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Review Article

Genetic disorders in domestic rabbits (*Oryctolagus cuniculus*)

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Abstract. This work paper is a long list of hereditary diseases observed by us or reported by others in domestic rabbit (or European rabbit, *Oryctolagus cuniculus*). Due to its large phenotypic and genetic variability, *O. cuniculus* is an excellent model for classical genetics, including here inheritance of color patterns and genetic disorders. For that reason, this mammalian model is widely used in human biomedical or veterinary research, together with rat, Guinea pig, and mouse. All these species are called also "human models" because of their similarity with humans in physiological response. Most part of the genetic disorders presented in this study was observed also in humans.
Key Words: Rabbit genetics, autosomal recessive, autosomal dominant, sex-linked, inherited disease, pathology.

Introduction. The domestic rabbit possess a number of advantages as high growth and reproductive rate, early sexual maturity and ability to rebreed shortly after kindling, do to their fast recovering endometrium (Orheruata et al 2006). Rabbits are one of the most efficient cellulose converter species, ensuring high production of low-cost meat, do to their herbivore nature, and not at least they are not in competition with humans regarding diet (Bud et al 2011). The main product, rabbit meat has several nutrition qualities as high protein level, low fat and low cholesterol (Bud et al 2011; Cheeke et al 2000). These qualities of the species, beside more others, make rabbits breeding one of the solutions for protein deficiency countries (Blaga & Burny 2014; Bud et al 2011; Obike et al 2010).

Also the rabbit is a valuable material in scientific research, in histology, virology (Zhao et al 2010), genetics (Covrig et al 2013; Petrescu-Mag et al 2013; Petrescu-Mag et al 2012b; Zhao et al 2010; Hayes et al 2008; Pandit et al 2002), cytology, embryology etc. Several publications related about importance of the European rabbit (*Oryctolagus cuniculus*) as an excellent laboratory animal (Hayes et al 2008). According to the same research team "To date, over 250 new genes have been mapped by fluorescent in situ hybridization (FISH) along the 23 chromosomes, thus increasing twelve-fold the number of genes mapped in rabbit". Normal rabbits serve as models to study human diseases as hyperlipidemia and related diseases (Shiomi & Ito 2008; Hoffmann et al 2011), cancer and diabetes mellitus (Zhao et al 2010), tuberculosis (Yukari 2008), papillomavirus infection (Christensen 2008), atherosclerosis (Lagrost 2008), obesity and type II diabetes (Gaudriault et al 2008), prion diseases (Sarradin et al 2008), lung and airway morphometry (Tovar 2012; Gallot et al 2008; Jani et al 2005; Wu et al 2000; Fauza et al 1994; Ohi et al 1976), P450scc deficiency CAH (Pang et al 1992; Yang et al 1993). The pharmaceutical industry also show interest for rabbit species as experimental animals (Soler et al 2008), they are also used as bioreactors to produce pharmaceutical proteins (Hoffmann et al 2011; Zhao 2010), recombinant human C1 inhibitor in milk (Salaheddine & Mannesse 2008). Transgenic rabbits are widely used as model organisms for biomedical research (Houdebine & Fan 2009; Zhao et al 2010). It is a new role for rabbits to serve as special tools, especially as models to image organs and tissues *in situ* and *in*

vivo (Al-Guborky & Houdebine 2008). Akdogan & Yonguc (2011) showed a chronic model for experimental epilepsy by injecting 10 µL zinc sulfate into rabbit hippocampus. In 1979 Natelson et al induced epileptiform convulsions in rabbits with corticotrophin, knowing that changes in blood components and blood pressure in rabbit resemble those in humans before an epileptic seizure, reported the same author.

Information transmission and genetic messages usually are sent from parents to offspring's very precisely, but sometimes there transcription errors occurs called mutations. Then these errors are inherited from generations to generations. Some of these transcription errors make the genetic information incomprehensible which leads to non-viable zygote, embryo or fetus (Holdas 2000).

The first report regarding frequency of congenital abnormalities in rabbits has been reported by Crary & Fox (1980) where data was drawn from 32,082 inbred and partially inbred individuals.

This paper aims to rank together the main genetic problems in domestic rabbits from the international literature and fifteen years of personal experience, seeing that there is no scientific paper that meets all or the most common genetic disorders. Most of these topics are addressed in old books difficult to find and obtain. This work is conducted to identify possible abnormalities during the first two new Romanian rabbit breed creation, Giant of Transylvania (Petrescu-Mag et al 2013, 2012a, 2012b, 2011, 2009) and Rabbit of Cluj (Botha et al 2013, 2011), knowing that inbreeding are inevitable. Not at least this paper also aims to serve to all those who engage in rabbit genetic improvement, to help selection and an adequate inbreeding management (considering its adverse consequences). A comprehensive study has been conducted by Ballou (1997) regarding ancestral inbreeding effects on inbreeding depression in mammalians, and in 2010 Casellas et al shown for the first time the epistatic inbreeding depression elucidating the complexity of the genetic architecture in mammals. Now classical genetic studies and modern molecular evolutionary approaches suggest that inbreeding depression are predominantly caused by the presence of recessive deleterious mutations (Charlesworth & Willis 2009).

Material and Method. Most of the materials are synthesized form research articles and specialty literature, supplemented with observations by the Giant of Transylvania and Rabbit of Cluj research and breeding team.

Results and Discussion

Pathology of the inherited disease is a branch of genetics which deals with the study of the inherited disorders, inherited predisposition, and heritable resistance of the organism against various diseases, presenting a special importance in the prevention of hereditary diseases through genetic prevention (Popescu-Vifor et al 1980).

According to Bura & Bencsik (2000) hereditary diseases can be classified by type of heredity in genetic disorders, which includes recessive and dominant genetic disorders, and genetic disorders with unknown heredity.

Genetic disorders

Recessive genetic disorders

Diaphragmatic hernia leads to newborns death do to respiratory failure. There are cases when diaphragm hernia is accompanied by phenotypic disorders, or the diaphragm can partially missing, more often on the left and posterolateral, when the abdominal content (spleen and the stomach) moves in to the thoracic cavity (Tovar 2012; Bura & Bencsik 2000; Sandu 1986) (Figure 1). Sandu (1986) mention that this kind of disorder can also be accompanied by heart diseases (ventricular septum).

Fox & Crary (1973) records only 30 % affected individuals from those predicted. They say that the recessive genes which causing diaphragm hernia are located on an

autosomal locus, carrying an *dh* noted gene with a penetrance of 30 %, or on two autosomal loci, genes *dh-1* and *dh-2* on the same chromosome but not very close.

Wu et al (2000) created diaphragmatic hernia in 39 rabbit fetuses on day 23 of gestation, where the results of the surgical diaphragmatic hernia in the late pseudoglandular phase reproduces many features of the pulmonary hypoplasia associated with human congenital diaphragmatic hernia, including maturation delay. The effects appeared within 2 days following experimental diaphragmatic hernia and progress over time.

Tovar (2012) says that the etiology of congenital diaphragmatic hernia (CDH) is unknown although clinical, genetic and experimental evidence points to disturbances in the retinoid-signaling pathway during organogenesis, with an occurrence of <5 in 10,000 live-births (in humans), and one third of cases have cardiovascular malformations and lesser proportions have skeletal, neural, genitourinary, gastrointestinal or other defects.

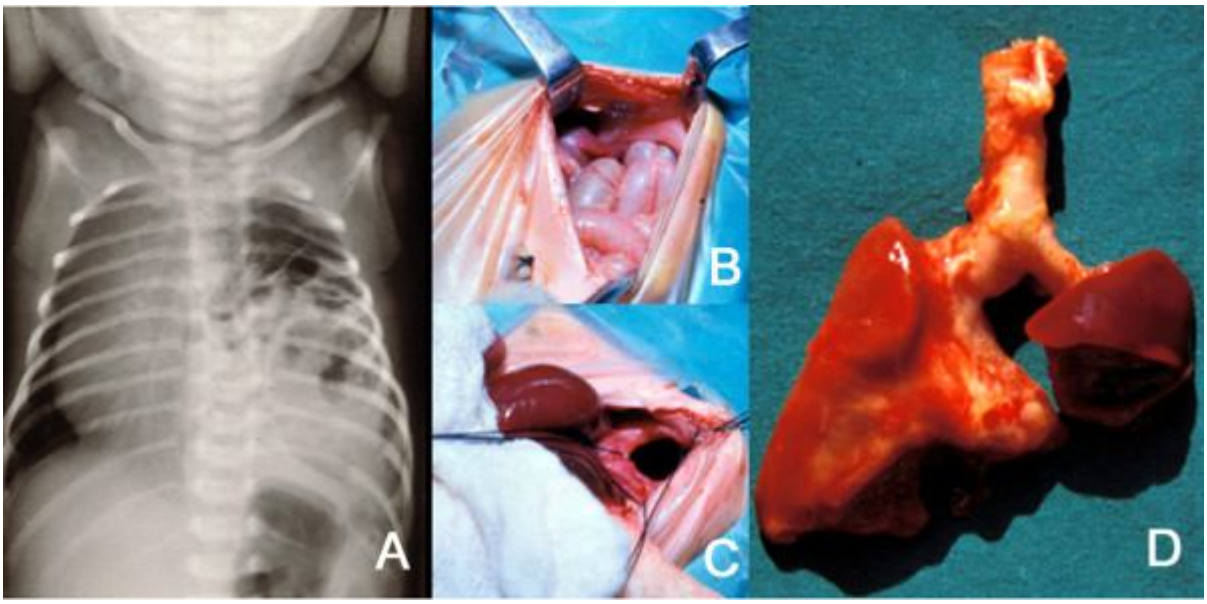


Figure 1. A: Plain X-ray of the thorax of a newborn with congenital diaphragmatic hernia (CDH). There are bowel loops in the left hemi-thorax, the mediastinum is displaced to the contralateral side and the space occupied by the lung is reduced. B and C: At laparotomy, a left, posterolateral diaphragmatic hernia was discovered. In B, small bowel loops can be seen entering the thorax through the orifice. In C, this is seen after reducing the contents of the hernia. D: The patient died of severe persistent pulmonary hypertension days later. At autopsy, extreme left lung hypoplasia and less severe right lung hypoplasia were discovered (Tovar 2012).

Adrenal hyperplasia can be observed from the 19th day of gestation. Due to the hypersecretion of adrenalin causes death right after parturition (Bura & Bencsik 2000; Fox & Crary 1978) (Figure 2).

As side effect can be mentioned a feminization of the phenotype (Yang et al 1993; Sandu 1986; Fox & Crary 1978). Fox & Crary (1978) shown on one-hundred-twenty-nine cases of adrenal hyperplasia in the rabbit that the disorder is caused by a fully penetrant autosomal recessive gene noted *ah*, a mutant maintained in strain IIIVO/ahJ.

The absence of the cholesterol side-chain cleavage enzyme cytochrome P450 (P450scc) expression in rabbits affected with congenital adrenal hyperplasia (CAH) were reported (Pang et al 1992; Yang et al 1993). Further molecular studies via Southern blotting analyses, using a full-length human P450scc cDNA probe and a cloned rabbit P450scc cDNA probe, demonstrated the absence of P450scc DNA fragments in CAH animals. Reverse transcriptase-based polymerase chain reactions revealed that P450scc mRNA was not detectable in the adrenals of CAH rabbits, confirming the previous findings of absent P450scc gene expression by Northern and Western blotting (Yang et al 1993).

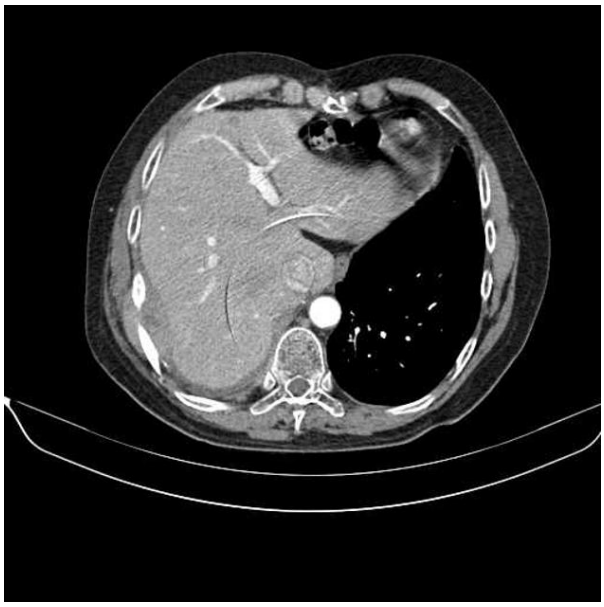


Figure 2. Bilateral adrenal hyperplasia (http://radiopaedia.org/articles/bilateral-adrenal-enlargement).

Hypotrichosis (Figure 3) is caused by an autosomal recessive gene (Nachtsheim 1934 quoted by Sandu 1986; Jelani et al 2008), mapped on chromosome 3q26.33-q27.3 (Aslam et al 2004). The mutation can be identified from the age of two weeks, when the unaffected individuals are normally covered by down, and the affected ones present a very poor pilosity on the neck and ears.

Figure 3. Congenital alopecia – Hypotrichosis (http://www.medirabbit.com).

The anomaly is accompanied by tooth defects, which can lead to their loss, the rabbits become more and more debilitated and die at the age of 1 month, when there are weaned and are enable to consume solid forage (Bura & Bencsik 2000; Sandu 1986).

Achondroplasia is a recessive autosomal trait results from mutation in an FGR receptor gene, FGFR-3, where the synthesis of cartilaginous ECM is reduced and there is much cell death and necrosis, especially in the centre of the cartilaginous primordial which suggest the involvement of the vascularity isolation (Hall 2005).

The abnormality can be noticed since birth through clinical signs as size reduction, disproportion of body parts, most marked in the extremities, and have an invariably lethal effect. Affected individuals are still-born or die very shortly post partum. Achondroplasia in the rabbit has a remarkable resemblance to the disease in man, cattle and dogs as shown by x-ray photographs the physical appearance and in the character of the skeletal changes. For the first time this condition in rabbits was recorder in offspring of pure bred Havana rabbits. It can be stated that the inheritance pattern is on the basis of a simple recessive unit factor and that the appearance of non-achondroplastic transmitters (heterozygotes) is that of normal animals (Brown & Pearce 1945).

The mutation is reported to be non sex-linked, despite of the fact that females are somewhat more frequently affected than males (Pearce & Brown 1945), statement confirmed by Crary & Sawin (1963).

Chondrodystrophy in rabbits have been shown to be associated with a fully penetrant autosomal recessive gene symbolized *cd*. The mutant is viable prenatally but does not survive post partum. It differs from the two other inherited chondrodystrophies, dachs and achondroplasia, but is very similar to the metatropic dwarf reported in man (Fox & Crary 1975).

Chondrodystrophy can be associated with errors in mineral metabolization do to abnormality in the specific mineral binding protein, and function of the anomaly type is characterized by cerebral degeneration, short stature, hemolytic anemia, hair changes, hepatolenticular degeneration, cirrhosis of the liver, and excessive mineral accumulation in tissues (Smart et al 1979).

Paralytic tremor is caused by lymph node lesions, and controlled by an autosomal recessive gene (Bura & Bencsik 2000; Nachtsheim 1934 quoted by Sandu 1986). This anomaly results from a point mutation in a *plp* gene and manifests itself by a broad range of neurological signs (Sypecka & Domańska-Janik 2005; Tosic et al 1996). Szendrő & Holdas (1985), and later Tosic et al (1993, 1994), Holdas (2000) and Papis et al (2005) stated that this anomaly is X-linked, and with a very few exceptions can be observed only on male individuals.

The disorder can be observed in a few days post parturition as shake movements. Before *exitus* there are three stages: in the first month dance looking violent movements occurs, in the second month limb paralysis can be observed (most frequently paraplegism), and in the third month complete paralysis and death installs (Bura & Bencsik 2000; Sandu 1986).

This genetic disorder has an incomplete penetrance, and shows a variable expressiveness, some individuals are so gentle affected that they even can be breed. The disease is similar in many respects with human pseudosclerosis (Wilson disease) (Nachtsheim 1934 quoted by Bura & Bencsik 2000).

Domańska-Janik et al (1992) studies on calcium-activated neutral protease (CANP) activity in normal and dysmyelinating mutant, paralytic tremor (PT) rabbits suggest a delayed myelination and/or a higher turnover rate of already formed myelin which suggest complex and specific roles for these isoenzymes during myelin formation. These results confirm the extensive degradation of myelin basic protein (MBP), proteolipid protein (PLP), and, to a lesser extent, the other myelin proteins by endo- and exogenous CANP. This degradation process was significantly elevated in PT rabbit myelin. Moreover as shown by two-dimensional gel electrophoresis, calcium-controlled proteolysis in nonmutant rabbits affected the net-charge of MBP in a manner similar to that reported for PT myelin, suggesting the possible involvement of CANP in the generation of charge isomers of MBP.

Left ostium straightness (Figure 4) occurs in some populations in a 5 - 7 % (Bura & Bencsik 2000; Crary & Fox 1981), and was described in 1955 as a first record (Sandu 1986). Left ostium straightness is caused by a recessive autosomal gene (*los*) with incomplete penetrance (Crary & Fox 1981).

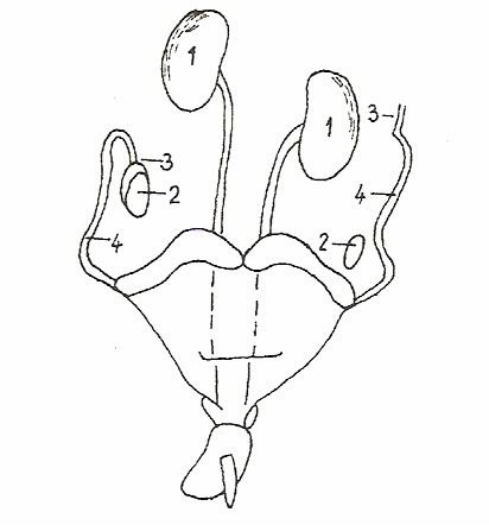


Figure 4. Left ostium straight in rabbit. 1- kidney; 2- ovary; 3- fallopian tube; 4- oviduct (Crary & Fox 1981).

The oviduct remains straight, as a result of an abnormal embryogenesis. Opening of the uterine tube is not rounded in order to set the ovary, which is also migrated in an unnatural place (Bura & Bencsik 2000; Crary & Fox 1981).

Cortical renal cysts are caused by an autosomal recessive gene (*rc*) with a penetrance of about 70 % (Bura & Bencsik 2000; Sandu 1986). Cortical renal cysts however it does not affect kidneys function (Fox et al 1971). Analysis of serum and urine show no pathological changes (Fox 1979).

Cysts can be observed only at 1 month of age or later. The cysts appear to be of tubular origin and are found in the cortex (Fox 1979).

Opara et al (2012) showed in a study conducted on young rabbits the renal function enhancement possibilities with aqueous extract of *Gmelina arborea* leaves.

Hypogonadia was detected in 1958 attributed to an autosomal recessive gene noted *hg* (Fox & Crary 1971b). Affected males present smaller seminiferous tubules and a single Sertoli cell line, and females have smaller ovaries and no follicles (Bura & Bencsik 2000; Sandu 1986). At necropsy in males instead of normal 1700 mg testicles 225 mg are found, and in females the ovaries weight just 12 mg instead of 150 mg (Holdas 2000; Szendrő & Holdas 1985).

Gonads can be affected totally or in mosaic at both sexes, secondary sexual characters are also affected and cause total or partial sterility (Sandu 1986; Fox & Crary 1971b; Fox & Crary 1971 quoted by Bura & Bencsik 2000). Iwuji & Herbert (2012) reported a possibility to enhance sexual drive and semen characteristics in matured rabbit bucks with *Garcinia kola* seed meal at 2.5 % dietary level.

Table 1

Metabolic characteristics of rabbits (Mallidis et al 2011)

Rabbits	*Total body weight (g)*	*Blood glucose (g/l)*	*Cholesterol (mg/dl)*	*Triglycerides (mg/dl)*	*Testosterone (nmol/l)*
Control					
Baseline	3225 ± 76	1.09 ± 0.15	33.7 ± 3.3	91.2 ± 9.4	7.54 ± 1.81
Week 12	4002 ± 159	1.17 ± 0.14	31.9 ± 4.3	90.6 ± 9.4	7.12 ± 1.13
HFD					
Baseline	3163 ± 69	1.36 ± 0.05	45.5 ± 3.1	90.1 ± 9.0	7.23 ± 1.70
Week 12	3805 ± 83	1.99 ± 0.15†,§	1247 ± 66.2‡,¶	301 ± 48.5†,§	2.20 ± 0.60*
HH					
Baseline	3330 ± 111	1.03 ± 0.08	33.3 ± 4.1	77 ± 11	6.10 ± 0.90
Week 12	4064 ± 126	1.24 ± 0.13	45.9 ± 7.2	146 ± 35	1.58 ± 0.08*

*P<0.05, †P<0.01, ‡P<0.0001 versus relative baseline values. §P<0.01, ¶P<0.0001 versus control week 12. Results were obtained from at least eight animals for each group and are expressed as means ± S.E.M.

Table 2

Organ weights and mean arterial pressure of rabbits after 12 weeks (Mallidis et al 2011)

Rabbits	*MAP (mmHg)*	*Weight*		
		Visceral fat (g)	*Seminal vesicles (mg)*	*Testis (g)*
Control	93.4 ± 4.8	27.9 ± 2.5	879 ± 98	3.50 ± 0.13
HFD	131.5 ± 5.4†	49.5 ± 3.2†	560 ± 45*	3.10 ± 0.12*
HH	85.4 ± 6.8	73.2 ± 5.5†,‡	337 ± 61*	2.76 ± 0.30*

*P<0.05, †P<0.01, versus control, ‡P<0.05 versus HFD. Results were obtained from at least eight animals for each group and are expressed as means ± S.E.M.

In table 1 & 2 Mallidis et al (2011) in a recent study shows a series of metabolic characteristics of rabbits with hypogonadal hypogonadism (HH) versus control and versus high feed diet (HFD) individuals. Histological assays result of the same authors is shown in figure 5 & 6.

Morelli et al (2013) underline that hypogonadism, showing a reduced immunopositivity for gonadotropin releasing hormone (GnRH) in the hypothalamus.

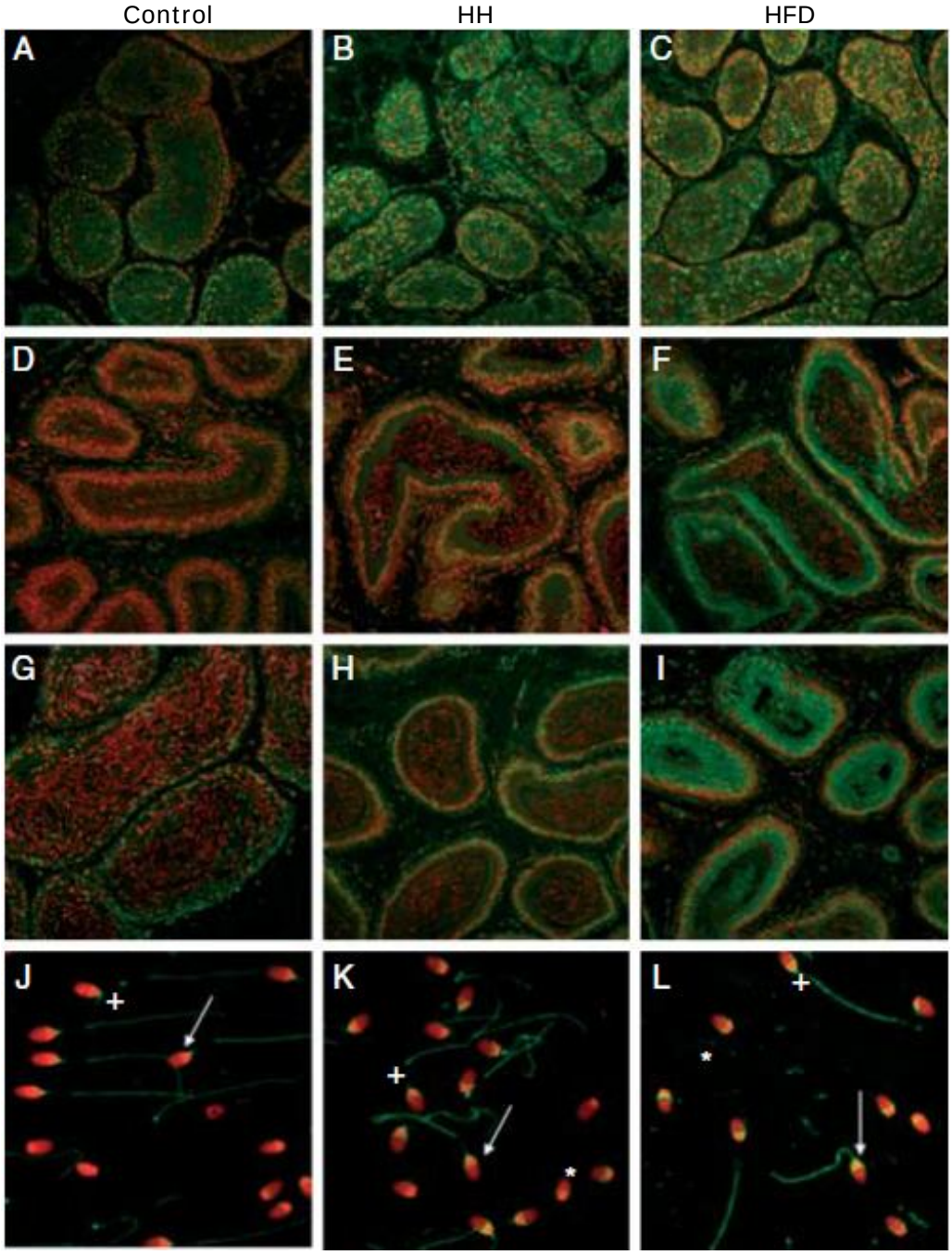


Figure 5. Immunolocalisation of N3-carboxymethyl-lysine (CML) in the testis (A–C), initial epididymal segment (D–F), caput epididymis (G–I) and sperm (J–L) of control, hypogonadal hypogonadism (HH) and highfat diet (HFD) rabbits. Variations in the staining of the head equatorial band and sperm mid piece are indicated by the arrow and cross respectively. The asterisk indicates sperm without tails (Mallidis et al 2011).

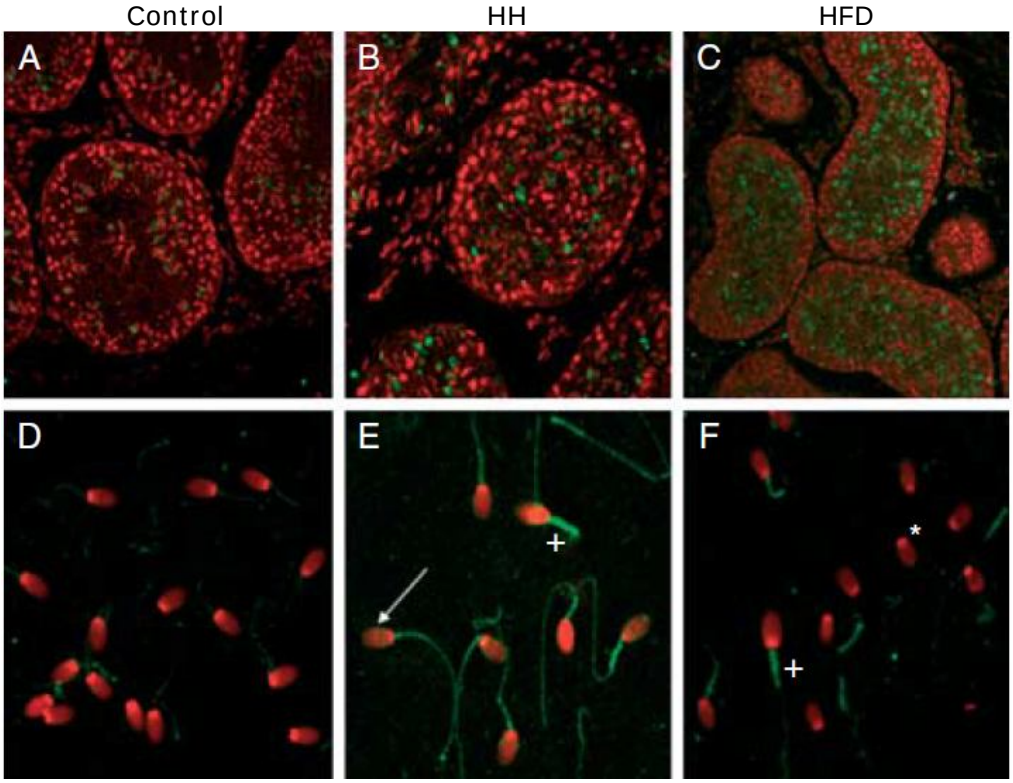


Figure 6. Immunolocalisation of the receptor for advanced glycation end products (RAGE) in the testis (A–C) and sperm (D–F) of control, hypogonadal hypogonadism (HH) and high-fat diet (HFD) rabbits. The speckled staining of the acrosomal region of the sperm heads from HH animals is indicated by the arrow and the more intense immunoreactivity of sperm mid piece in both HH and HFD animals by the cross. The asterisk indicates sperm without tails (Mallidis et al 2011).

Buphtalmia (hydroftalmia or congenital glaucoma) is described by Nachtsheim (1937) quoted by Sandu (1986) as a result of an autosomal recessive gene action, which by Knepper et al (1997) leads to loss of function of a gene(s) required for the differentiation of the trabecular meshwork (TM).

In rabbits the main diseases of the eyeball met in practice mainly affect the fibrous coat, especially the cornea (Barthelemy & Monnereau 2001) (Figure 7). Glaucoma is a term encompassing a variety of diseases that end in the death of retinal ganglion cells (RGC). Increased intraocular pressure (IOP) is one of the major risk factor beside the variety of factors which can initiate the disease onset (Beit-Yannai et al 2007; Solomon et al 2003).

Kauffman (1926) quoted by Sandu (1986) obtained through selection a similar character which manifests in a dominant manner. Hanna et al (1936) quoted by Sandu (1986) continue the studies and provide evidence for an incomplete penetrance of a recessive gene (*bu*). All mentioned authors consider that the gene is located on the same chromosome, near by gene *c* for albinism, because the anomaly has poor frequency in pigmented rabbits (Sandu 1986). The authors of this paper, the Rabbit of Cluj and Transylvanian Giant Rabbit breeding team can confirm this statement, observing this anomaly more often in albino individuals with an occurrence of less of 1 %, based on observation during over 10 years and over 4,000 individuals. Bennett et al (1973) report a distance of 40 M, while Bauer & Bennett (1964) quoted by Sandu (1986) report a distance of 16 M. Fox et al (1969) quoted by Sandu (1986) it adds a series of pleiotropic effects as it shown in figure 8.

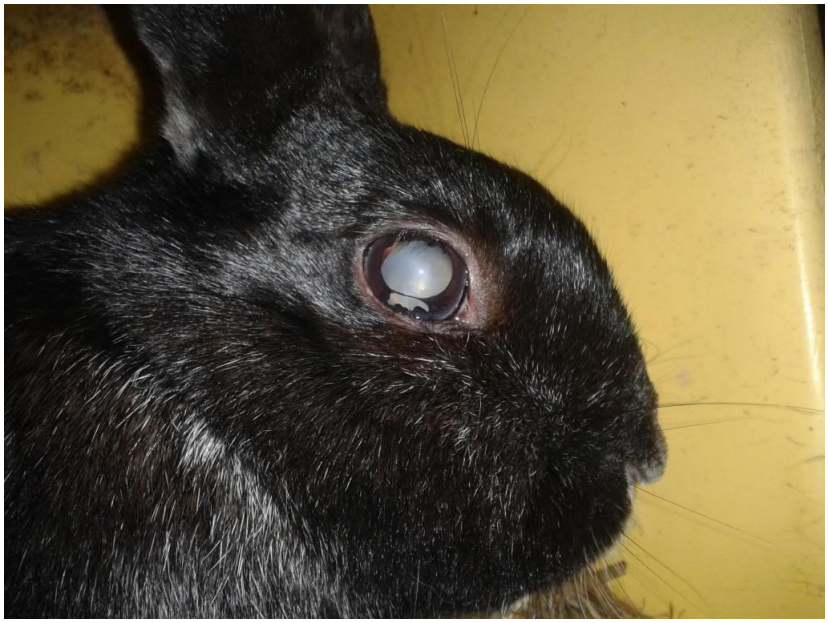


Figure 7. Glaucoma in rabbit (http://forums.rabbitrehome.org.uk).

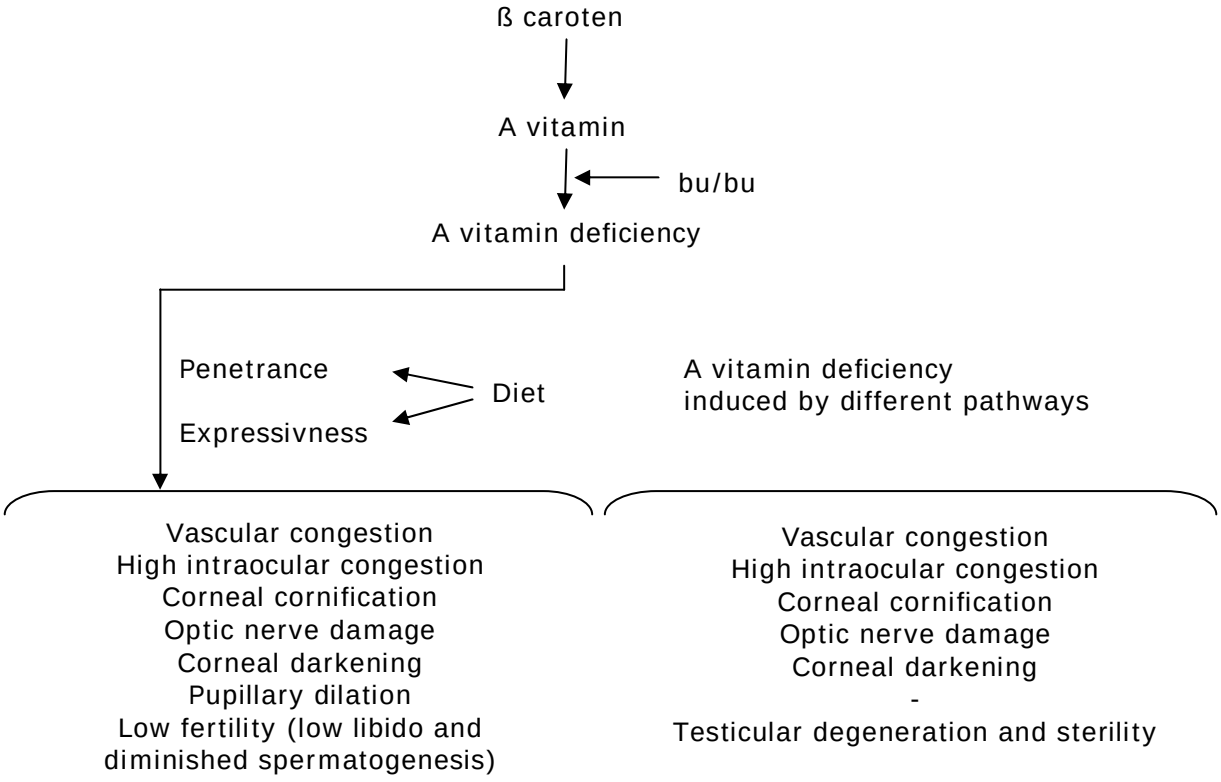


Figure 8. Pleiotropic effects of the *bu* gene (Fox et al 1969).

Rabbit with early congenital glaucoma is a useful infantile glaucoma surgical model (Sun et al 2000).

Macrostomus caused by a single autosomal recessive gene (*mst*), with incomplete penetrance (30 – 35 %), seems to be a fourth linkage group gene beside *Dw* and *w* genes (Fox & Crary 1979). The affection is apparent in the 25th day of gestation and

manifested by increasing mouth and existence of one or rarely more papillae on one or both commissure (Bura & Bencsik 2000; Fox & Crary 1979) (Figure 9).

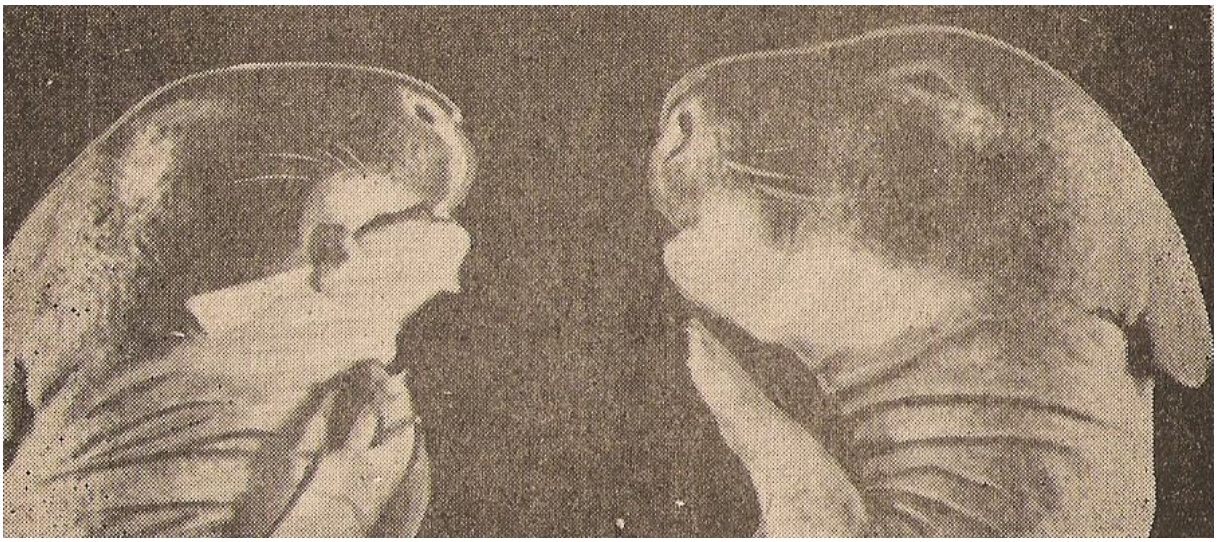
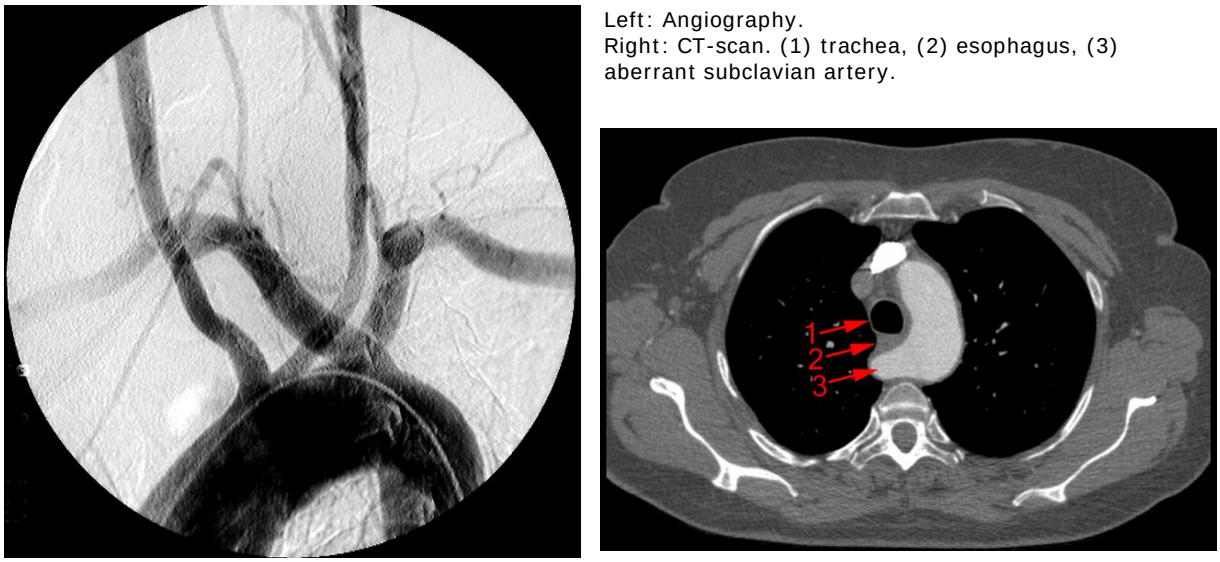


Figure 9. Macrostomus: left – affected; right – normal (Fox & Crary 1979).

While macrostomus in the rabbit is manifested externally by the presence of papillae at the corners of the mouth, internally the effect is on the zygomatic complex and is extremely variable. Macrostomus in the rabbit is a model for the Treacher Collins syndrome, one form of mandibulofacial dysostosis in humans (Fox & Crary 1979).

Misslocalization of the right subclavian artery has been reported since 1891 by Smith quoted by Sandu (1986) with an occurrence of 1 % (Figure 10).

In this case after the detachment of the aortic trunk, right subclavian artery reaches this part, behind the trachea and esophagus. In the 80's in some populations the disorder reaches an occurrence up to 15 %, caused by an autosomal recessive gene (*res*) with incomplete penetrance (Sandu 1986).



Left: Angiography.
Right: CT-scan. (1) trachea, (2) esophagus, (3) aberrant subclavian artery.

Figure 10. Aberrant subclavian artery (http://en.wikipedia.org/wiki/Aberrant_subclavian_artery).

Mandibular prognathism (maxillary brachygnathism). As the lower jaw appears relatively too long, some authors (Harcourt-Brown 2009; Verstraete & Osofsky 2005) use the term maxillary brachygnathism instead of mandibular prognathism. This hereditary

disease is most common in dwarf rabbits (Legendre 2002), caused by an autosomal recessive gene (*mp*) which causing differential growth of dorsal and basal skull bones, with resultant anterior displacement of the mandible (Fox & Crary 1971a). Huang et al (1981) report a penetrance of 81 %. Currently the particular gene or genes responsible for incisor malocclusions are unidentified. The only way of judging if an animal is a carrier or likely to be a carrier is from knowledge of whether any of its relatives, particularly siblings and offspring, are affected.

Locomotor abnormalities are cause by non sex linked recessive genes according to Sandu (1986), and sex-linked according to Bura & Bencsik (2000), namely gene *S* which is responsible for abnormal gait (Audigier & Renous 2002). Gene *S* carrier rabbits show an abnormal rising of the posterior body part, or an acrobatic walk on the forelimbs (Audigier & Renous 2002). Mutant rabbits appear normal at rest or when they covering short distances, "but when they are running longer distances the hind part of the body is raised in the air and the animals go along on their forefeet like an acrobat walking on his hands" (Letard 1935). Affected individuals were called "jumping rabbits" by Letard (1935) or "acrobats", and "waltzing rabbits" by Cole & Steel in 1922, cited by Sandu (1986).

Hereditary vestigial pulmonary arterial trunk. Crary & Fox (1975) report a malformation involving the heart and great vessels in a population of IIIVO/J rabbits at the Jackson Laboratory as an expression of hereditary vestigial pulmonary arterial trunk, and propose the symbols *vpt-1* and *vpt-2* for the genes responsible for the disease and its related abnormalities. Inheritance pattern appears to be due to two autosomal recessive factors both of which must be homozygous for the expression of the condition. This mutation can be lethal in its most extreme forms, but some individuals who are somewhat less severely affected may live for a short time. No effect was seen on birth weight or litter size. There appears to be a series of effects from a completely absent pulmonary trunk through a vestigial but patent pulmonary trunk and/or pulmonary valve stenosis on the one hand to a vestigial or absent ascending aorta on the other. In a few cases the pulmonary trunk is bulbous and the ductus arteriosus is vestigial or absent. In almost all cases of this syndrome, there is also a high ventricular septal defect. The animals appear perfectly normal in every other respect.

Narrow axis has been observed in strain X/J rabbits by Crary & Fox (1983) and described as an inherited anomaly resulting in a marked narrowing of the second cervical vertebra. Authors propose the *nx* symbol as gene notation for narrow axis in rabbits. In 20 years of genetic analysis of 3,244 rabbits X rays elucidate the inheritance of this condition which appears due to a single autosomal recessive gene with incomplete penetrance. This condition is first recognizable at 32 - 33 days gestation through X ray investigation. The expression of the disease is variable. Premature fusion of the centrum with its neural arches appeared to be the primary effect. The secondary and adaptive appeared effect is on the posterior articulation of the atlas. The other cervical vertebrae and the foramen magnum were relatively unaffected. The condition is neither sex-linked nor sex-limited.

Brachydactylia was reported by Greene & Saxton (1939) as determined by simple recessive hereditary factors (*br*/*br*) and that the various types were genetically related and were not distinct hereditary entities. The first abnormal change, showed by embryological investigation, was a dilatation of blood vessels in affected buds. This was followed by hemorrhage and necrosis of the involved parts. Sloughing subsequently occurred, and the deformity was completely expressed by the 25th day of fetal life. X-ray analysis reveals poorly formed phalanges that are functionally compromised by their anatomical abnormality (Figure 11). Morphologically brachydactylia is characterized mainly by shortening of the digits, and the severity of the disease is extremely variable, ranging from minor brachydactylia to complete acheiropodia, affecting one or extended to all feet.

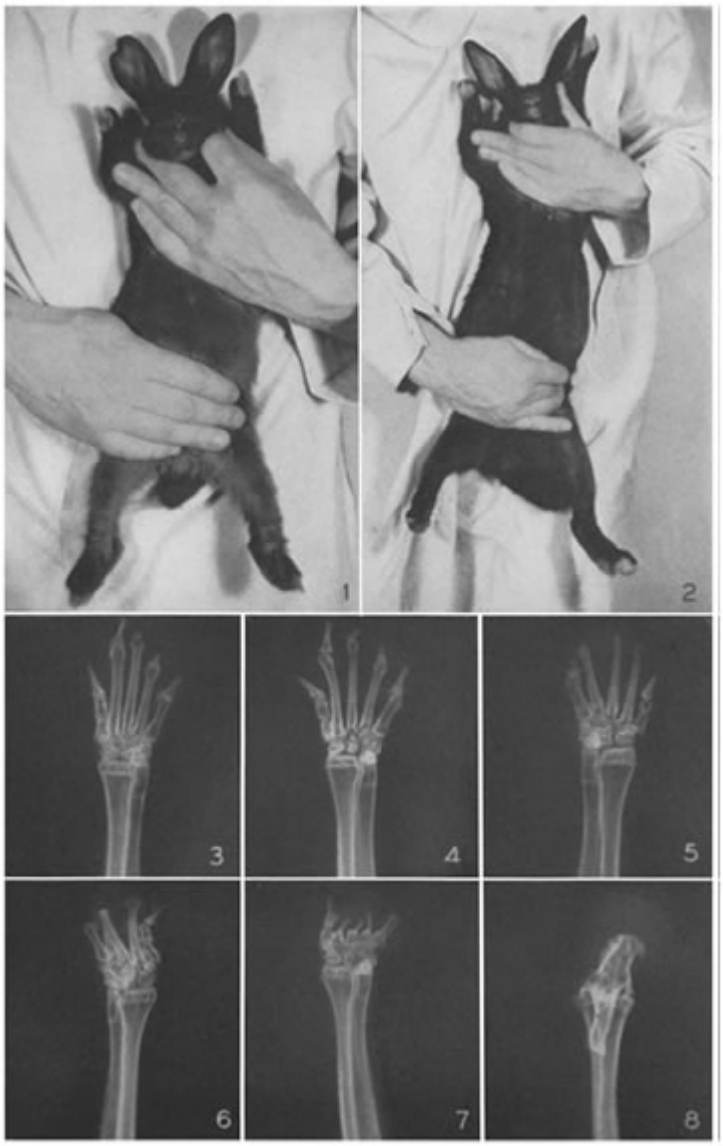


Figure 11. Brachydactylia and Acheiropodia malformation of rabbit limb, x-ray outlines bone degeneration (Greene & Saxton 1939).

Microphtalmia in rabbits was described by Nachtsheim (1934, 1949) quoted by Sandu (1986), and probably caused by recessive genes (Sandu 1986). In contrast Rivera et al (2010) says that microftalmia which is the clinical sign of Oculodentodigital Dysplasia (ODDD) is an autosomal dominant syndrome.

Is expected that individuals affected by this mutation to show a reduced ovulation rate activity as Watanabe et al (1997) showed that mice with mutation at the microftalmia (*mi*) locus, exhibit functionally defective macrophages and low numbers of mast cells, also show defective ovulation which is restored after bone marrow transplantation.

Anophtalmia in rabbits was described by Nachtsheim (1934, 1949) quoted by Sandu (1986), and is suspected to be caused by recessive genes (Sandu 1986).

In many cases certain causes of the mutations which lead to microphtalmia and anophtalmia cannot be identified. There are several possible causes for both of these conditions, including genetic changes. Researchers also believe environmental factors (such as exposure to X-rays, chemicals, drugs, pesticides, toxins, radiation, or viruses) can increase the risk of anophthalmia and microphthalmia. These rare disorders develop during pregnancy and can be associated with other birth defects (NEI 2014).

Milleman et al (2007) reported from France a case when cows with a history of maternal malnutrition produced calves with microphthalmia, aphakic globes with retinal dysplasia, and optic nerve hypoplasia.

Ikeda et al (1999) obtained anophtalmic rat litters from females treated with the food-derived carcinogen, 2-amino-1-methy-6-phenylimidazo [4,5-b] pyridine (PhIP) (Figure 12). Toward Zhu et al (2003) showed that PhIP is the most abundant heterocyclic amine (HCA) in cooked food, and it is mammary carcinogen in female rats, and humans.

All these results suggest that anophtalmia can even be caused by endocrine disruptors.

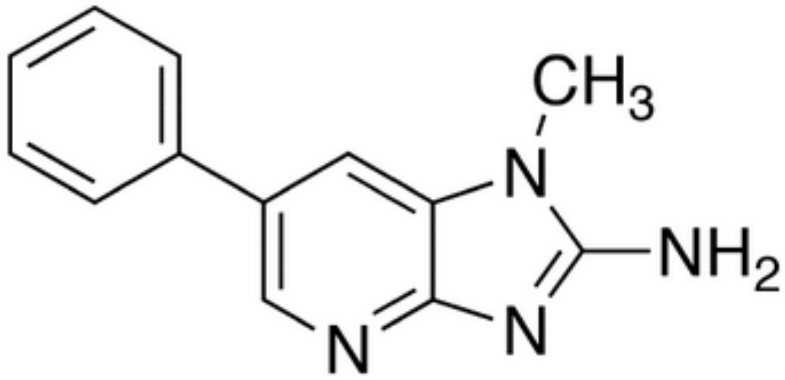


Figure 12. 2-Amino-1-methyl-6-phenylimidazo [4,5-b] pyridine.

Epilepsy and syringomyelia according to Nachtsheim (1934, 1949) quoted by Sandu (1986) are caused by autosomal recessive genes. Syringomyelia is a condition due to altered cerebrospinal fluid dynamics that results in fluid-containing cavities within the parenchyma of the spinal cord, as shown in figure 13 & 14 (Rusbridge et al 2006).

Ivetic et al (2002) showed through bioelectric intervention a high (100%) repression of epileptic activity in Chinchilla rabbits which received single dose 1 mL/kg intramuscular BW water fraction (mass concentrations 0.1 g/mL) of raw *Hypericum perforatum* ethanol extract.

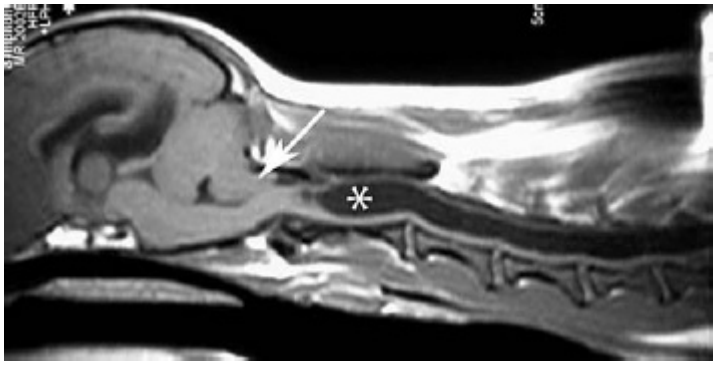


Figure 13. Midsagittal T1-weighted image of the brain and cervicalspinal cord of an affected dog. Syringomyelia (asterisk) secondaryto occipital hypoplasia in a 21-month female CKCS presented witha 3-month history of yelping and a tendency to scratch at the rightshoulder area. Cerebellar herniation through the foramen magnum (Rusbridge et al 2006).

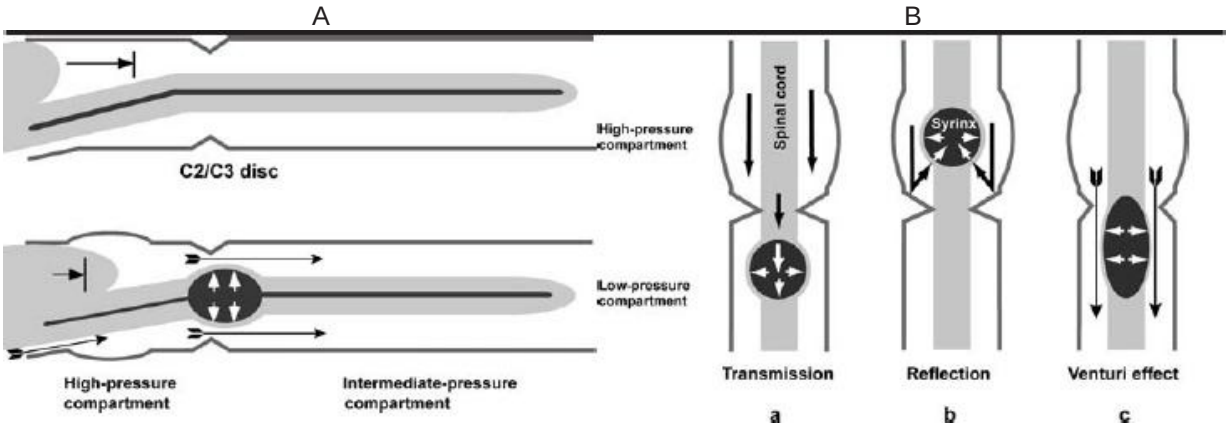


Figure 14. A) Syringomyelia secondary to Chiari malformation. In Chiari malformation, the increased cerebellar motion in the vertebral canal increases the systolic CSF pulse pressure distal tothe obstruction at the foramen magnum and a shock-like spinal pressure wave is created. The systolic CSF flow jet ventral in the foramen magnum decreases the hydrostatic CSF pressure, but this pressure difference is rapidly equalized in the cervical high-pressure compartment. At more caudally located physiologic impingementof the subarachnoid space, such as C2-C3 intervertebral disc level, the Venturi effect or the suction effect of the systolic CSF flow jet is unrestricted. Therefore, syringomyelia typically develops at and caudal to the C1 spinal segment. B) Posttraumatic syringomyelia. Subarachnoid adhesions cause a fixed type of obstruction that decreases the transmission of systolic CSF pulse pressure (ie, the pressure wave of CSF displaced during systole) distal to the obstruction. (a) Systolic CSF pulse pressure (represented by the black arrows) is transmitted through the spinal cord at the obstruction. The increase in spinal cord pressure and decrease in subarachnoid pressure results in distention of the spinal cord just below the obstruction (represented by white arrows). (b) Part of the systolic CSF pulse pressure simultaneously is reflected into the spinal cord at the obstruction, resulting in an increase in spinal-cord pressure and consequently distention of the spinal cord just above the obstruction. (c) At partial subarachnoid obstructions, the CSF flow jet (represented by arrows with tails) decreases the hydrostatic pressure in the CSF (Venturi effect), which in turn distends the spinal cord. Syringomyelia develops by collection of extracellular fluid in the distendedspinal cord (Rusbridge et al 2006).

Lysozyme deficiency in rabbits as mutation was first reported and described by Prieur et al (1974) as a condition inherited doe to autosomal recessive genes. The analyzed tissues (bone marrow, liver, lung, spleen and bone) of lysozyme-deficient rabbits had levels o lysozyme which was 1 % or less of the levels in the corresponding tissues of normal rabbits when measured with the lysoplate method (Table 3). At controls levels of lysozyme in the kidney and serum were 6 %, but the thymus of the lysozyme deficient rabbits had normal levels of the enzyme. Oil immersion light microscopy was performed in order to examine blood-bacterial smears, and the qualitative presence of lysozyme activity in individual leukocytes was determined by lysis of the surrounding micrococci (Figure 15). Clinically, was no morphologic lesions detected in any of the tissues of the lysozyme deficient rabbits (Figure 16).

Table 3

Lysozyme activity in tissues and fluids of normal and lysozyme-deficient rabbits (Prieur et al 1974)

Tissue	*Lysozyme activity**		
	Normal rabbits (N=6)	*Lysozyme-deficient rabbits (N=6)*	*Approximate percent of control*
Adrenal	93 ± 39	2.5 ± 1.4	3
Bone marrow	22144 ± 3268	4.9 ± 2.1	<1
Cerebellum	34 ± 8	0	<1
Cerebrum	4.9 ± 1.5	0	<1
Costochondral junction	1116 ± 264	0.6 ± 0.3	<1
Duodenum	428 ± 157	98 ± 36	23
Femur	506 ± 156	5.0 ± 2.5	1
Harderian gland	276 ± 34	1.1 ± 0.4	<1
Kidney cortex	13441 ± 637	806 ± 330	6
Kidney medulla	836 ± 117	53 ± 29	6
Lacrimal gland	793 ± 454	3.4 ± 1.0	<1
Liver	821 ± 127	0.3 ± 0.1	<1
Lung	6644 ± 1186	19 ± 9	<1
Muscle (skeletal)	24 ± 3	0.5 ± 0.3	2
Pancreas	2114 ± 218	14.6 ± 4.2	<1
Parotid gland	99 ± 15	2.6 ± 0.7	3
Scapula	509 ± 120	7.5 ± 1.8	1
Skin	402 ± 57	1.0 ± 0.2	<1
Spleen	23470 ± 4126	42 ± 20	<1
Stomach	125 ± 27	14 ± 4	11
Testes	322 ± 106	2.0 ± 1.0	<1
Thymus	4520 ± 490	4551 ± 662	100
Serum †	65 ± 11	4.2 ± 0.4	6
Tears †	≈100	≈10	10
Urine †	0	0	-

* - Expressed as mean ± SE hen egg white lysozyme equivalent µg/mg protein, † - Expressed as mean ± SE hen egg white lysozyme equivalent µg/mL.

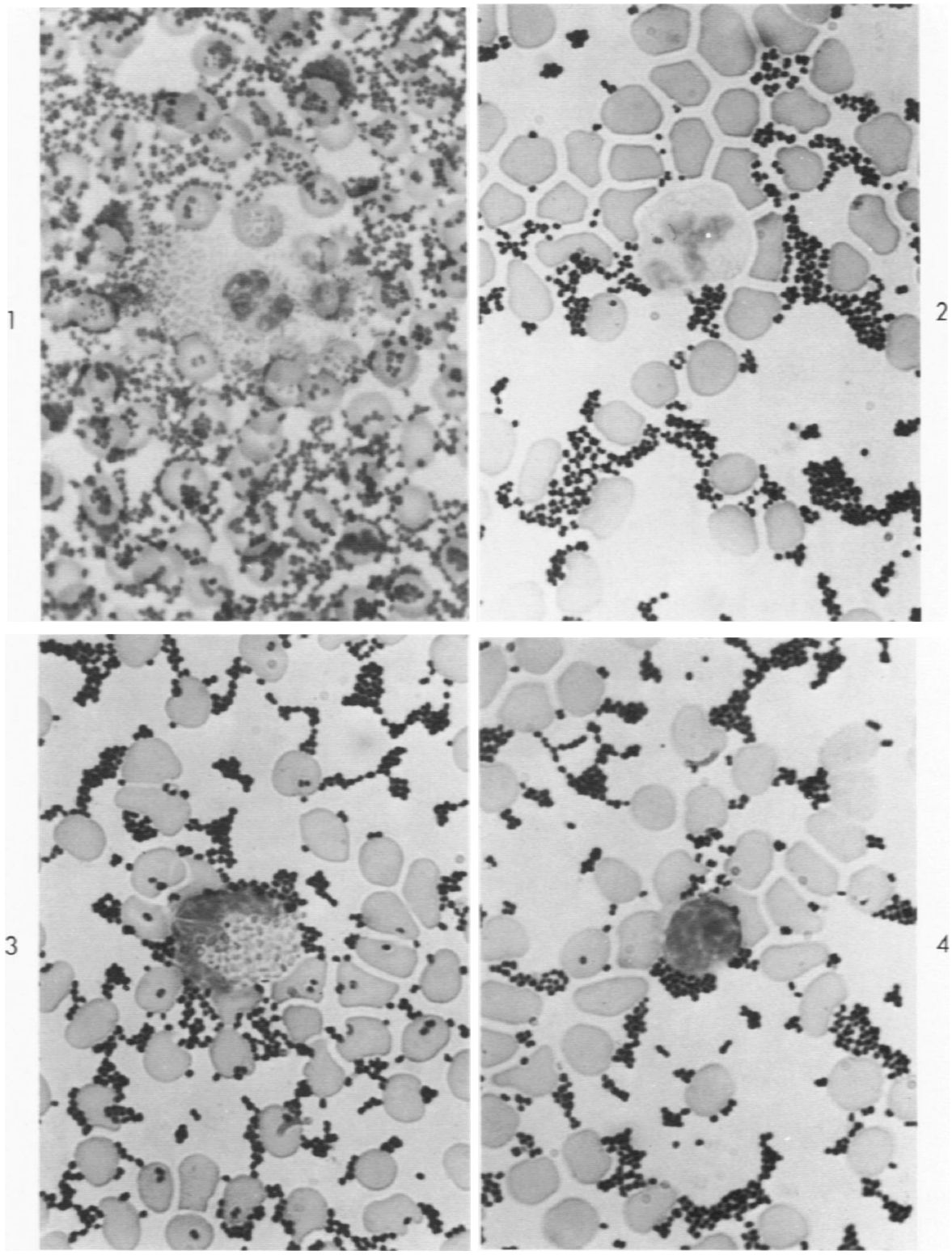


Figure 15. Histobacterial assay preparation of blood smear from: (1) a normal rabbit illustrating lysis of the micrococci around heterophil; (2) a lysozyme-deficient rabbit illustrating absence of lysis around a heterophil; (3) a normal rabbit demonstrating lack of lysis around an eosinophil; a normal rabbit illustrating lack of lysis around a lymphocyte (Wrights stain, x 1050) (Prieur et al 1974).

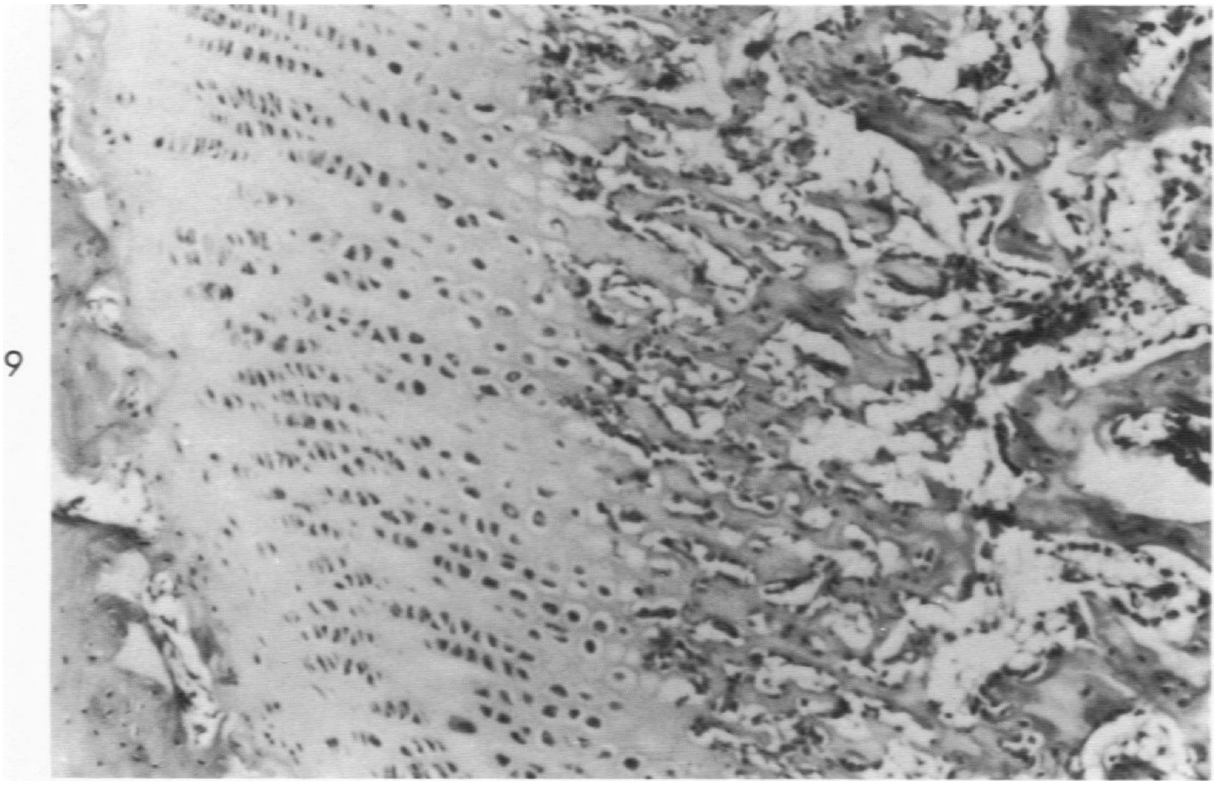


Figure 16. Cartilage plate from the distal femur of a lysozyme-deficient rabbit illustrating the absence of morphologic alterations (H&E, X 105) (Prieur et al 1974).

Hereditary osteopetrosis occurring as an expression of a simple recessive non sex-linked unit factor (*os/os*), affected individuals being homozygous at the incriminated locus. Heterozygous individuals for this condition are identified only by appropriate breeding tests. The condition can be identified at birth and is invariably fatal, generally at the 4th and 5th week of age. As conspicuous characteristic symptoms can be mentioned retardation and eventual cessation of growth with marked reduction in size (Pearce & Brown 1948). A more complex clinical picture of this condition was described by Pearce (1950), who performed macro and microscopic observations on the skeleton, which includes tooth abnormalities, dense homogeneous shadows of the skeleton, retardation of growth, progressive anemia, general deterioration, malnutrition and cahexia with a rapid course to fatal outcome in accordance with Pearce & Brown (1948) at 4 – 5 weeks of age.

In all cases all the bones were invariably and similarly affected. As an outstanding abnormalities can be mentioned the persistence of spongy bone and the presence of fibrous tissue together with abnormal medullar system exteriorized by the failure of development of a marrow cavity and medullary marrow. Also The amount of hemopoietic tissue was greatly reduced, which was present only in comparatively small foci. The essential defect concerned the mesenchymal cell as suggested the character of the lesions and their development as determined by examination of material at various stages of the disease. “The pathologic features observed generally resembled those of human osteopetrosis as did the manifestations of the disease during life” (Pearce 1950), so the presented studies can be used as animal models for human conditions.

Stark & Savarirayan (2009) described osteopetrosis so called "marble bone disease" as a group of rare, heritable disorders of the skeleton characterized by increased bone density on radiographs. They assign this condition both to autosomal recessive factors which determine autosomal recessive osteopetrosis (ARO) with an incidence of 1 in 250,000 births, and to autosomal dominant genes which cause autosomal dominant osteopetrosis (ADO) with an incidence of 1 in 20,000 births. The symptoms are characteristic for both cases. ARO is characterized by fractures, short stature, compressive neuropathies, hypocalcaemia with attendant tetanic seizures, and life-

threatening pancytopaenia, while whereas onset of primarily skeletal manifestations such as fractures and osteomyelitis in late childhood or adolescence is typical of ADO (Stark & Savarirayan 2009).

Osteopetrosis is caused by mutations in at least 10 genes accounting for 70% of all cases. These conditions can be inherited as autosomal recessive, dominant or X-linked traits with the most severe forms being autosomal recessive ADO. The severe forms of osteopetrosis at infantiles are associated with diminished life expectancy, in the most untreated situations *exitus* occurring in the first decade as a complication of bone marrow suppression. Life expectancy in the adult onset forms is normal (Stark & Savarirayan 2009).

Carolino et al (1998) presented three forms of osteopetrosis as follows: osteopetrosis tarda, osteopetrosis congenita and "marble bone" disease, with they inheritance patterns, pathophysiology, clinical features, age of onset, and prognosis presented in table 4. The only chance for survival of the affected individuals is the bone marrow transplant for the osteopetrosis congenita (Carolino et al 1998).

Table 4

Three variants of Osteopetrosis (Carolino et al 1998)

Variant	*Inheritance pattern*	*Pathophysiology*	*Clinical features*	*Age of onset*	*Prognosis*
Osteopetrosis tarda	Autosomal dominant	Abnormal osteoclastic bone resorption	No bone marrow failure; brittle bones; increased susceptibility to fractures but with normal healing; degenerative joint disease; 50% of patients are asymptomatic	Adulthood	Good
Osteopetrosis congenita	Autosomal recessive	Abnormal osteoclastic bone resorption	Severe bone marrow failure; pancytopenia; bleeding; infection; failure to thrive; growth retardation; proptosis; blindness; deafness; hydrocephalus	Infancy	Poor
Marble bone disease	Autosomal recessive	Abnormal osteoclastic bone resorption	No bone marrow failure; renal tubular acidosis; intracranial calcifications; sensorineural hearing loss; psychomotor retardation	Childhood	Poor

Femoral luxation (Luxatio femoris congenitalis) (Figure 17) it is one of the most commonly occurred anomaly in rabbit populations, with a frequency of 1 – 2 %. Szendrő et al (2010) describe autosomal recessive inheritance pattern. Manning et al (1994) completing that indeed the pattern of inheritance is consistent with an autosomal recessive gene (*lu*), with a few exceptions when appeared to behave as a partial dominant.

Animals show no clinical or functional disorder until the age of 2 to 4 months, when they usually began carrying on leg in a laterally extended position, supporting the weight on the other three legs. There also bilateral cases were reported. Do to

development of flattened and shallow acetabula the hip joints subluxation occurred as basic lesion (Manning et al 1994).

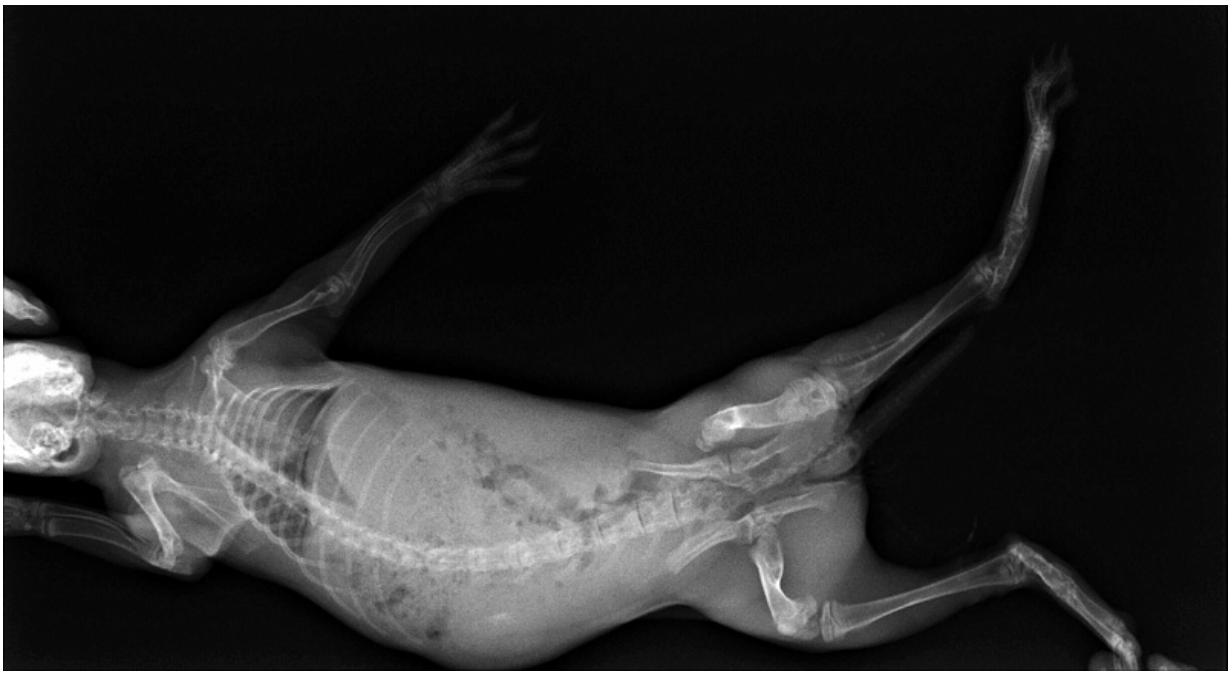


Figure 17. Top view showing joint laxity and luxation of the shoulder in rabbit (van Praag 2003-2014).

Dominant genetic disorders

Intrauterine lethality is caused by a dominant gene *Pg*, and was described by Pelgerov as stated Sandu (1986). In the same paper are also mentioned another two lethal genes *Z* and *zw*.

Chai & Degenhardt (1962) describe a series of anomalies observed on a stock do to inbreeding (brother x sister) of tenth and eleventh generations, which cause intrauterine mortality or post-partum death in a couple of days. These anomalies are namely: cephalodysplasia, cranioschisis, and dyostosis mandibularis. The authors consider that all these anomalies are caused by major genes but didn't elucidate the genetic determinism (Sandu 1986).

Cephalodysplasia consists in almost a total lack of skull. The skull is limited to a diminished cavity bordered by the rudiments of the occipital bone and the front jaw has teeth facing down (Bura & Bencsik 2000; Sandu 1986). Chai & Degenhardt (1962) report completely absent brain, abnormally shaped lower jaw with front teeth bending downward, greatly reduced occipital bones, very small posterior cavity of neurocranium and fairly normally developed tongue

Cranioschisis is a developmental birth defect involving the skull, where the cranium fails to close completely, without affecting the facial skeleton but missing the parietal bones, and a diminished the occipital region and frontal bones. Commonly a part of the brain is missing (Bura & Bencsik 2000; Sandu 1986).

Dyostosis mandibularis consist ia a such severe reduction of the jaw that the front teeth disappears (Bura & Bencsik 2000; Sandu 1986).

Pelger-Huët anomaly (PHA) is a benign, autosomal dominant haematological trait characterized by abnormal nuclear shape and chromatin organization in blood granulocytes (Hoffmann et al 2002).

Homozygosity for PHA was first detected and described in rabbits by Undritz (1943) and later in man and rabbits (Nachtsheim 1950), and in man (Oosterwijk et al 2003). PHA homozygosity is associated with skeletal abnormalities, increased intrauterine

lethality or peri-natal death, and severe chondrodystrophy with limb defects in rabbits (Oosterwijk et al 2003). Nachtsheim (1950) conclude that PHA homozygosity in rabbits leads to short-limbed chondrodysplasia. The mainly Homozygous PHA rabbits exhibit phenotypic similarities to Greenberg/HEM dysplasia (Oosterwijk et al 2003).

Hoffmann et al (2002) mapped the PHA locus to 1q41-q43, the region that contains the lamin B receptor gene (LBR; 600024) by genomewide linkage scan. Through positional cloning, mutations in the lamin B receptor gene (LBR) on 1q42 were found to cause PHA. Waterham et al (2003) stated that autosomal recessive HEM/Greenberg skeletal dysplasia is caused by 3β-hydroxysterol Δ^{14}-reductase deficiency due to mutations in the lamin B receptor gene.

Despite the haematological picture in humans and rabbits are the same, it was shown that the disorder is not necessarily lethal in humans and does not always lead to skeletal anomalies (Oosterwijk et al 2003).

Congenital absence of incisors in rabbits (Figure 18) is induced by an autosomal dominant gene (Bura & Bencsik 2000; Sandu 1986), with lethal effect (Bura & Bencsik 2000).

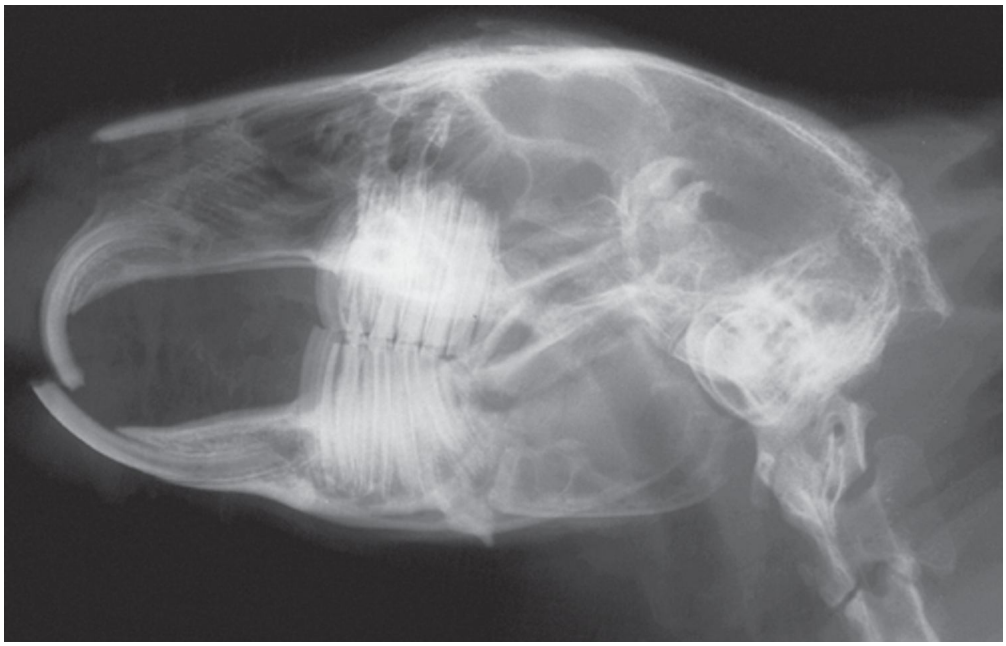


Figure 18. Rabbit with congenital absence of second upper incisors (peg-teeth) (Harcourt-Brown 2006).

Prognathism was studied in harlequin rabbit breed by Nachstheim (1936) cited by Sandu (1986) and Bura & Bencsik (2000). Non-proper alignment of incisors bring about they exaggerated growth, which if are not shorten by human intervention lead to animals death by starvation (Bura & Bencsik 2000; Sandu 1986). The author suspect a dominant gene but without a clear proof (Sandu 1986).

Coloboma is an ocular abnormality caused by a dominant gene, which was described by Nachtsheim (1934) cited by Sandu (1986) and Bura & Bencsik (2000). Nielsen & Carlton (1995) suspected this mutation do be due to vitamin E deficiency.

Coloboma takes the form of a hole in one of the structures of the eye, such as the iris, retina, choroid, or optic disc. The hole is present from birth and can be caused when a gap called the choroid fissure (Figure 19), present during early stages of prenatal development, fails to close up completely before birth (Kelberman et al 2014). The classical description in medical literature is key-hole shaped defect. A coloboma can occur in one eye (unilateral) or both eyes (bilateral). Most cases of coloboma affect only the iris. Individuals with coloboma may have no vision problems or may be blind, depending on severity. In humans Coloboma affects about 1 individual in every 10,000 births.

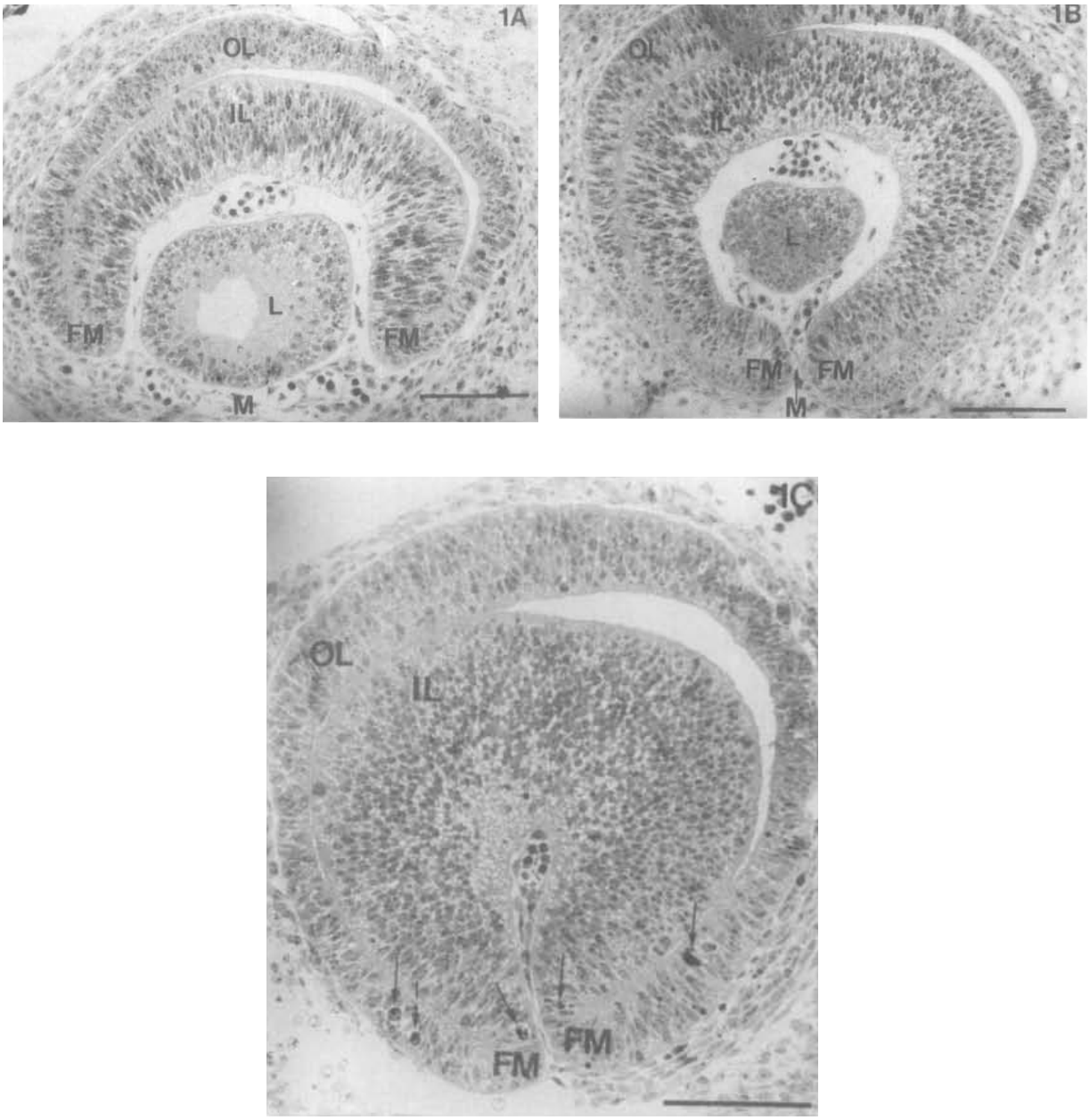


Figure 19. Coronal section of a microphtalmic mice fetus at gestational day 12, highlighting the choroid fissure. Thickening of the outer layer (OL) of optic cupin all sections occurs. L – lens, M – mesenchyme, IL – inner layer of optic cup. (A) Section at interior lenticular level shows that the fissure margins (FM) are far apart anteriorly. Invagination is not as well developed anteriorly as it is posteriorly. Bar = 100 µm. (B) Section at posterior lenticular level. Fissure margins (FM) are much closer, but mesenchyme is prominent in the optic fissure. Bar = 100 µm. (C) Section at the level of developing optic disc. Posteriorly, the fissure margins (FM) are becoming apposed. Note the pyknotic cells (arrows) in the fissure margins and elsewhere in the optic cup. Bar = 100 µm (Hero et al 1991).

Dachs in rabbits is an inherited skeletal abnormality (Figure 20) which is neither a severe nor early lethal, nor one which can be said to ensure a relatively complete and normal life span. In contrast, in other species (cattle) this mutation in homozygous state is lethal at a relatively early age in the most severely affected cases, but in Bassett hound and Dachshund the *Da* gene provide normal live. Studies conducted on

homozygous dachs rabbit population (*DaDa*) at 21 days after copulation highlighted a remarkable absence of the generalized reduction of both body size and skeletal measurements, particularly length of centra, observed at 22 days (Table 5; Figure 21 & 22). The *Da* gene effect starts his influence close to day 21 of gestation as indicate the skeletal development together with the relatively high incidence of ossified vertebral centra for this age (compared with the other genotypes) (Figure 23). A closely similar pattern regarding localized reduction effects was reported from 22-day fetuses and adults (Sawin et al 1958).

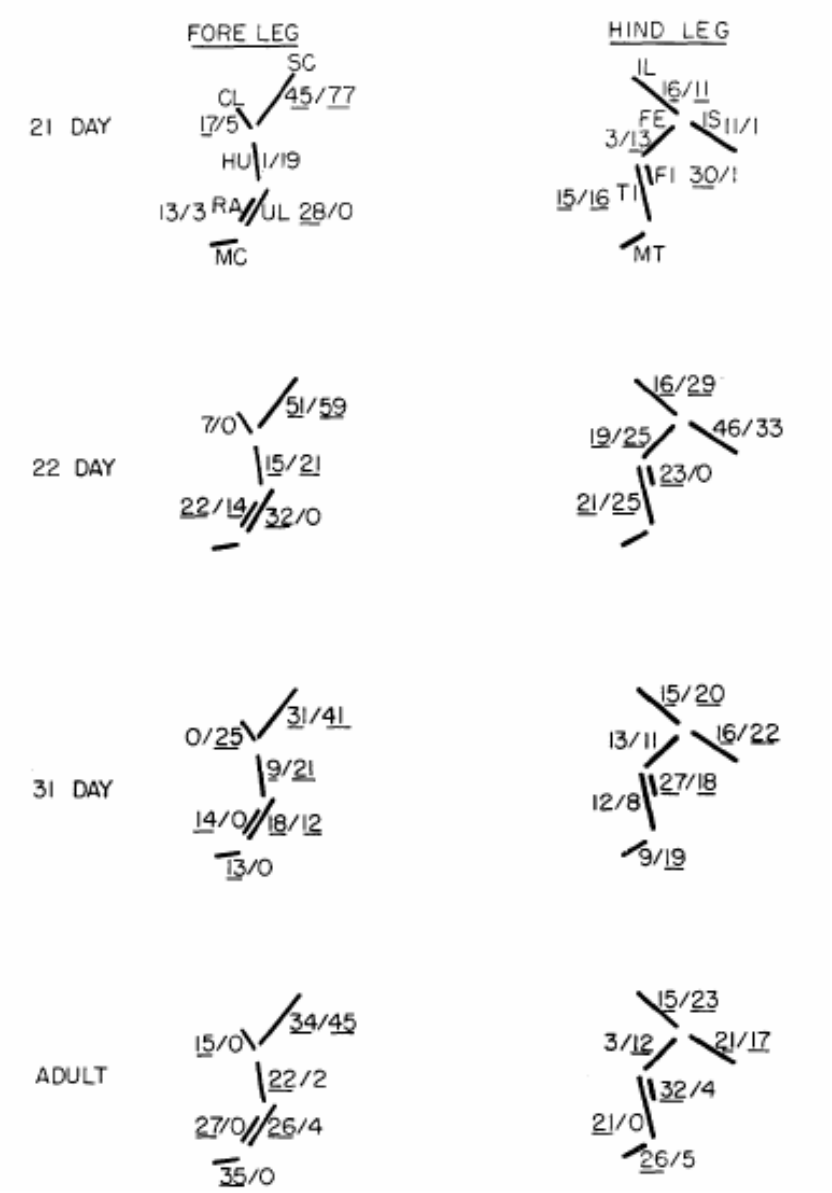


Figure 20. Percent reduction of the fore and hind limb bones affected by the dachs gene and their significance at the several ages. Length is given first, followed by width. Statistically significant reductions (P = <.01) are underlined. Bones are indicated by their first two letters. Metacarpals and metatarsals are not ossified in 21 and 22 day fetuses (Sawin et al 1958).

Table 5

Mean fetal weights (g), standard deviations (S.D.), variability (C.V.), and tests of variance in the three genotypes segregating from heterozygous parents (Dada) (Sawin et al 1958)

Specification	*DaDa*	*Dada*	*dada*
Number	9	34	16
Mean	5.02	5.16	5.31
S.D.	0.39	0.70	0.53
C.V. percent	7.77	13.57	9.98
	DaDa vs. *Dada*	*DaDa* vs. *dada*	*Dada* vs. d*ada*
SE	0.23	0.25	0.18
t	0.61	1.16	0.83
	F = n.s.		

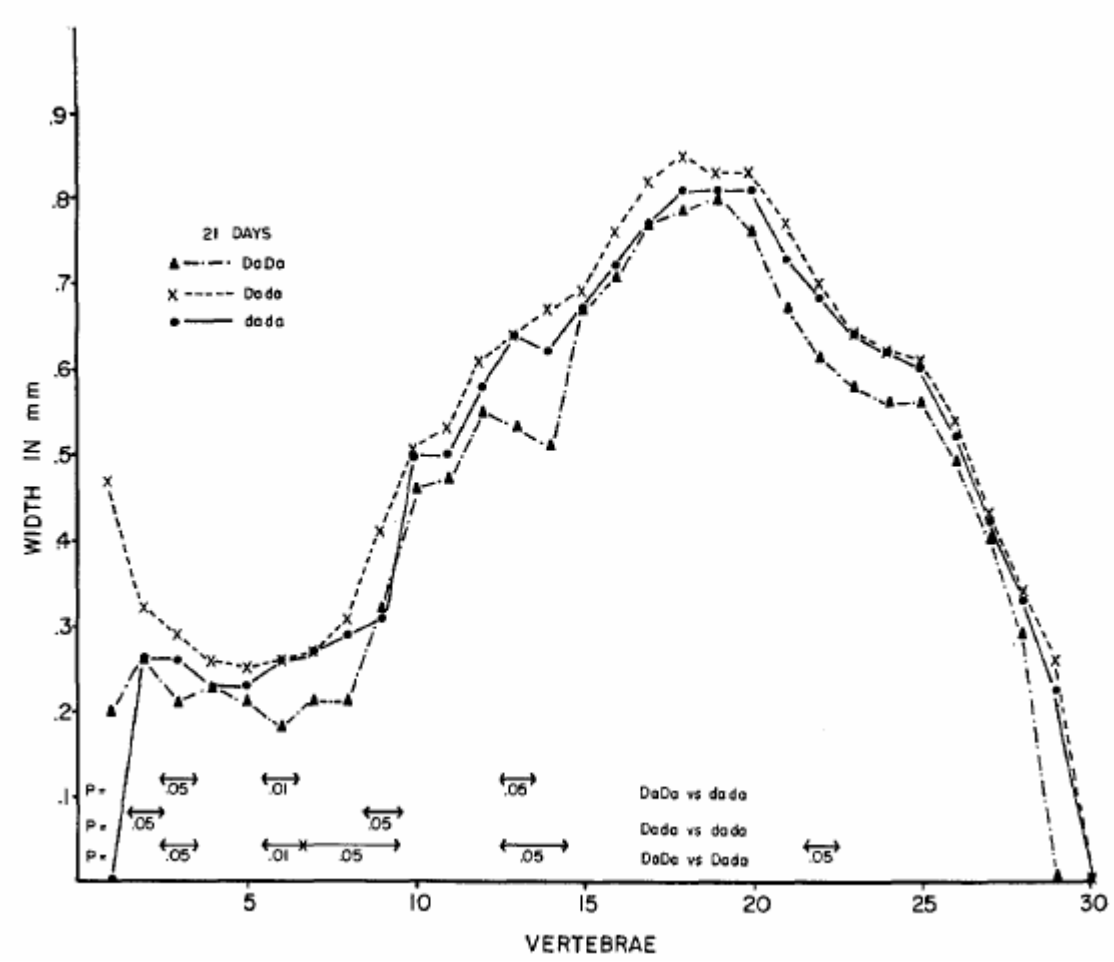


Figure 21. Width of ossification centers of the vertebral centra (Sawin et al 1958).

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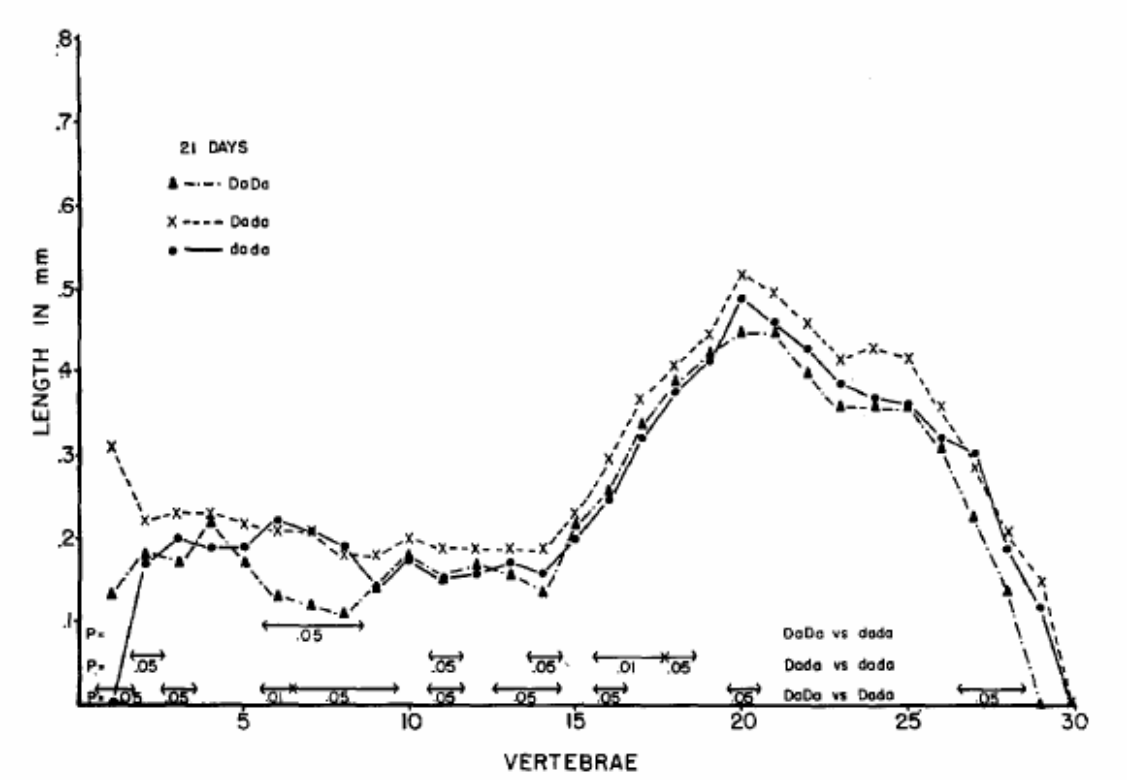

Figure 22. Length of ossification centers of the vertebral centra (Sawin et al 1958).

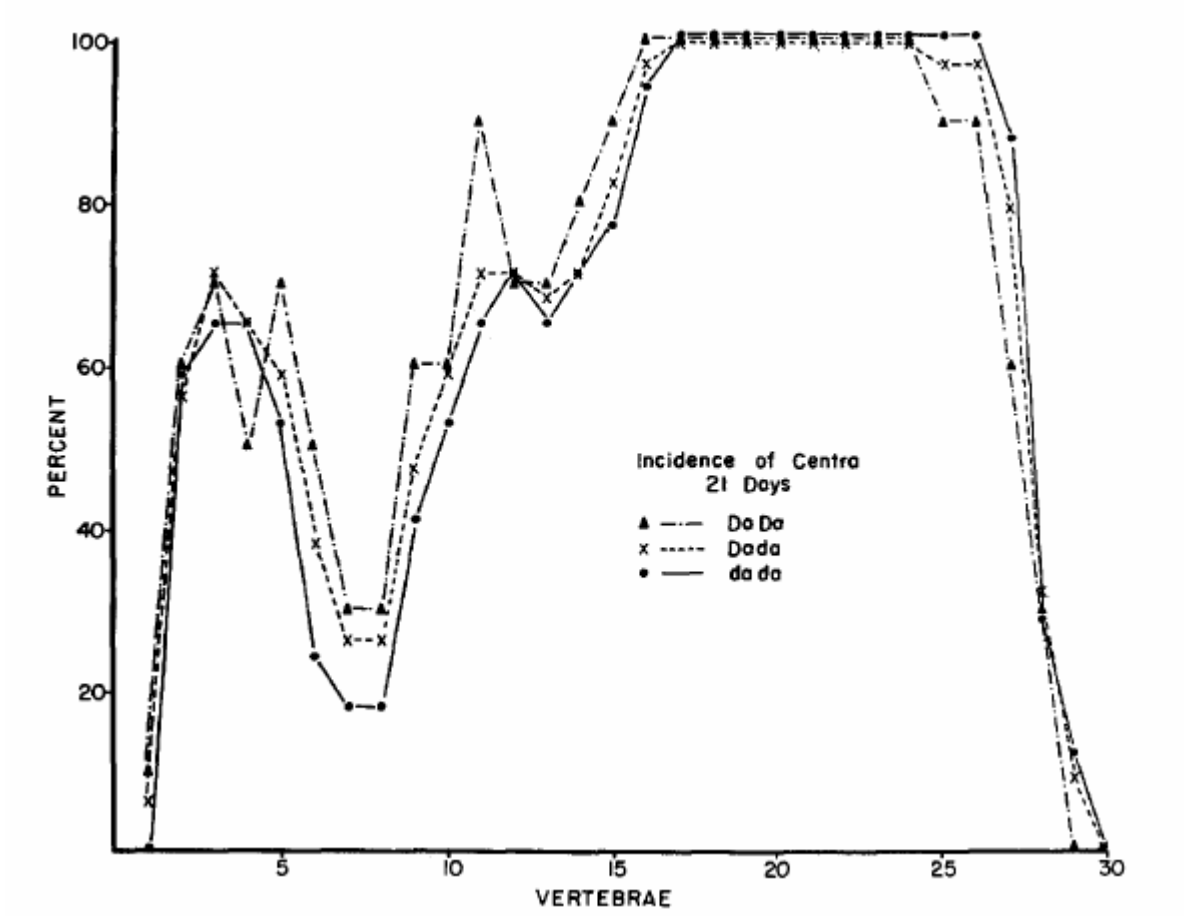

Figure 23. Incidence of centers of ossification of centra (Sawin et al 1958).

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Blood vascular mutants

Atropine esterases. It has been shown that some rabbits have a serum enzyme known as atropine esterase which is capable to hydrolyze tropine esters, among which also atropine. This advantage permit rabbits to digest belladonna leaves without any side effects. The atropine esterase serum presence is due to a semidominant gene *Est-2*^{F}, previously designated *As*. There are three known genotypes: *Est-2*^{F}/*Est-2*^{F} in case of high level of enzyme; *Est-2*^{F}/*Est-2*^{f} when there is a reduced level of enzyme; and *Est-2*^{f}/*Est-2*^{f} individuals with absence of enzyme. The enzyme first occurrence in the serum of about 1 month of age individuals can be observed only in homozygous or heterozygous state for the *Est-2*^{F} gene, and can be observed in a higher rate in females than in males. The atropine esterase serum enzyme is linked with the gene *E*, which is responsible for the extension of black pigment in the coat. There are no reports about harmful effects of an absence of serum atropine esterase on the health of rabbits, but the presence or absence of the serum gives significant differences in the response to atropine (Manning et al 1994).

Red cell esterases. Tree systems of esterase isozymes were identified in the blood of rabbits by starch gel electrophoresis. Each system rests three phenotypes (A, B, and AB) Which are determined by a pair of codominant autosomal alleles designated by the following gene symbols: *Es-1*^{A}, *Es-1*^{B}, *Es-2*^{A}, *Es-2*^{B}, and *Es-3*^{B}. Earlier were assumed that all three systems of esterases are found in the red blood cells, but recent studies revealed that *Es-2* locus controls isozymes derived from platelets. Also it has has been shown that *Es-1* and *Es-2* loci are closely linked. Only in the atropine esterase mutants there were no evidence of any detrimental health effects in rabbits with a particular genetic constitution regarded to the red cell esterases. On the contrary a benefic peculiarity has been reported in individuals with *Es-1*^{A}/*Es-1*^{B} genotype, which is more resistant to “mucoid enteritis” (Manning et al 1994).

Genetic disorders with unknown heredity

Hydrocephalus and palatine fissure (Figure 24) was reported by Phillips & Bohstedh (1937) as an anomaly which can occur in immature rabbits and in 1962 the disorder was widely described and published in 1966 by Robertson et al.

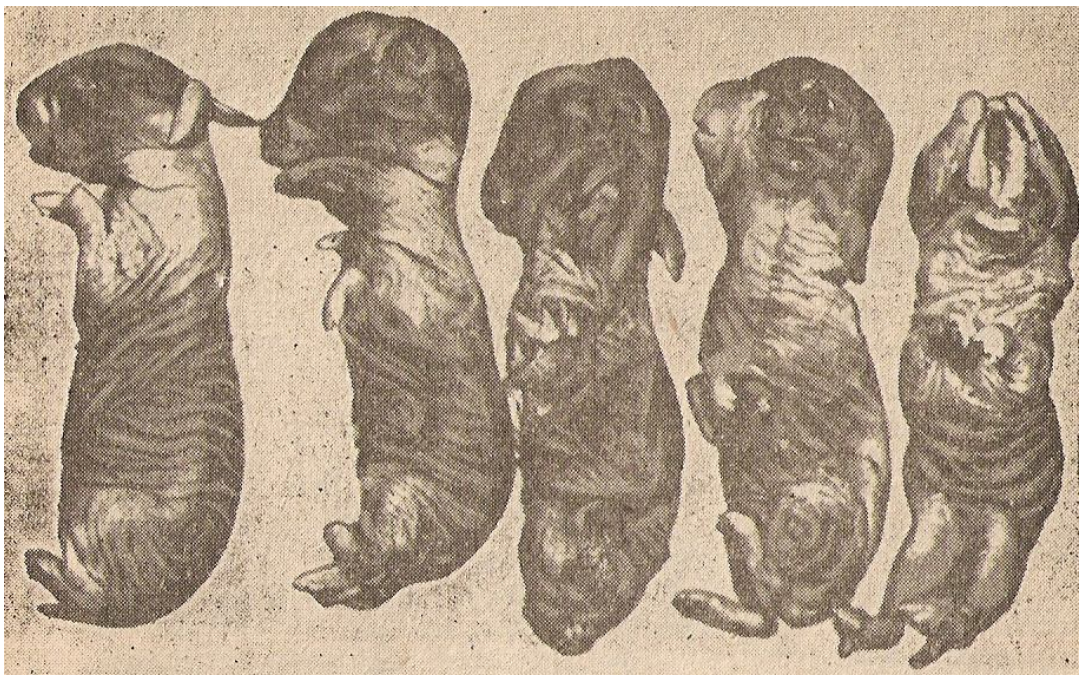


Figure 24. Hydrocephalus and palatine fissure. From the left to the right: normal, hydrocephalus, palatine fissure (Robertson et al 1966).

Some of the affected individuals show only one of the clinical signs, hydrocephalus or cleft palate. Same abnormalities were observed in a case of maternal A vitamin deficiency, but due to the fact that by inbreeding the frequency of anomalies increase suggests a genetic control (Bura & Bencsik 2000; Sandu 1986).

Oosterwijk et al (2003) reported congenital hydrocephaly in PHA homozygote Lbr -/- mice. Nesterov et al (1981) stated that in opinion of several researchers (without displaying references) hydrocephaly it is a hereditary anomaly caused by lethal recessive genes.

Bent ears different from the normal floppy-ears meet at the lop breeds is an abnormal wearing of ears in an angle of 60°. Asymmetric floppy-ears are also reported (Bura & Bencsik 2000; Sandu 1986). In case of alert, for a short time, the ears can be lifted up close to a normal "V" hold (Sandu 1986).

Figure 25 has shown a White of Debrecen rabbit with bent ears. The individual was obtained from inbreeding crosses in 2013, Cluj-Napoca, Romania. Half of the kits (50 %) from this nest also exhibit this anomaly.

Figure 25. White of Debrecen rabbit with bent ears (lopsided).

Chai & Clark (1967) stated that the anomaly is also controlled genetically, proving with normal x normal crosses which gives more healthy individuals whereas affected x affected crosses resulted more droopy-eared rabbits. This affection can be attributed to several gene pairs some of which are dominant, seeing that a normal x affected cross generated more affected individuals. Such a different expressiveness suggests the combination of these genes (Bura & Bencsik 2000; Sandu 1986).

Abnormal mouth closing described by Grüneberg (1947) cited by Sandu (1986) caused by overgrowth teeth, wolf teeth, walrus teeth or irregular growth (Figure 26 & 27). Weisbroth & Ehrman (1967) show changes in dental formula but doesn't elucidate the genetic control. Later Bura & Bencsik (2000) report that there is still not explained the genetic determinism for this kind of anomalies.

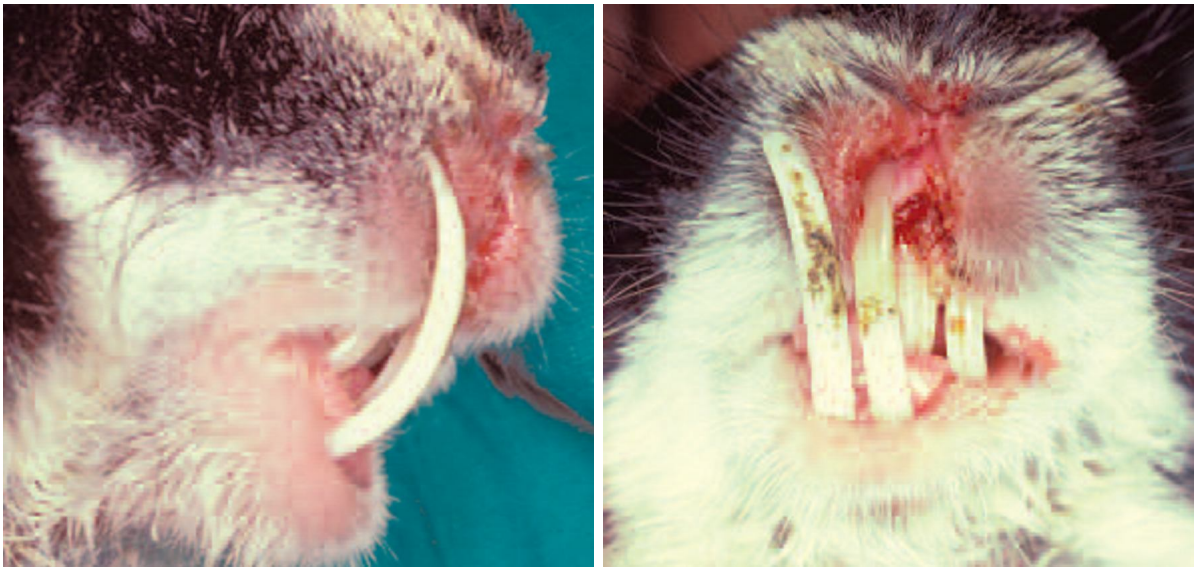
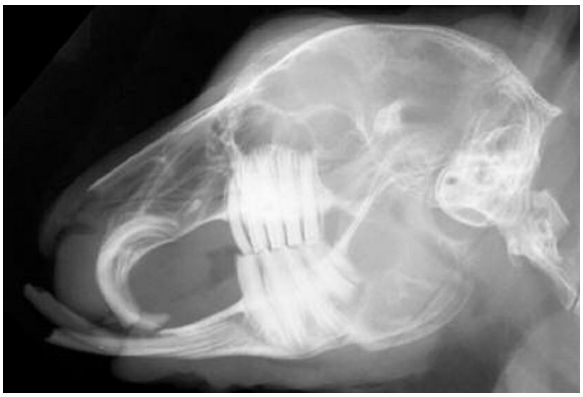
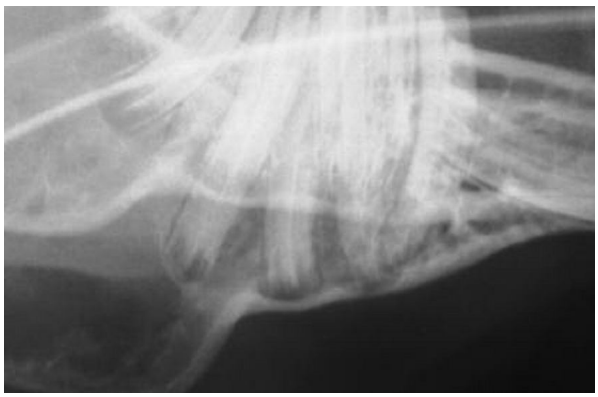


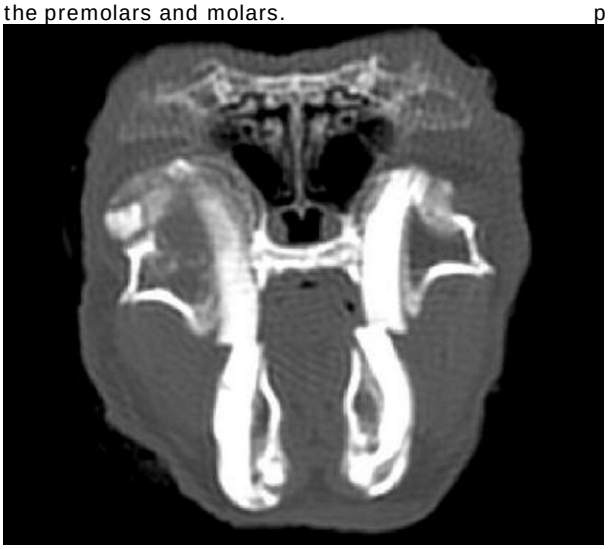
Figure 26. A rabbit with severe incisor malocclusion. Note the soft tissue trauma to the upper lips caused by the mandibular incisors (Verstraete & Osofsky 2005).



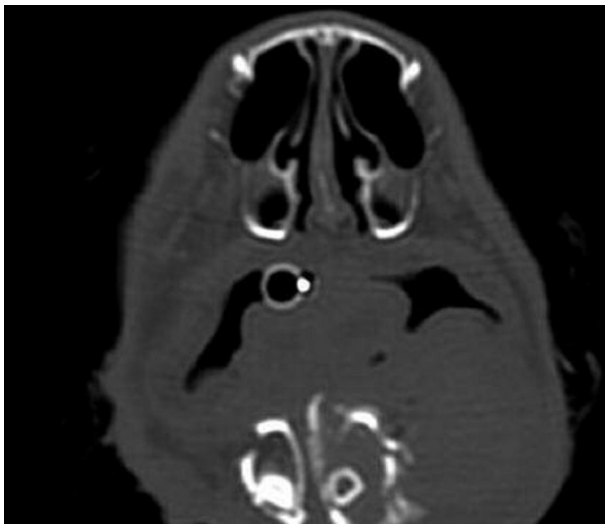
Incisor malocclusion with mild coronal elongation of the premolars and molars.



Apical elongation and near perforation of the mandibular premolars and molars.



Periapical changes, apical bone penetration, and abnormal premolar–molar occlusion.



Osteomyelitis of the mandible and associated soft tissue abscessation.

Figure 27. Incisor–premolar–molar malocclusion with periodontal and endodontic disease (radiologic and CT findings) (Verstraete & Osofsky 2005).

Twisted maxilla can be observed since birth by abnormal closure of the mouth. Later this anomalie lead to an overgrowth of incisors which need to be cut periodically (Chai & Degenhardt 1962).

We observed the same situation on a purchased mature doe, so we cannot assume from what kind of breeding she was obtained (inbreeding or not), and after the adjustment of the incisors in a month she cannot intake forages, so we was obligated to cut the incisors at normal in every 3 weeks for a correct prehension. We also noticed drooling in the moment when she couldn't close its mouth appropriately, so this kind of manifestation alerts for dental disorder.

Researches conducted by Szendrő & Holdas (1985) showed that individuals affected by overgrowing incisors have the same growth rate as the unaffected animals till week 10 of age. After the age of 10 weeks function by the severity of affection they growth rate may decrease. So this abnormality seems to affect more the breeding stock then the fattening rabbits, which are capitalized by the age of 10 - 11 weeks.

Distal forelimb curvature was described by Pearce (1960) and Chai & Degenhardt (1962). The anomaly became obvious at 2 weeks of age (Pearce 1960; Chai & Degenhardt 1962), developed rapidly, and reached its final and permanent stage at 2 to 3 months of age Pearce (1960) and reduces longevity to 12 - 14 months (Chai & Degenhardt 1962).

Despite of Bura & Bencsik (2000) and Sandu (1986) who include this anomaly into genetic disorders with unknown heredity category, Pearce (1960) stated that the mode of inheritance is based of a single recessive unit factor noted *fc*.

Bone formation or remodeling errors is manifested by skeletal dysplasias which are a group of defects associated with short limbs, abnormal bone shape and/or increased bone fragility. This kind of abnormalities is linked to a complex group generically named skeletal dysplasias. Despite the formulation of an extensive classification system for human skeletal displasia a complete system for the corresponding animal conditions has not been reported. A brief overview of the recognized conditions in rabbits is summarized in table 6 (Pulker et al 2011).

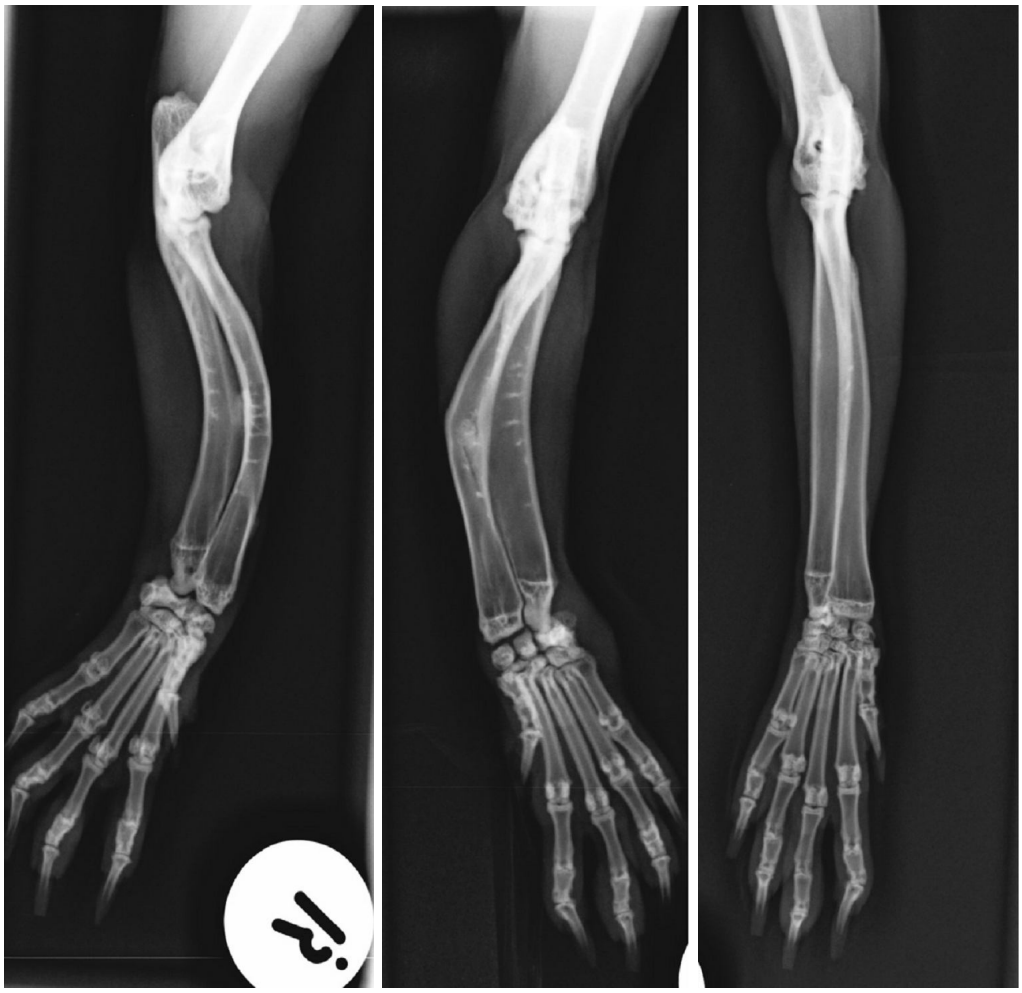
Table 6

Recognized gene mutations resulting in skeletal dysplasia in rabbits (Pulker et al 2011)

	Alleles	*Description*
Achondroplasia	ac/ac	Disproportionate dwarf Lethal mutation
Chondrodystrophy	cd/cd	Disproportionate dwarf Lethal mutation
Dachs	Da/Da or Da/da	Viable chondrodystrophic dwarf Non-lethal mutation
Distal foreleg curvature	fc/fc	Foreleg deformities Non-lethal autosomal recessive mutation
Dwarf	Dw/Dw	Pituitary/proportionate dwarfism Semi dominant lethal mutation
Dwarf	nan/nan	Proportionate dwarf-nansomia My be the same as Dw
Dwarf	zw/zw	Proportionate dwarf (zwergwuchs) My be the same as Dw
Pelger	Pg/Pg	Chondrodystrophic dwarf, leukocytes affected Semi dominant mutation

Radiographic findings performed by Pulker et al (2011) on 3 months old 18 New Zealand White female rabbits highlighted varying degrees of lateral deviation of the forelimbs from the mid ulna–radius diaphyses distally, with the manus directed laterally away from the body. Mild cranial (143 – 160°) and moderate medial (131 – 148°) bowing of the

mid-radial and, to a similar extent, mid-ulnar diaphyses was noted in all affected animals with no indication of metabolic bone disease (Figure 28).



A B C

Figure 28. Distal foreleg curvature in rabbits. A: Craniocaudal view of the right antebrachium and manus demonstrating the forelimb deviation and rotation. B: Craniocaudal view of the left antebrachium and manus demonstrating the forelimb deviation and rotation. C: Craniocaudal view of right antebrachium and manus (unaffected animal) (Pulker et al 2011).

Paralysis of the hindquarter. The same authors (Chai & Degenhardt 1962) report the paralysis of the hindquarters at the age of 3 weeks and leads to death at age of 2 - 4 months.

Lethal dwarfism was reported by Greene et al (1934) cited by Sandu (1986) where the presumed incomplete recessive mutant homozygote newborns had the half weight of heterozygote individuals and third of the normal. Beside dwarfism the authors also reported osteomalacia and ossification deficiency, which suggests hormonal imbalances.

Acromegaly was observed in an inbred population of Dutch Papillion rabbits, where the anomaly occurred in the first 2 weeks post partum via edematous hypertrophy and skin hyper congestion reaching sometimes to the hardened leather cute associated with abnormal hair growth. Lethality is installed overwhelmingly after a few days of disease setting. Study results regarding genetic determinacy are contradictory as shown some crosses which even seem to suggest existence of a recessive gene, at least a recesivity, penetrance and incomplete expression adding clause is required (Hu & Greene 1935 quoted by Sandu 1986).

Double biliary vesicle has been reported by van Praag (2003 - 2014) in a parasitological work without any mention about the nature of this inherited anomaly (Figure 29).

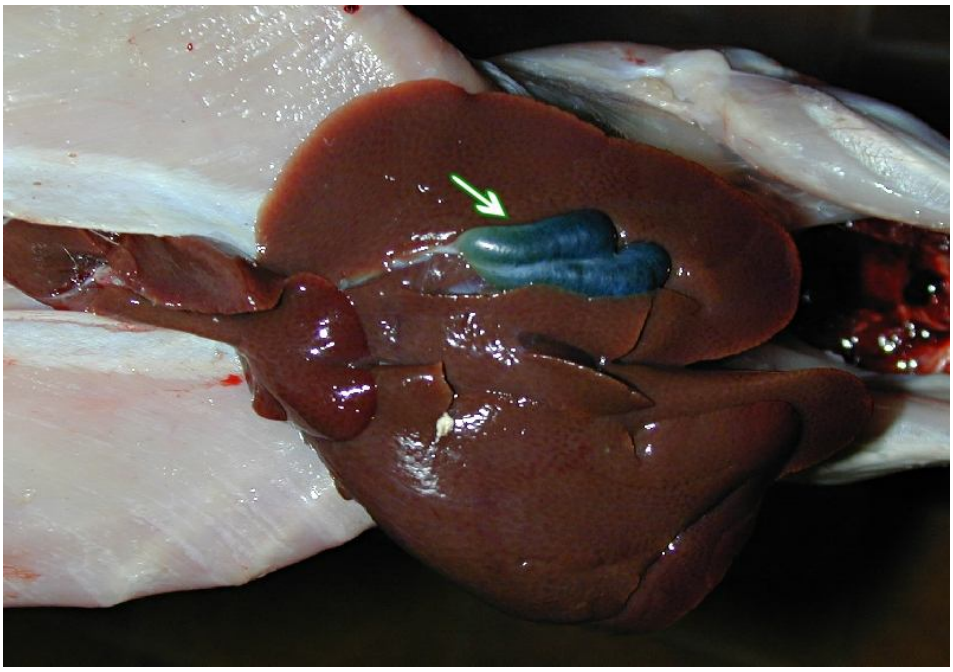


Figure 29. Healthy rabbit liver with rare congenital anomaly, double biliary vesicle (van Praag 2003 - 2014).

Compulsive self-mutilation. In the '90s Iglauer et al (1995) reported an increasing tendency of extensive automutilation in a rabbit breeding colony of Checkered crosses (Figure 30). The traumatized body parts were the digits and pads of the front feet. There were no other evident behavioral abnormalities or signs of disease. Self-mutilation was observed in several conditions and situations, in breeding and experimental animals, in rabbits kept singly in cages and in those housed in groups on the ground, in rabbits kept in different buildings and under the care of different staff members. This behavioral abnormality of Checkered crosses has also been observed in animals after they were placed into other environments (institutions or private homes). Parasitological, mycological, histological, clinical or haematological examinations showed no evidence of an agent which may be responsible for the occurrence of self-injury. Statistically the frequency of this abnormality was reflected by 12 to 16 animals affected yearly in a colony varying in size between 130 and 230 individuals.

Relapses, following complete healing, occurred up to 3 times per year, on either the same or the opposite front foot. Haloperidol (dopamine antagonist) administration has been shown to be the solution for the interruption of automutilations in the last 21 occurred cases. Similar signs of automutilation were never seen in animals of another breeding line kept in the same building and under the same conditions nor in animals brought in from other breeding colonies.

Because this Checkered crosses breeding colony was 15 years old, a relatively high coefficient of inbreeding can be presupposed. A genetic predisposition for the behavioral anomaly described appears very likely.

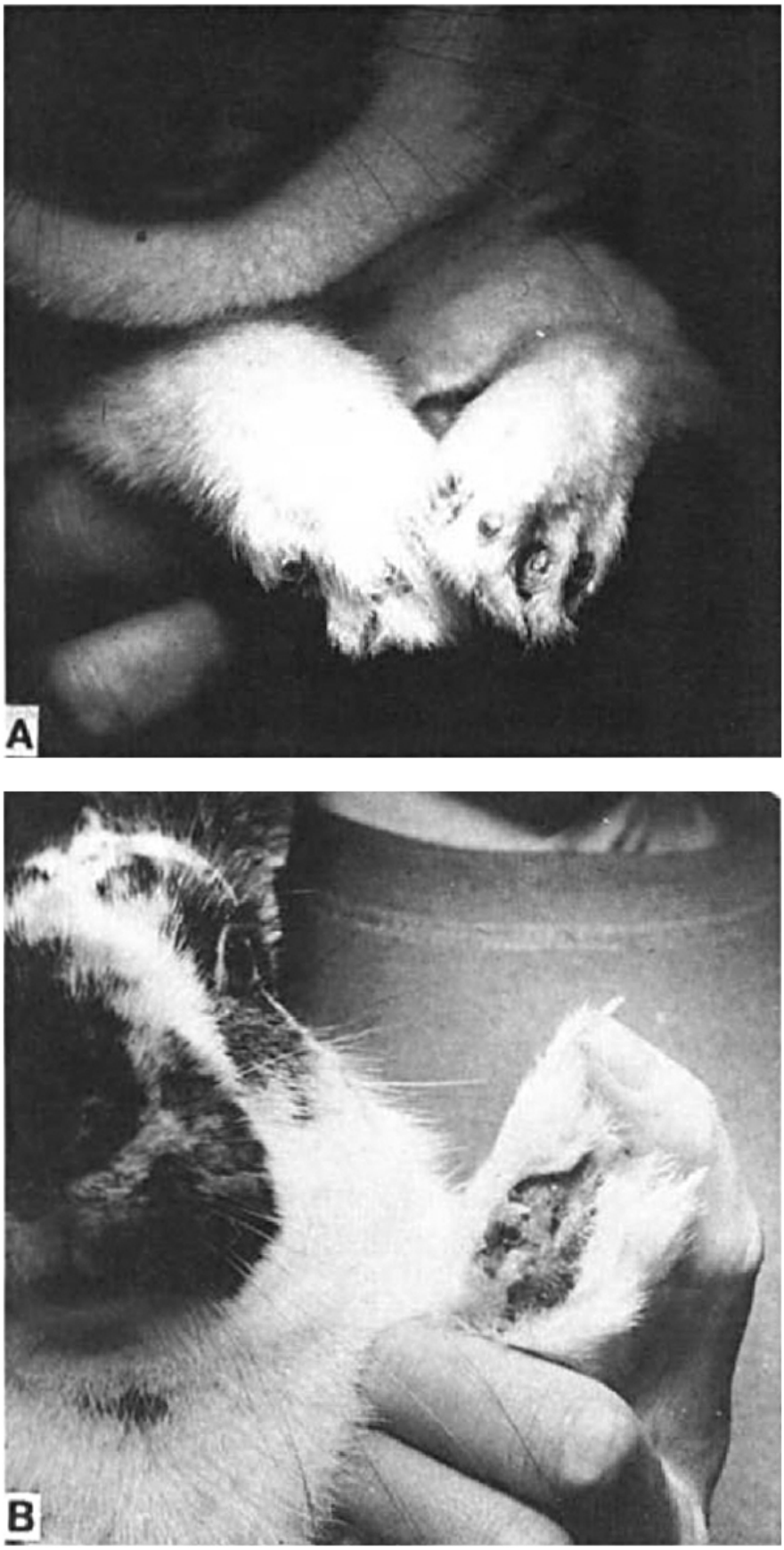


Figure 30. Lesions of digits and pads due to self-mutilation with increasing degrees of severity (Iglauer et al 1995).

In table 7 are presented a series of inherited disorders in rabbits classified by the affected features or organs.

Table 7

The most frequently inherited disorders occurred in rabbits (Fox 1974 cited by Szendrő & Holdas 1985)

Anomalie	*Gene encoding*	*Type of mutation*	*Description*
Mutations affecting behavior			
Epilepsy	ep	recessive	Seizures and stroke
Acrobat	ak	recessive	Often moving only on the forehand
Mutations affecting the function of the muscle nerve			
Ataxia	ax	recessive	Lack of voluntary coordination of muscle movements
Tremor paralysis	pt	recessive	Shake paralysis similar to human Parkinson. X sex chromosome linked anomalie. ♀: pt/pt, ♂: pt/-
Tremor	tr	recessive	Epileptic seizures, continuous tremor
Syringomyelia	sy	recessive	Cyst or cavity forms within the spinal cord, assymetric spasm paralysis
Hydrocephalia	hy	recessive	Hydrocephalus, spongios skull top, fluid collection in brain ventricle
Lethal muscle atrophy	mc	recessive	Muscular dystrophy
Bone malformations			
Achondroplasia	ac	recessive	Intra uterine development of symetric dwarfism do to cartilage formation disorder
Brachydactylia	br	recessive	Shortening or leack of claws, toes or limbs
Spina bifida	sb	recessive	Incomplete closing of the embryonic neural tube, lack of the vertebral arches closing
Chondrodystrophia	dc	recessive	Assymetric dwarfism do to ossification disorder
Congenitalis luxatio	lu	recessive	Hip dislocation do to a significantly smaller femoral head

Anomalie	*Gene encoding*	*Type of mutation*	*Description*
Dachshund anomaly	Da	dominant	Viable dwarfism do to cartilage formation disorder
Dwarfism	Dw	dominant	Symmetric dwarfism
Dwarfism	nan	recessive	Symmetric dwarfism
Hypoplasia pelvis	hyp	recessive	Paralysis do to backward hip
Osteopetrosis	os	recessive	Fragile bones and teeth do to abnormal development
Eye disorders			
Buphtalmia or hydrophtalmia	bu	recessive	Intraocular fluid luxuriance
Cataract	cat-1	recessive	Cataracts
Cataract	Cat-2	dominant	Cataracts
Cyclopia	cy	recessive	One eye
Oral cavity disorders			
Missing secondary incisors	I^2	dominant	Lack of secondary incisors
Over no. of incisors	i sup	recessive	Over no. incisors
Mandibular prognathismus or Brachygnathia superior	mp	recessive	Incisors overgrowth do to the incorrect mouth close because jaws protrudes
Renal agenesis	na	recessive	One or both kidney are missing
Renal cyst	rc	recessive	Cysts in the adrenal cortex
Hypogonadia	hg	recessive	Sterility do to hipofunction of gonads: testis 225 mg instead of 1700 mg, ovaries 12 mg instead of 150 mg
Pelage disorders			
Rex - 1	r_1	recessive	Short hair and mustache
Rex - 2	r_2	recessive	Short hair and mustache
Rex - 3	r_3	recessive	Short hair and mustache
Waved hair	wa	recessive	Waved hair, occurring only at rex
Harsh hair	Wh	dominant	Down hair lack
Hairlessness	f	recessive	Hairless
Denudation	n	recessive	Naked
Matted	wu	recessive	Matted, messed hair

Chai (1970, 1969) reports some disorders do to inbreeding as fusion of 3rd, 4th, and 6th vertebrae of stern, and fusion of the last rib pear, and vertebral spine defects respectively.

Conclusions. Most of the inherited disorders in rabbits are due to recessive genes which are carefully tracked by breeders following their own lines to remove unwanted defects.

However, some breeds, which are bred for pets by non-fancier breeders, are not carefully screened for health problems, and may still develop these genetic defects.

It is a fact that nowadays genetic disorders have a descendent evolution due to the elimination of individuals which bear such inherited abnormalities. Scrapping breeding stock is easier and less economically burden in a case of dominant disorders, where just the affected individuals are removed, toward recessive disorders where the whole family is need to be eliminated from further breeding.

The most complicated forms of inheritance are shown by the disease which is represented by the inheritance of occasional tendency or susceptibility, where a very significant role is attributed to the environment, particularly to the possibility of contamination. In rabbit species the most of occurred genetic disorders appear according to Mendelian laws, namely the occurrence is based on one or more gene absence or presence (Holdas 2000; Szendrő & Holdas 1985).

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