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From recognition to acknowledgement
of genetic individuality

Prof.dr J.E. Kammenga

Inaugural lecture upon taking up the position of Personal Professor of
Functional genetics at the laboratory of Nematology
at Wageningen University & Research on 8 December 2016



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Introduction

Esteemed Rector Magnificus, colleagues, family, friends and students,

Today I will outline and explain the problem of understanding genetic individuality and hidden genetic variation as part of my vision on research. Next to this I will give my view on the attitude of today's students with respect to their study and the need to foster new relationships with immigrant pupils.

Characteristics of individuals are determined by genes, the environment and the interaction between genes and the environment. Already early at school have we learned that many traits are determined by single genes, for instance, the eye colour in fruit flies and the colour of peas. Dominant and recessive forms determine the effect of these genes. More recent research has shown that the overall appearance and position of twigs is determined by a single gene in sweet pepper [1]. Such traits are called monogenic or Mendelian traits, named after Gregor Mendel (1822-1884), the founding father of genetic research. Contemporary genetics still involves intensive research based on his ideas and experiments, assuming that many traits are considered monogenic. A very recent example of a single gene study was published in the top journal Nature this year. It involved the classic case of genetic adaptation of the peppered moth to a polluted and black environment caused by industrial emission in the United Kingdom. A phenomenon called melanism where black coloured phenotypes are favoured over the light coloured wild type (Figure 1). This adaptation was found to be determined by a mutation in a single gene caused by a so-called transposable element (piece of DNA that is inserted into the gene) that landed in the cortex gene[2], a cell cycle regulator[3].

Monogenic traits have also been studied extensively in humans, in particular monogenic rare diseases like cystic fibrosis (disease of the lung)[4], the Miller syndrome (genetic disorder of facial expression, arms and legs)[5] and specific cases of mitochondrial diseases caused by mutation in polymerase- γ [6]. Mutation in polymerase- γ leads to clumps of diseased mitochondria (the machines where energy is produced) in muscle tissue. Overall, our knowledge about single gene mutations and their effect on a range of disease traits has tremendously increased over the past couple of decades. The bigger picture is well known. Currently, more than 5000 genes have been identified where mutations in these genes give rise to approx. 4500 types of disease and disorders (<https://www.genetests.org/>).

But humans are notoriously difficult to study for ethical and technical reasons. Experimentally induced mutant screens in model organisms have been powerful for identifying genes and mutations that underlie phenotypes of interest, including complex human diseases. These screens involve the induction of DNA mutations called mutagenesis by exposing model organisms like flies, mice and worms in the laboratory to mutagens or rely on insertional mutagenesis such as transposable elements. Subsequently, mutated individuals are isolated by selective breeding for the phenotypes of interest, after which the gene is mapped and characterized. I now focus a bit more on the nematode *Caenorhabditis elegans* that was introduced (actually, it was taken from a compost heap) as a genetic model in the early seventies by Sydney Brenner who was interested in the developmental biology of neurons [7]. *C. elegans* is 2 mm long and has a rapid life cycle of 2.5 days. Because the worm was transparent they studied how cells develop into a worm. Together with Jonathan Sulston and Rob Horvitz did he map out the entire cell lineage (egg to worm)



Figure 1. The black variant of the moth *Biston betularia* is a genetic adaptation to industrial pollution due to a mutation in a single gene. <https://commons.wikimedia.org/w/index.php?curid=868091>

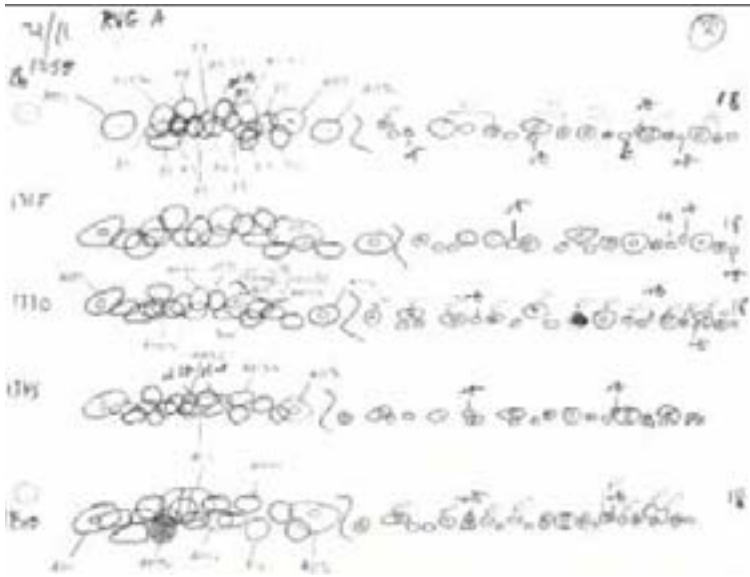


Figure 2. Dividing cells drawn by J. Sulston. <http://www2.mrc-lmb.cam.ac.uk/achievements/lmb-nobel-prizes/2002-sydney-brenner-bob-horvitz-john-sulston/>

of *C. elegans*. Figure 2 shows the drawings they made. During their endeavors they discovered the phenomenon of programmed cell death or cell suicide (Figure 2). This facilitated research into understanding cancer formation in humans. As John Sulston explained about the unity of life: "...nature is not reinventing but is reusing whole mechanisms. From worms to humans.." For their discoveries and their work they received the Nobel prize in 2002. Their research was driven by their pursuit of understanding neuronal development in a worm. Just for the sake of it because the worm was so transparent.

At the time Sidney Brenner saw profound research potential in the nematode. He also was not distracted by questions about relevance to society and potential application. Or questions like: why would you do this? Today, it would be virtually impossible to obtain grants for his type of research. Here I adopt the contrarian view by taking away the negative flavour that we witness today in the research funding landscape. There should be more room for building Ivory towers. Yes, perhaps it should be more possible to have a lab in the ivory tower again which is designated as an environment of intellectual pursuit disconnected from the practical concerns of everyday life.

Genetic individuality

Since the discoveries by Brenner and colleagues all research in *C. elegans* has been carried out in a single genetic background. Thousands of mutants have been generated to study genetic pathways, and to elucidate complex disease pathways underlying cancer or Alzheimer's disease. Because many genes and their functions are conserved across other species, the results generated from these single backgrounds are often interpreted in a general way as being relevant for humans. And the same applies to other model organisms.

Evidence is growing that we not fully understand the effect of mutations and that we are caught by surprise about the complexity of individual plants and animals. I will address the importance of genetic individuality regarding the effect of mutations and provide insight into understanding this individual complexity. This will be my first message. Here, I define genetic individuality as the total of all other genes that possibly interact with the mutation and that give rise to phenotypic variation. So, each individual has its own unique genetic background.

Before I continue, I would like to walk you through the next figure (Figure 3). Figure 3A looks like a soccer field. And that is what it is. You see the formation 4-5-1. Now I do not want to engage into an endless discussion with you about the formation, but what you need to remember is that the striker, the goal keeper and the wing player are considered as "key" players. The other members of the team play a different, background, role but may very well determine the success of the whole team. If you change these background team members, you will change the characteristic of the team. Of course this depends on the team itself. In Figure 3B, you see a figure not resembling a football field. And that is also not what it is. It is a cell, and you can see different genes. Now I do not want to engage into an endless discussion with you about the type of cell, but what you need to remember is that the red genes are considered as "key" players. The other genes play a different, background, role but may very well determine the success of the cellular functions. If you change these background genes, you will change the characteristic of cell and the individual. Of course this depends on the individual.

Mutations and genetic individuality

Genetic individuality plays an important role in the effect of mutations affecting disease phenotypes. In case of cystic fibrosis (CF) we know that up to half of all CF patients which carry the homozygous DF508 CFTR mutation (CFTR encodes for a plasmic membrane in the chloride channel of epithelial cells) [4] display a large variation in CH clinical symptoms such as differences in infection levels and tissue damage and repair. This variation is caused by differences in the genetic background of the individual patients. A strong background effect has been reported for mutations in polymerase- γ (POLG), a major human disease gene that accounts for

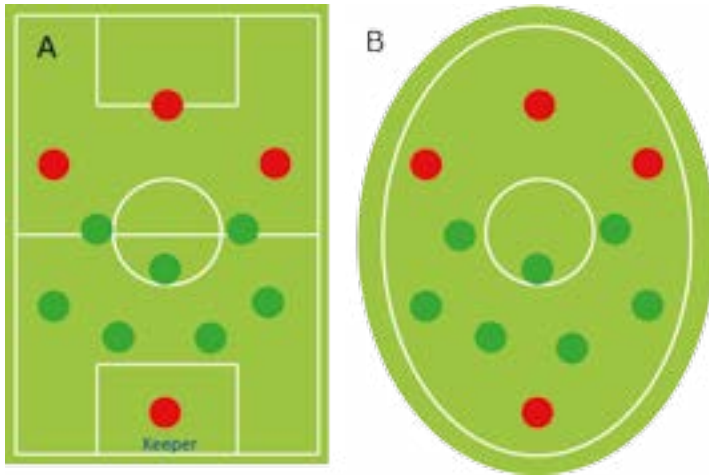


Figure 3. A. Soccer field depicting red “key” players. Blue dots are background players. Together they work as a team but the blue players can enhance or diminish the effect of the key players. B. Cell with red “key” genes. Blue dots are background genes. Together they determine phenotypic traits but the blue genes can enhance or diminish the effect of the key genes.

almost 30% of mitochondrial diseases in the UK and in Italy. Although many patients are homozygous for this mutation, clinical phenotypes are highly variable. All patients are epileptic, 80% have other neuropathologies and 60% have eye muscle disease [8].

The importance of the genetic background has been recognized for a long time. Yet, it has not been widely acknowledged. It is important to make this distinction because recognition means that “we know that everybody is different”, whereas acknowledgement means that “we know how it works”. In medical research as well as plant and animal breeding the genetic individuality is recognized. Every breeder of tomatoes can tell you which variants you need to cross in order to obtain a tasty fruit. And a dog breeder would give you advice on which variant not to cross because of its aggressive nature. So, genetic individuality has long been recognized but very few attempts have been made to understand the genetic background effects in a mechanistic way. This is illustrated in medically oriented research focusing on human disease pathways in mice. Mice are very important animals that are widely used to in medical research. A Genetic Background Manual is available from The Jackson Laboratory, an institute with long standing record in mouse genetics. The manual describes clear examples where the genetic background has been



Figure 4. Effect of genetic background on expressivity of a mutation in the gene *dad-1* in *Petunia*. The mutation leads to a compact phenotype. The homozygous recessive mutation (a transposon insertion) crossed into variants *EasyRider* (*EzR*) en *EasyWave* (*EzW*) yields different phenotypes. The red boxes show the *F2* generation for 3 offspring. Data kindly provided by Georgios Vlachakis, Scienza Biotechnologies.

misleading – that is – confounds the phenotypic effect of a mutation, and explains how to take this into account (correct for it) in experiments involving mice. So, the problem of the background is recognized but not acknowledged. In conclusion, mutant screens do not acknowledge genetic individuality where the genetic background might overshadow the effect of gene functions, a concept called “hidden genetic variation”.

Hidden genetic variation: from flowers to cancer

Hidden genetic variation affects many traits in plants, animals and humans. Scientists from a plant breeding company contacted me recently regarding problems they encountered with a specific mutation in a gene affecting compactness in *Petunia*. Compact plants are easier to store and transport. Figure 4 shows two wild type variants of *Petunia*, the ones you can buy at your local nursery. These variants are not compact; they have a more stake-like appearance if you do not prune them, as shown on the left hand side of the figure. A mutation in the gene *dad-1* (decreased apical dominance-1) yields a much more compact type of plant[9]. Yet, unexpectedly, enormous variation has been observed regarding compactness. Every offspring originating from a cross has a different appearance, and strikingly, these differences

are also pronounced in a variable way in the two different plant varieties – that is – a different genetic background. Although this variation could be due to background mutations which came along with the *dad-1* mutation, these differences are seen across both varieties suggesting a strong background effect. We are now working with this breeding company to unravel the mechanism of these background effects.

Figure 5 shows an interesting case about the effect of a cancer causing mutation (the mutation in the adenomatous polyposis coli gene on position R850 *Apc*R850X/+ (Min) in the intestinal tract of mice. The picture shows thin slices of three parts of the intestinal tract (duodenum) of a two mice A and B, and a piece of the colon. Here the phenotypic readout is the number of adenomatous polyps. You can clearly see the polyps which are blue stained. Polyps signify a first stage in cancer formation. Mouse type A has many polyps whereas mouse type B has hardly any. You would expect the mutant is A and the non-mutant is B. This is not the case. Both strains carry the mutation. This is a very clear case of hidden genetic variation in cancer phenotypes where we see the effect of the genetic background on polyp formation in the mouse.

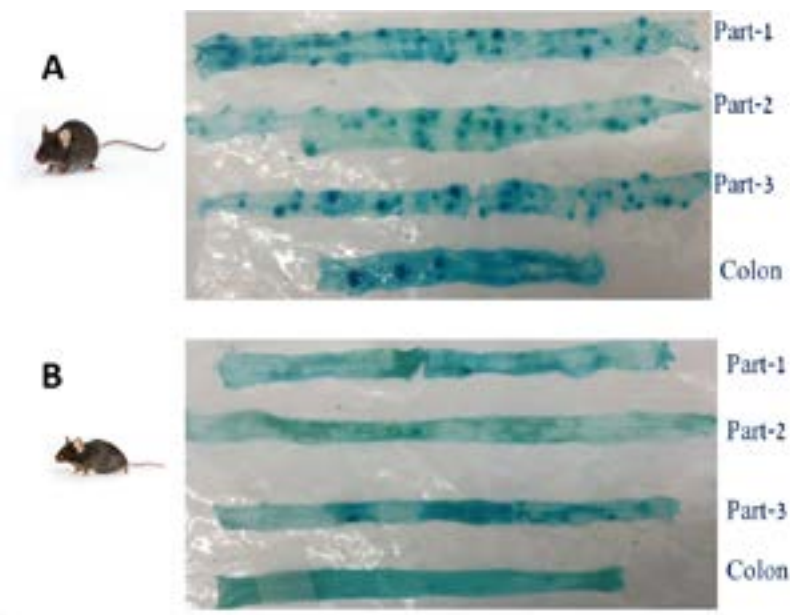


Figure 5. Effect of genetic background on polyp formation in the digestive tract of mice. Both strains A and B carry the same mutation in the adenomatous polyposis coli gene. Many polyps are formed in strain A but not in strain B. Courtesy of F. Iraqi.

A very recent paper reported on the background effects of a mutation in a gene known to be associated with type-2 diabetes[10]. Many mouse researchers study mutations in a strain called B6. But here they crossed the mutation with 30 different backgrounds and then analysed these for its effect on activity, blood glucose levels and fear response. It was noted that in case of the other backgrounds, results were highly different and even opposite to the observed effects in B6.

Over the past few years our understanding of “monogenic” disorders and diseases has shifted, and it is clear that there is a great deal of variability in the phenotypes associated with specific “causal” genes. A recent study identified human adults harbouring mutations for a number of severe Mendelian conditions, but no evidence of associated disease symptoms[11]. Instead of focusing on causal mutations in diseased individuals, the authors examined healthy people of disease-causing mutations. They sequenced the DNA of healthy individuals and looked for mutations in disease genes. They found people with mutations in disease genes but had no disease. These people were healthy individuals who buffered the effects of rare, highly penetrant, deleterious mutations. These findings suggest that incomplete penetrance disease genes may not be un-common and depends on the so-called background[12].

What is the mechanism of the background effect on mutant phenotypes?

The aforementioned cases in flowers and cancer in mice and complex diseases in humans find their origin in the fact that mutations are implicitly regarded as independent, isolated cases of gene changes. Thereby assuming that the mutant phenotype is related on a one-to-one basis with the mutation. But this is quite misleading. The phenotype is not the result of a mutation but of the mutation in interaction with the genetic background. This is a fundamentally different concept. To understand this a bit more we look at two genetic backgrounds in worms, one from England and one from Hawaii. Colleagues of ours reported that the severity of a mutation in a gene could be predicted from the expression level variation of the affected gene [13]. For instance, if a phenotype was determined by three genes with equal expression levels, than a mutation in one of the genes was moderate. But if one of the three genes had a lower expression level because of the genetic background, than the mutation was severe. If a gene has a higher expression level than the mutation was mild.

To understand the mechanisms of background effects we have crossed the two worm strains from England and Hawaii and let them have many offspring with different genetic backgrounds. So, each offspring has a different genetic background. We then knocked down different genes in this suite of different genetic backgrounds (called recombinant inbred lines) and compared these to normal worms. The genes were

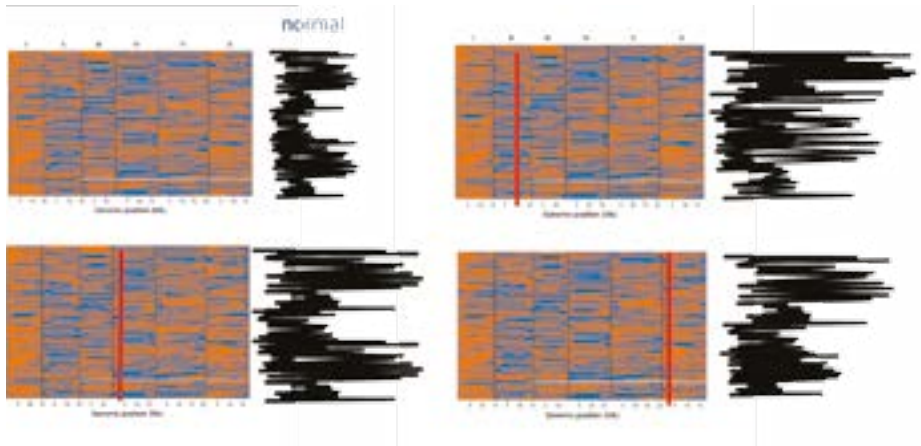


Figure 6. Effect of gene knock-downs in different genetic backgrounds. The four panels show a range of different strains (vertical) and 6 chromosomes (horizontal). The above-left panel is the control treatment where the strains have not been affected by a gene knock-down. The phenotype (fitness) shows a normal variation across the strains. The other three panels show the same range of different backgrounds but here they are affected by a gene knock-down (the red line). Depending on the position of the gene and the genetic background, fitness varies

knocked down in Chr IV, II and X. We found that overall health depended on i) the gene that was knocked-down, and ii) the genetic background in which the gene was knocked-down[14] (Figure 6).

Opposite mutants

To gain an understanding of the background effects of mutations at the genome level we created two different populations in *C. elegans*, these are the so-called “opposite” mutants. The first population consists of the English background with small Hawaii mutations (orange-blue worms) the other consists of the Hawaii background with small English mutations (blue-orange worms) (Figure 7). This allows for studying the effect of each mutation at each part of the genome for background effects. It should be mentioned here that these populations are unique and do not exist for any other species yet. So each strain is a sort of mutant.

Analysis of stress reactions in the worm has revealed some interesting aspects of background interactions. We studied stress responses because these are determined by the same pathways that are involved in human diseases. Heat-shock is a relevant treatment in *C. elegans* because it induces genetic pathways which are associated with developmental diseases in mammals (Figure 8).

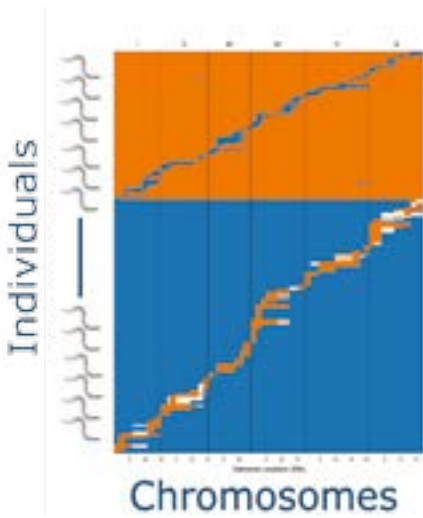


Figure 7. Two opposite mutant populations of *C. elegans*. The figure shows the genomic positions of the allelic markers (horizontal) and the different individuals (vertical). Allelic variants of Hawaii are in blue and England in orange. Thanks to A. Doroszuk, L.B. Snoek and M. Sterken.

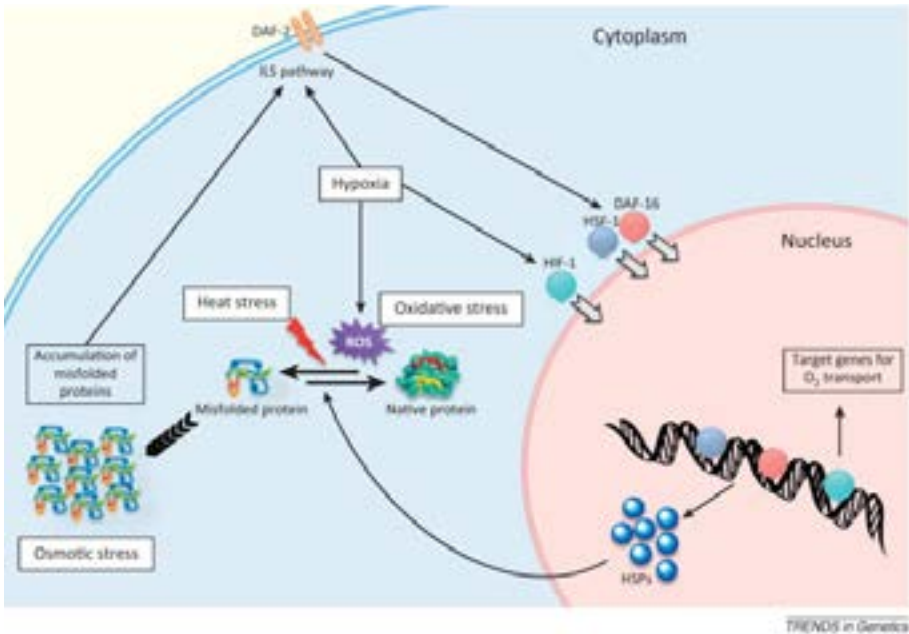


Figure 8. Exposure of *C. elegans* to abiotic stress factors like hypoxia, heat stress or oxidative stress induces genes and pathways that underlie complex diseases in mammals, including humans [15]. Therefore, studying these stress factor responses in *C. elegans* is relevant for understanding disease phenotypes.

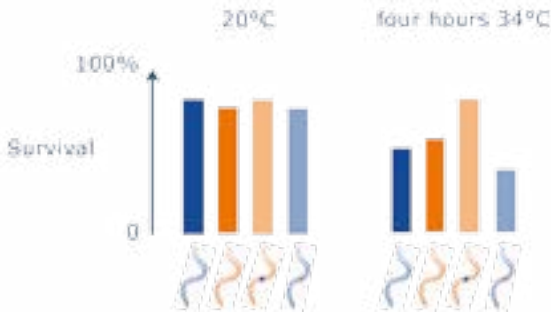


Figure 9. Survival after heat-shock, measured in blue-orange worms, orange-blue worms, orange and blue worms. The survival is determined by an interaction between the introgression and the genetic background (ANOVA, $p < 0.01$). Thanks to M. Sterken.

We exposed young worms to a heat-shock of 35°C for 4 hours after which we recorded survival of the worms. We detected a position on chromosome IV that controlled the heat-shock response. Selected individuals (orange worms with a bit of blue; and blue worms with a bit of orange) were tested. Figure 9 shows there is hardly any difference in survival at 20°C between blue worms, orange worms, orange-blue worms and blue-orange worms. But after the heat-shock of 4 hours, we recorded a survival of 50% for blue worms, approx.. 60% for orange worms, up to 80% for orange-blue worms, and 40% for blue-orange worms. In conclusion, survivorship is determined by the interaction between the mutations and the background.

It is evident that pathways cannot be disconnected from their genetic background. Indeed, the mutation effects in pathways can be overshadowed. We took this a step further and investigated the genetic mechanism underlying the background effect of a mutation in a gene that is known to cause cancer (the *let-60* oncogene) under certain conditions. Over-activating the gene leads to clear swellings of the body of the worm (Figure 10).

So the normal development is disrupted. Analogous mutations in mammals lead to a disrupted cell division and onset of cancer formation[16]. In our research together with Swiss partners[17] we introduced the activated oncogene into a large number of different genetic backgrounds. These individuals developed a wide range of external swellings, more as well as less than their parents (Figure 11).

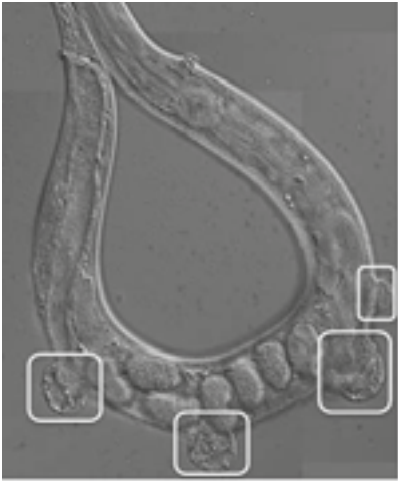


Figure 10. Activation of the oncogene *let-60* in *C. elegans* leads to developmental disruption which is visible by external swellings of the worm. Picture by T. Schmid.

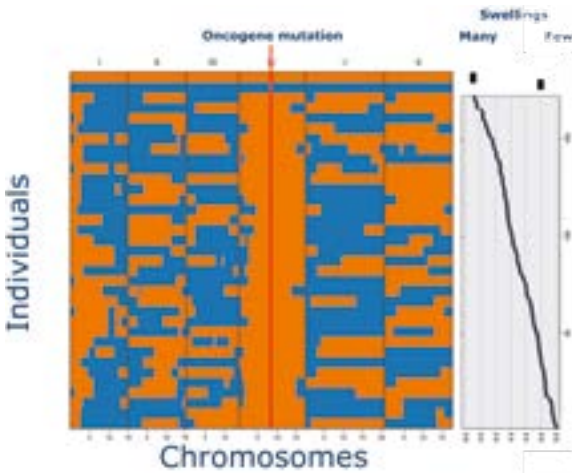


Figure 11. Effect of genetic background (*C. elegans* strains) on the number of external swellings due to the mutation in oncogene *let-60*. Thanks to L.B. Snoek, T. Schmid and A. Hajnal.

Many more than could be expected compared to the original mutant, a clear background effect. We revealed a “modifier” background gene on chromosome I that encodes for monoamine oxidase A (MAOA). The monoamine oxidase A catalyzes the formation of 5-Hydroxyindoleacetic acid (5-HIAA). Worms activated for 5-HIAA displayed increased number of swellings due to the oncogene than worms that did not have an activated form of this gene. We then asked if this compound would affect human cancer. We found that 5-Hydroxyindoleacetic acid inhibits the development of colon cancer human cell lines (in prep.). So we found that for the oncogene on chromosome IV there was a modifier gene on chromosome I.

These results all illustrate that the genetic background can have a surprising effect on the impact of mutations. This may have consequences for the latest fancy tool in genetics: genome editing; where very specific mutations are tailor made and investigated for their phenotypic effects. For instance we can very precisely cut and paste in a gene to make a worm glow like a light bulb or make it obese. But given what we know about background effect on mutations, we should be cautious in our interpretation and promises about this technique. At the moment we know very little about the relation between genetic background and genome editing. We will be testing the effect of genome editing in the worms that we have. More interestingly perhaps is that we will introduce huge amounts of variation by not using two parents but four, to increase diversity. In this case we sampled worms from different locations like rotting apples and hogweed plants.

Genetic individuality: tailor made?

Why are these worm experiments so important? These experiments show that a genomic change is not the cause of the phenotype but the results of the genomic change PLUS the interaction between the genomic change and the background. These results provide mechanistic insight and imply that the effect of each mutation must be evaluated within the context of the individual: from recognition to acknowledgement. This may ring a bell regarding personalized medicine, or in other words, tailor made therapies and medication on the basis of the individual genomic characteristics. But here we should tread cautiously. Even in case of a personal passport of the genomic constitution of animals, humans or plants or crops perhaps highlighting the type of mutations they carry. Simply because we do not know the complex interactions between the mutation and the genetic background. A genetic passport based on gene sequence is too simplistic. Clearly this goes beyond the dominant or recessive character of a particular gene. But let's be modest about our promises and objectives. The publication of the human genome sequence[18] was presented as the holy grail. By then, promises were made that the elucidation of the human DNA-sequence would unlock the secrets for developing new medicine and medication. Unfortunately we have to admit that these developments do not match up to the promises made (NYT, 2010). Ten years after the presentation of the first draft of the human genome, medicine has not matched up to the promises made. Only recently have we made progress in applying gene therapies based on the genome sequence. This means that we cannot make the step from single gene mutation to medical treatment or, in case of plants, for instance, compactness in *Petunia*. We should be more careful in making promises about societal relevance and potential applications and try to understand the complex genetic interactions because we are far from understanding this complexity yet. We have seen a huge variation between different backgrounds within species, and perhaps we should be a bit more

modest in conveying our message to the public. Editing humanity and promises about the gene machine should be taken with a pinch of salt.

Only a few weeks ago this paper came out in Nature[19]. It emphasized that current genomic insights fall short on the diversity and variation that we witness in human populations. This is about the challenge of understanding genetic individuality. Let's hope we can provide a little bit of mechanistic insight into this pressing problem by exploring the hidden genetic diversity in the worm.

Dear students

You have been a source of inspiration for my work. I regard myself a privileged person to work amidst young, enthusiastic and intelligent people. From me it is expected to supervise you in a professional way. This has been a challenge because there is the risk of being your waiter rather than supervisor. In my opinion we ask "Are you being served?" to often. We guide you through the lectures, the practical's, and tutorials. We work on assignments, design of experiments after which these need to be analyzed and discussed. You receive a wide variety of support which often is tailor made. All different kinds of services and products are at your disposal. Examples are provided galore and you are allowed to rate everything, from whole courses to individual teachers. These are typical characteristics of customers. In my opinion you should also behave as investors. Now the balance has shifted a bit too far to the customer side. As investor you struggle on the road to success, you expect nothing and invest in yourself (Figure 12).

My role as waiter should be transformed into supervisor. It is not enough to teach you how to design experimental setups, to conduct proper experimentation and how to analyze the data and writing reports. To achieve this, I would like to paraphrase Rikard Nordraak, the famous Norwegian composer. He said: to understand music you need to go beyond music itself. This should apply to you: To understand science you need to go beyond science itself. By this I mean that apart from all the skills, expertise, knowledge and insights that we offer you, you need to doubt your results. You need to question your own data and ask, apart from all proper scientific conduct, whether it makes sense. You will not find any rules for this; we need to train you to do this. This is important because it lays the foundation to the road of success. This is my second message.

Beste scholieren

Ik kom regelmatig op basisscholen om kinderen het belang en de schoonheid van wetenschap te laten zien. Dit vindt plaats iHKV het wetenschapsknooppunt was als missie heeft om de nieuwsgierige en onderzoekende houding van kinderen en (aankomende) leraren te bevorderen. Ik kom op diverse scholen en zie hoe kinderen



Figure 12. *The attitude and behavior of students is shifted to the customer side of the balance. More weight should be emphasized on the role of personal investor*

enorm enthousiast zijn en zich werkelijk vastbijten in de wetenschappelijke voorbeelden die ze voorgelegd krijgen. Zo leg ik het verschil uit tussen goochelen, toveren en wetenschap; en neem ik ze mee op een zoektocht naar de vraag hoe het toch zou kunnen dat een schildpad 200 jaar wordt, je konijn maar 3 jaar en onze worm maar 3 weken. En dit is dankbaar werk want ik krijg hele mooie tekeningen van ze (Figure 13). Maar ik ben pas tevreden als ik bijna zeker weet dat ze 's middags naar huis gaan en voluit vertellen over hun speciale les. Tegelijkertijd zie ik op die scholen ook een enorme diversiteit aan bevolkingsgroepen. Allemaal zijn ze vol interesse en leergierigheid. Een eigenschap van veel kinderen natuurlijk. Maar bij de studenten die naar Wageningen komen is deze etnische diversiteit niet hoog. Er zijn weinig studenten bij met allochtone achtergrond. En die mis ik. De medelanders. In een tijd waarin de kloof tussen verschillende bevolkingsgroepen groter wordt en er minder ruimte is voor dialoog en begrip is het essentieel dat de thema's waar wij hier in Wageningen aan werken worden opgelost door een verscheidenheid aan mensen uit diverse bevolkingsgroepen. Ja, degenen met een andere immigratie achtergrond. Alleen door verbondenheid komen we verder. Dit is mijn derde en laatste boodschap: een verbondenheid die moet leiden tot toewijding en betrokkenheid binnen onze samenleving. Ik zie dit als een manier om een meer coherente maatschappij te vormen waarbij allerlei groepen niet naast elkaar maar met elkaar het hoofd bieden aan de huidige uitdagingen waar Wageningen University en Research zich voor gesteld ziet. Ik heb hierover intussen al contact opgenomen met de afdeling onderwijsbeleid van Wageningen University om te zien hoe we dit vraagstuk op kunnen pakken.



Figure 13. Enthusiastic drawing of *C. elegans*. Group 5.

Woord van dank

Hiermee kom ik aan het eind van mijn inaugurele rede. Dit is het moment om de mensen te bedanken die het mogelijk hebben gemaakt dat ik hoogleraar ben geworden. Jaap Bakker, mentor vanaf het eerste uur. Jij schonk me het vertrouwen en gaf me de ruimte om dit te bereiken. Maar nooit zonder een kritische blik en waardevolle tips en suggesties. Jaap, jouw visie op wetenschap en mensen is ongeëvenaard en van grote betekenis geweest voor mij. Joost Riksen: ik heb dit niet kunnen doen zonder jou. De wijze waarop jij het lab al jaren organiseert en je uitstekende manier van praktische begeleiding van studenten en PhD's vormen één van de pijlers van de *C. elegans* groep. Je bent deskundig, stress bestendig en hebt een groot verantwoordelijkheidsgevoel. Bedankt voor al die jaren dat ik met je mocht samenwerken. Basten Snoek: wie anders is er in staat om op een heldere manier grote hoeveelheden data te analyseren en dit terug te brengen tot iets wat iedereen kan begrijpen en waar iedereen mee verder kan. Je bent een kei in het onderhouden van contacten met andere collega's en om met hun samen te werken op een vruchtbare manier. Rita Volkens, dankzij jouw inzet hebben we goed inzicht gekregen in de wilde isolaten van *C. elegans*. Mark Sterken; ik wil je danken voor je enorme loyaliteit naar de leerstoelgroep en de wijze waarop je al die studenten hebt begeleid die bij ons een thesis hebben gedaan.

begeleid die bij ons een thesis hebben gedaan. Daarnaast is jouw bijdrage aan het onderzoek van groot belang geweest voor de lange termijn strategie van het *C. elegans* onderzoek. De stafleden van de leerstoelgroep Nematologie, Aska Goverse, Geert Smant, Hans Helder en Arjen Schots wil ik bedanken voor hun support en enorme collegialiteit die van belang is om onze gezamenlijke doelen na te streven. Ik bedank all aio's, postdocs en studenten die een enorme bijdrage hebben geleverd aan het *C. elegans* onderzoek en alle collega's met wie ik gezamenlijk onderwijs geef. Ik wil graag de Rector Magnificus en leden van de benoemingsadvies commissie bedanken voor het door hun in mij gestelde vertrouwen. Lisette Groeneveld en Christel van Geelen dank ik voor hun bereidheid om altijd klaar te staan om mijn haastklussen goed af te handelen en voor het scherp in de gaten houden van administratieve zaken omtrent de projecten en het onderwijs. Alle leden van de leerstoelgroep Nematologie wil ik bedanken voor de enorm goede sfeer. Dit maakt het een hele prettige werkomgeving.

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There is general consensus that gene mutations are considered as separate entities. But their phenotypes do not result from isolated mutations but from the interaction between the mutations and the genetic individuality. At the moment we do not understand this hidden genetic variation and are surprised by the intrinsic complexity of individual plants and animals. I draw upon the importance of genetic individuality for the expression of mutations and explain how we can understand the individual complexity of gene mutations.