and plasticity in the large poxvirus genome (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015).

Comparative analyses show that virus evolution in the UK and Australia proceeded along largely distinct genomic pathways, despite similar broad selective regimes and comparable rates of molecular evolution (Kerr et al 2015; Kerr et al 2017). In Britain, modern field isolates fall into at least three long separated lineages with diverse clinical phenotypes, from highly nodular cutaneous myxomatosis to amyxomatous disease with sparse skin lesions and a novel syndrome of acute death accompanied by pulmonary edema and widespread bacterial invasion in the absence of inflammatory cells (Kerr et al 2017). Reading frame disruptions in genes considered essential for virulence in the original Lausanne strain can coexist with high virulence in field isolates, again emphasizing that different constellations of mutations can reconstruct similar or even more severe disease outcomes (Kerr et al 2017).

In Australia, genomic surveys likewise document a mosaic of insertions, deletions and gene duplications, particularly in genes associated with host range, apoptosis inhibition and innate immune modulation (Kerr et al 2013; Kerr et al 2015). Some modern Australian strains carry frameshifts or premature stop codons in multiple virulence genes, yet maintain or even increase virulence, implying that combinations of other genes or duplicated loci compensate functionally (Kerr et al 2013; Kerr et al 2015). One prominent example is the recurrent disruption of the putative ubiquitin ligase gene M009L and alterations in serpins and NF κB pathway inhibitors, which likely reshape the balance between immune evasion and host survival in ways that favor transmission (Kerr et al 2013; Kerr et al 2015).

Ongoing evolution has produced especially dramatic disease phenotypes in recent decades. Experimental infections with MYXV isolates collected between 2012 and 2015 in Australia show that all studied viruses can cause an acute fatal syndrome resembling neutropenic septicemia, characterized by minimal classical myxomatous lesions, pulmonary edema, heavy bacterial invasion of organs, and an absence of inflammatory response (Kerr et al 2017). More attenuated lineages produce a mixed pattern: some rabbits die acutely, while others develop pronounced swelling of cutaneous tissues with extremely high local virus titers, but reduced systemic pathology, an amyxomatous disease that may prolong infectious periods and enhance vector borne transmission (Kerr et al 2017).

A separate experimental comparison of historical and 1990s Australian MYXV isolates in naïve laboratory rabbits without genetic resistance showed that many 1990s strains, unlike those from the 1950s, induce a lethal immune collapse syndrome akin to septic shock, rather than classic myxomatosis (Kerr et al 2017). This indicates that, in response to widespread host resistance in the field, MYXV has escalated its virulence along new pathophysiological routes, altering the mechanisms of disease, while retaining or even increasing lethality (Kerr et al 2017) (Table 2).

Table 2

Genetic mechanisms of viral adaptation and host interaction (summarized by Consensus, 2026)

Viral change type	*Functional theme*	*Coevolutionary relevance*	*Citations*
Point mutations and small indels	Alter coding sequences of many virulence and host-range genes	Support rapid fine-tuning of virulence and immune evasion; multiple paths to similar phenotypes	Kerr et al 2012; Kerr et al 2013; Kerr et al 2015
Loss-of-function in virulence genes	Premature stops, frameshifts in BTB/kelch proteins, serpins, NF-κB inhibitors	Can attenuate or, in new genetic backgrounds, accompany high virulence; reshape host–virus interaction	Kerr et al 2013; Kerr et al 2015; Kerr et al 2017
Gene duplications	Especially in potential virulence/host-range genes	May increase expression or diversify function, facilitating adaptation to resistant hosts	Kerr et al 2013; Elsworth et al 2014; Kerr et al 2015
Recombinant insertions	Acquisition of novel poxviral genes in hare-adapted MYXV	Extend host range (e.g., jump to Iberian hare) and potentially alter immune modulation	Águeda-Pinto et al 2019; Dalton et al 2019

Molecular Interplay: Innate Immunity and Viral Counter Adaptation. The coevolutionary interaction between rabbit immune defenses and viral immune modulating proteins can be seen at several molecular levels. In rabbits, polygenic changes in immune genes, including interferon pathways, have increased the antiviral activity of key innate components; for example, allelic changes in an interferon protein enhance its ability to restrict MYXV replication (Alves et al 2019). Pathogenesis studies show that resistant rabbits restrict viral amplification in lymphoid tissues and peripheral organs, consistent with more rapid or potent innate responses that limit dissemination and allow effective cellular immunity to develop (Best et al 2000).

On the viral side, MYXV encodes numerous proteins targeting host innate pathways, including inhibitors of apoptosis, IFN induced protein kinase R (PKR), and NF κB signaling (Kerr et al 2013; Kerr et al 2015). Field evolution has frequently altered these genes. A mechanistic dissection of the M156 protein, a PKR antagonist, revealed that many MYXV field isolates produce M156 variants that no longer effectively inhibit rabbit PKR, correlating with observed attenuation and altered host specificity (Burgess & Mohr 2016). This work provides a direct molecular illustration of coevolution: as rabbit PKR and other innate effectors evolve, virus antagonists such as M156 are reshaped, sometimes losing activity against particular host genotypes, but potentially gaining or retaining functions in others (Kerr et al 2013; Kerr et al 2015; Burgess & Mohr 2016).

Virus induced modulation of host immunity also feeds back into selection on rabbits. Modern Australian MYXV lineages that cause profound immunosuppression and bacterial sepsis may impose different selective regimes than earlier, more purely viral diseases, potentially favoring host genotypes that better preserve inflammatory responses under viral assault (Kerr et al 2017). Conversely, the evolution of rabbit resistance can favor viral traits that minimize visible skin pathology, while sustaining high titers in tissues most accessible to insect vectors, as seen in amyxomatous phenotypes (Kerr et al 2015; Kerr et al 2017).

More broadly, the parallelism observed at both host and viral levels—polygenic immune adaptations in rabbits across continents, and multiple independent viral genetic routes to similar virulence grades—highlights a coevolutionary dynamic in which both sides exploit large mutational and functional "solution spaces." Rather than a single, linear arms race centered on one resistance gene and one viral counter gene, the rabbit–MYXV system exemplifies distributed, network level coadaptation involving many interacting loci (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015; Alves et al 2019; Miller & Metcalf 2019).

Wider Ecological and Evolutionary Implications. The coevolution of rabbits and MYXV has reshaped rabbit population dynamics and, indirectly, entire ecosystems. Initial MYXV release caused massive rabbit declines; subsequent evolution of attenuated viruses and resistant rabbits allowed partial recovery, modifying grazing pressure and predator–prey relations (Fenner & Marshall 1957; Kerr 2012). Genetic resistance to myxomatosis now appears common across Australian and British wild rabbit populations, although its current magnitude is uncertain because systematic testing largely ceased after the mid-1990s (Ross & Sanders 1984; Cooke et al 2023).

The rabbit–MYXV model also provides insight into other emerging rabbit pathogens. Work on rabbit haemorrhagic disease virus (RHDV) in Australia shows a contrasting evolutionary trajectory: virulence has increased rather than attenuated, likely because carcass mediated mechanical transmission by insects favors rapid host death and because rabbits are again evolving genetic resistance (Elsworth et al 2014). This comparison underscores that the direction and form of pathogen evolution depend on specific transmission ecology and host resistance architecture, even within the same host species (Kerr 2012; Elsworth et al 2014; Cooke et al 2023).

Recent detection of recombinant MYXV strains infecting Iberian hares and reports of MYXV expansion into new geographic regions such as Finland suggest that the virus continues to explore novel host and spatial niches (Águeda-Pinto et al 2019; Dalton et al 2019; Kauppinen et al 2025). Genomic characterization of these emergent strains consistently reveals a combination of conserved backbone structure and targeted innovations—such as inserted host range genes or unique patterns of mutations—that may facilitate infection of new leporid hosts with distinct immune landscapes (Águeda-Pinto et al 2019; Dalton et al 2019; Kauppinen et al 2025). These events represent new coevolutionary "experiments" that may, over time, parallel the historical trajectory seen in European rabbits.

Finally, the rabbit–MYXV system has influenced broader theory. It is widely used to illustrate how trade-offs between transmission and virulence, shaped by host resistance and vector ecology, constrain pathogen evolution and can drive intermediate virulence levels that maximize spread (Fenner & Marshall 1957; Kerr 2012; Kerr et al 2013; Miller & Metcalf 2019). The discovery that both rabbit resistance and viral virulence are polygenic and highly flexible, rather than governed by single major effect genes, adds depth to this paradigm and highlights the importance of genome scale data for understanding coevolution in natural populations (Kerr et al 2012; Kerr et al 2013; Kerr et al 2015; Alves et al 2019; Miller & Metcalf 2019).

Conclusions. The genetic coevolution between European rabbits and myxoma virus is one of the clearest empirical demonstrations of an arms race between a vertebrate host and a viral pathogen. Following the introduction of a highly lethal virus into naïve rabbit populations, selection rapidly favored both attenuated viral strains with improved transmission and rabbits carrying polygenic combinations of alleles that enhanced innate and cellular immune control of infection. Genome scale studies show that resistance evolved in parallel across continents from standing variation in immunity genes, while MYXV diversified through numerous independent mutations, gene losses and duplications affecting virulence and host range factors.

Pathogenesis experiments reveal that resistant rabbits limit systemic virus spread without fundamentally altering cell level permissivity, and that modern MYXV strains have evolved novel disease syndromes, including immune collapse and amyxomatous phenotypes, likely shaped by the need to overcome host resistance while maintaining vector mediated transmission. Molecular dissection of viral immune antagonists such as M156, and interferon related adaptations in rabbits, provide mechanistic snapshots of this ongoing conflict at the innate immunity interface.

Ecologically, the rabbit–MYXV interaction has transformed rabbit populations and landscapes in Australia and Europe and continues to evolve, with MYXV expanding its host range into hares and rabbit populations facing additional viral challenges such as RHDV. As a whole, this system exemplifies how coevolution proceeds through distributed, polygenic changes on both sides, constrained by ecological context and transmission routes, and it remains a foundational model for understanding the genetics of host–pathogen coadaptation in the wild.

Conflict of Interest. The authors declare that there is no conflict of interest.

References

Águeda-Pinto A., De Matos A., Abrantes M., Kraberger S., Risalde M., Gortázar C., McFadden G., Varsani A., Esteves P., 2019 Genetic characterization of a recombinant myxoma virus in the Iberian hare (*Lepus granatensis*). Viruses 11(6):530.

Alves J., Carneiro M., Cheng J., De Matos A., Rahman M., Loog L., Campos P., Wales N., Eriksson A., Manica A., Strive T., Graham S., Afonso S., Bell D., Belmont L., Day J., Fuller S., Marchandeau S., Palmer W., Queney G., Surridge A., Vieira F., McFadden G., Nielsen R., Gilbert M., Esteves P., Ferrand N., Jiggins F., 2019 Parallel adaptation of rabbit populations to myxoma virus. Science 363:1319-1326.

Best S., Best S., Kerr P., 2000 Coevolution of host and virus: the pathogenesis of virulent and attenuated strains of myxoma virus in resistant and susceptible European rabbits. Virology 267(1):36-48.

Burgess H., Mohr I., 2016 Evolutionary clash between myxoma virus and rabbit PKR in Australia. Proceedings of the National Academy of Sciences 113:3912-3914.

Cooke B., Taggart P., Patel K., 2023 Quantifying resistance to myxomatosis in wild rabbits produces novel evolutionary insights. Epidemiology and Infection 151:e182.

Dalton K., Martín J., Nicieza I., Podadera A., Llano D., Casais R., Giménez S., Badiola I., Agüero M., Duran M., Buitrago D., Romero L., García E., Parra F., 2019 Myxoma virus jumps species to the Iberian hare. Transboundary and Emerging Diseases 66:2218-2226.

Elsworth P., Cooke B., Kovaliski J., Sinclair R., Holmes E., Strive T., 2014 Increased virulence of rabbit haemorrhagic disease virus associated with genetic resistance in wild Australian rabbits (*Oryctolagus cuniculus*). Virology 464-465:415-423.

Fenner F., Marshall I., 1957 A comparison of the virulence for European rabbits (*Oryctolagus cuniculus*) of strains of myxoma virus recovered in the field in Australia, Europe and America. Journal of Hygiene 55:149-191.

Kauppinen A., Isomursu M., Pekkarinen H., Nylund M., Laamanen I., Nokireki T., Gadd T., 2025 Epidemiology and genetic characterization of myxoma virus from the first outbreak in Finland. Research in Veterinary Science 185:105544.

Kerr P., 2012 Myxomatosis in Australia and Europe: a model for emerging infectious diseases. Antiviral Research 93(3):387-415.

Kerr P., Best S., 1998 Myxoma virus in rabbits. Revue Scientifique et Technique 17(1):256-268.

Kerr P., Cattadori I., Liu J., Sim D., Dodds J., Brooks J., Kennett M., Holmes E., Read A., 2017 Next step in the ongoing arms race between myxoma virus and wild rabbits in Australia is a novel disease phenotype. Proceedings of the National Academy of Sciences 114:9397-9402.
Kerr P., Cattadori I., Rogers M., Fitch A., Geber A., Liu J., Sim D., Boag B., Eden J., Ghedin E., Read A., Holmes E., 2017 Genomic and phenotypic characterization of myxoma virus from Great Britain reveals multiple evolutionary pathways distinct from those in Australia. PLoS Pathogens 13(3):e1006252.
Kerr P., Ghedin E., DePasse J., Fitch A., Cattadori I., Hudson P., Tscharke D., Read A., Holmes E., 2012 Evolutionary history and attenuation of myxoma virus on two continents. PLoS Pathogens 8(10):e1002950.
Kerr P., Liu J., Cattadori I., Ghedin E., Read A., Holmes E., 2015 Myxoma virus and the leporipoxviruses: An evolutionary paradigm. Viruses 7:1020-1061.
Kerr P., Rogers M., Fitch A., DePasse J., Cattadori I., Twaddle A., Hudson P., Tscharke D., Read A., Holmes E., Ghedin E., 2013 Genome scale evolution of myxoma virus reveals host-pathogen adaptation and rapid geographic spread. Journal of Virology 87:12900-12915.
Miller I., Metcalf C., 2019 Evolving resistance to pathogens. Science 363:1277-1278.
Păsărin B., Oroian I., Rusu T., Brasovean I., Bora F. D., Papuc T., Popescu M., Petrescu-Mag I. V., 2025 Coevolution of mushroom toxicity and animal consumer behavior. AAB Bioflux 17(1):16-23.
Petrescu-Mag I. V., Păsărin B., 2025 Predation-driven evolution of locomotor performance in guppies: Experimental evidence and field-based convergence. Poec Res 15(1):19-22.
Proorocu M., Oroian D., Papuc T., Odagiu A., 2020 Fighting rabbits in Australia by infection with viral strains is just a delay of the invasion. Rabbit Gen 10(1): 15-18.
Ross J., Sanders M., 1984 The development of genetic resistance to myxomatosis in wild rabbits in Britain. Journal of Hygiene 92:255-261.
Williams C., Moore R., Robbins S., 1990 Genetic-resistance to myxomatosis in Australian wild rabbits, *Oryctolagus cuniculus* (L). Australian Journal of Zoology 38:697-703.
*** Consensus, 2026 An AI-powered search engine for research. Available online at https://consensus.app. Consensus NLP, Inc. [Consensus is not an author].

Received: 25 January 2026. Accepted: 24 March 2026. Published online: 17 April 2026.
Authors:
Zsolt Attila Grabán, National Association of Pigeon and Small Animal Breeders of Hungary, Budapest, Hungary, 1433 Budapest, Pf. 575, Hungary, e-mail: grabanzsolt@gmail.com
Tudor Păpuc, Faculty of Animal Science and Biotechnologies, University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Calea Mănăștur 3-5, 400372 Cluj-Napoca, Romania, e-mail: tudor.papuc@usamvcluj.ro

How to cite this article:
Grabán Z. A., Păpuc T., 2026 Genetic coevolution between rabbits and myxoma virus. Rabbit Gen 16(1):14-20.