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ITALO BARRAI

THE GENETICS OF CANCER (*)

Cancer may be studied in populations, in families, and in the individuals it affects; further, the carcinomatous cells themselves may be studied as an independent line living in a specific medium, the body of the patient.

It is convenient to examine orderly the possible results from the different types of study, in order to assess the contribution each type can give to the evaluation of a genetic component in the predisposition, and in the actual insurgence, of the tumour.

1. STUDY OF CANCER AT THE POPULATION LEVEL

Many health services in developed countries tabulate at least the rate of death due to cancer per year per 100,000 inhabitants; typically, the death rate has been steadily increasing in the present century, and it is now close to 20% of all causes of death.

This single cause is then second only to cardiovascular disease as a killer and a great research effort has been dedicated to the problem of cancer in the past twenty years, unprecedented for the amount of resources and manpower employed.

The prevalence and the incidence of tumours have been observed to increase proportionally to the sixth power of age (Reif 1981); it is well established that increasing frequencies are mainly due to the increase in the average life span in most countries after control of infectious and parasitic diseases.

Population studies of cancer incidence and prevalence have resulted in the construction of cancer registers, where the biology of a specific entity is tabulated and considered statistically. Screening programmes have been initiated, typically for female breast and cervix, with considerable success in early diagnosis and survival of treated patients.

One interesting fall-out of the screening programmes has been in some cases, as for example in breast cancer, the possibility of identification of high risk groups; this implies possible advantages for early diagnosis and treatment.

Population studies also offer some information on the possible genetic basis of cancer. In different populations the same cancers are observed with different frequency; then, once the recognizable environmental carcinogenetic agents

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have been excluded, it is possible to infer from population studies the concept of a genetic basis for cancer proneness and susceptibility. Recently, sophisticated statistical techniques have been used to identify the biological variables which seem to be significantly associated with some types of tumours; in particular, breast cancer has been used more often than other cancers for this purpose. Discriminant functions between patients and controls have been constructed, to define high risk groups; this, in genetic language, means that attempts have been made to identify a "cancer prone phenotype" (Toti 1980). Whatever the practical results of such endeavours in the early diagnosis and treatment of some forms of cancer, and in the minimization of screening costs, it appears that the main biological variables which cause the emergence of malignancy—then the genetic causes of cancer—are dimly perceived at this day. In any case, the perspective for the future of population studies of cancer, and for screening programmes, promises important results for prevention and treatment, in particular for those entities, like breast cancer and cervix cancer, where early surgical treatment results in complete healing of the patient from the disease.

2. THE STUDY OF TUMOURS IN FAMILIES

In the terminology of classical genetics, cancer is a discrete trait, in the sense that an individual either has the disease or not, exactly as peas are green or yellow. The main difference is that cancer appears, when it does, at some stage in the life cycle, fortunately very often when reproduction is terminated. Because of this considerable correlation of the appearance of most cancers with post-reproductive age, it is not easy to obtain family data on several generations for tumours; the vertical appearance of cancer in the same family is too removed in time to be easily and generally studied.

It would seem feasible, however, to test transmission hypotheses, to introduce segregation analysis (Morton 1959) for the study of the genetics of cancer. In most cases, family studies, although showing aggregation, are far from showing a clear cut mode of transmission of cancer in general.

Family studies have shown that there are some specific cancers which segregate in families according to simple mendelian rules; for example, retinoblastoma is a phenotype under the control of a single dominant allele; xeroderma pigmentosum is due to the homozygous state for a recessive allele (see also appendix). In general, the multitude of cancers which cannot be ascribed to an environmental causative or predisposing factor, show familial aggregations which defy segregation analysis, and do not fit any simple mendelian model of transmission.

Multifactorial models, with calculation of heritability are the alternative hypothesis to mendelian transmission in this case; again, the calculation of heritability for discrete non mendelian traits has been a difficult endeavour until 1965 when the model of Falconer for the calculation of heritability in such cases was formulated; previously, the comparison of concordance in monozygotic and dizygotic twins was used in the methodology of estimation of heritability.

Twin studies are inefficient in the sense that twins are rare, one pair in eighty births on average, and even a cancer with a frequency of 7 per thousand would be seen in a member of a twin pair once every ten thousand individuals. The cancer records of a town of one million inhabitants would contain enough twin data for a small study of a given type of cancer. Twin registers have been useful in retrospective studies of concordance for cancer in twin pairs, and heritability was calculated for some tumours, notably breast, cervix, stomach (Stern 1970).

The Falconer method, which has the advantage of exploiting individuals having a genetic correlations of $\cdot 5$, instead of individuals having a genetic correlation of 1.0 , namely sibs against twins, is easily applicable; however, it is necessary in order to compute heritability, to have the incidence of cancer in the general population and in the sibs of cancer patients.

3. STUDY OF TUMOURS IN THE INDIVIDUAL

Studies of heritability of tumours have been rather sparse; the field has not appealed to human geneticists as it deserves. The calculation of heritability of a given non-mendelian syndrome or trait, including tumour, is of extreme importance for medical genetics. It is now apparent (Barrai 1970) that the morbidity of the future, at the pediatric level, will be due mainly to genetic entities segregating in families, or to multifactorial factors. From this the importance of assessing either genetic risks or recurrence risks under the multifactorial model, to provide the medical geneticist with an indispensable tool of his trade, the quantitative evaluation of the risk of recurrence of a syndrome or genetic disease or disorder in the progeny of a couple.

I maintain here that it is equally important, once established the genetic or partially genetic basis of a cancer, to assess its heritability, in such a way that the physician has the potentiality to advise the members of a family, or of a sibship, of a quantitative risk, so that opportune preventive action may be counseled and initiated. A limiting case is the cancer of purely genetic origin, like retinoblastoma; here, the offspring of the affected have a fifty-fifty chance of developing the disease in the first months of life, and therefore are kept under constant supervision by the ophthalmologist, so that the cancer can be countered at its first appearance; as a consequence, metastases are avoided, and the cancer is not lethal.

Cancer is also indirectly under genetic control, in the sense that there are genotypes which predispose to the insurgence of specific types of tumours. A case in point is albinism, which is determined by the homozygous state of a recessive gene; the consequent lack of melanin in the affected persons makes the skin more sensitive to ultra violet radiation, and skin cancer is very frequent in albinos. It is to be noted that since it is easily and promptly diagnosed, this type of cancer is rarely lethal. This is true for most types of skin cancers other than melanoma.

Many recessive syndromes which are characterized by high frequency of chromosome breakages, like Bloom syndrome, show also a high rate of cancers. The syndromes are often severe diseases by themselves and cancer is an additional complication in the features of the expression of the genotype. Its appearance in these cases may be attributed to the chromosomal rearrangements taking place after chromosome breakage; this is an important point, and many cancers show abnormal karyotypes.

It is to be noted that we know very little of specific genotypes predisposing to specific cancers; a second consideration, not less important and very similar, is the existence of genotypes which are more sensitive than others to carcinogens. Again, one many refer to albinism; the genotype *per se* does not induce malignant transformation of epithelial cells; it is the diminished protection against UV, a potent carcinogen, which causes cancer. In this sense, the genotype makes the phenotype more sensitive to the carcinogen.

This may be generally true, particularly in a world where the amount of new chemicals diffused in the environment is unprecedented.

Studies on the association of specific genetic markers with tumour susceptibility have given inconclusive evidence for some cancers of the digestive tract and blood groups; more recently, the study of association between HLA markers and cancers has initiated, and there is evidence that at least some HLA antigens are associated with specific cancers. The field is under intense study and several chronic and malignant cancers are under investigation. Here also, the purpose of the immunogeneticist is to assess the risk of cancer in the presence of a given antigen, implicitly to propose preventive measures for the individuals who are at high risk.

4. THE GENETICS OF THE TUMOUR

It is not my purpose to consider the environmental origin of the cancers; suffice it to say that we swim in a sea of carcinogens (Reif 1891) and that it is likely that most cancers have an environmental origin. However, once the tumour has initiated, whatever the initiating agent, it becomes a genetic phenomenon, since the changes which make a cell malignant are heritable.

Whatever its origin, the tumour constitutes a line of cells which breed true, with their own genotype—often perceivably different from the host—which grow free from the rules which have differentiated the host itself.

The heritable change or changes which have conferred to the cell its phenotype must be genetic mutations; the individuality of the tumour cannot be maintained unless it is based on the DNA of the cell, and unless it is transmissible.

The main theory on the genetic changes which result in malignancy has been introduced by Knudson (1971), who worked on retinoblastoma families. On the basis of segregation frequencies of the entity, Knudson was able to formulate a theory, according to which two mutational events are necessary for the induction of malignancy in a cell.

The theory of the two mutations, proposed by Knudson on the basis of genetic evidence in retinoblastoma, is consistent with the findings of chemical carcinogenesis. Students of chemical carcinogenesis have found that the process can be separated in two stages: initiation and promotion of malignancy. A group of chemicals has the property of being an initiator of cancer; however, although this phase of initiation is typical of some hydrocarbons which are commonly considered as carcinogens, these will not under certain conditions, induce the emergence of cancer *by themselves alone*. Other chemicals, among them the one which is best known is tetradecanoyl phorbol acetate, by themselves alone will not induce cancer. The chemicals belonging to the class of this substance are called promoters—an unfortunate terminology, since in genetics initiator and promotor have quite a different meaning. However, substances which act as initiators of cancer, will not at given concentration produces cancer when they act alone; however, if after treatment with an initiator, a promotor substance is administered, cancer will appear (Temin 1980). Therefore, it appears that the two mutations theory advanced by Knudson is supported by the findings of chemical mutagenesis, and that an initiation and a promotion mutation are necessary for the development of malignancy. Other subsidiary evidence is given by the fact that most carcinogens are also mutagens, although the reverse does not seem to be true, and although many mutagens are in fact also carcinogens.

Considerable progress in the elucidation of genetic mechanisms which result in tumour formation has taken place very recently, particularly through the study of DNA papova viruses and of retroviruses; these are RNA viruses which cause tumours in many vertebrates, and possibly in man. Also, the techniques of chemical genetics consent nowadays to test exact hypotheses about specific states and phases of cancer cells.

5. VIRUSES AND CANCER

The Papova (papilloma-polyoma-vacuolating) DNA viruses present a complex life cycle, which may be summarized in a lytic cycle and in the equivalent of a lysogenic cycle. In the lytic cycle, the infected cell will lyse, and produce a progeny of viruses; in the equivalent of the lysogenic cycle, the virus may stay in the cell integrated or not in the chromosome, in one or more copies. The cell which carries the temperate virus may undergo transformation, and the transformation may be malignant. One well known among the DNA viruses is SV40, the virus causing cancer in monkeys and having two integration sites in chromosomes 7 and 17 in man (SV40-IS-17). Modern techniques of DNA isolation, fragmentation, electrophoresis and blotting, followed by hybridation, consent the identification of specific viral sequences of DNA. It is important to distinguish between stringent and non-stringent hybridization. Stringent hybridization is equivalent to renaturation with a complementary strand of DNA; it gives evidence of almost perfect homology of sequence. Recently (Zachow *et al.* 1982) it was shown that the DNA extracted from anogenital neo-

plasias hybridates with the DNA of papillomaviruses; namely there is sequence homology at least in one case between DNA extracted from the human cancer and the viral genome. This does not mean that the cancer was produced by viral infection; only, that either the virus is present in the cells of the tumour, or that the genome of the tumour has sequences homologous with those of the virus.

However, present techniques permit to test if whole viral genomes, transfecting the cell, can induce cancer; also, when cancer is induced by the viral DNA, it is possible through digestion with restriction enzymes to identify the transforming segment in the genome. Such techniques, which can be used on cells cultured in vitro, do not give the ultimate demonstration that the cancer may be caused also in vivo by the transforming fragment (or genome); however, they are suggestive that this may be the case.

6. RETROVIRUSES AND CANCER

The life cycle of retroviruses is not greatly dissimilar from the cycle of DNA viruses; once the RNA has infected the cell, inverse transcriptase produces a complementary DNA strand, which may be incorporated in the cellular genome, and produces many copies of the viral RNA.

This diffuses to the cytoplasm, where it may be condensed with proteins of its own capsid, and buds from the cell wall to the extracellular environment, ready for subsequent infection. Retroviruses have been known for a long time as cancer-producing agents, in vertebrates; Rous avian sarcoma, murine sarcoma viruses, murine leukemia viruses, and plasmacytoma viruses are well described instances of such cancer inducing viruses.

The study of retroviruses resulted in the identification of oncogenes, namely, in the identification of genes which cause cancer; they are the genes called *onc*, and the term was introduced to classify genes which, trasmitted to the cell in retroviral genomes, were able to cause transformation.

The oncogenes can transform cells, but they are non-essential for virus growth inside the cell. It was demonstrated very early (Duesberg and Vogt 1970; Martin 1970) that some strains of Rous Sarcoma Virus (RSV) have a shorter chromosome than the wild type RSV; also, they are non-transforming, do not induce tumour. However, they reproduce normally. Then, the segment of nucleic acid which lacks from the genome of these defective mutants is inessential for the viral reproduction; it may cause transformation of the cell when present in the viral genome, but the virus can cope without it. The RNA segment which is inessential for virus function but causes transformation is the *onco*-gene. The nomenclature of genes with three letters applies also to the *onc*-genes; for example, the gene which causes avian sarcoma is the *src* oncogene.

In most retroviruses which cause cancer, oncogenes have been identified; the Murine Leukemia Virus (MuLV) of Abelson carries an oncogene which produces leukemia in mice; it is called the *abl* oncogene. Viruses which induce

sarcomas in mice have the oncogene *ras*, homologous to the *src* oncogene of the RSV. Viruses causing plasmacytomas in mice have oncogenes which are called *myc* oncogenes. In short, there is now a number of recognized oncogenes in viral genomes which produce specific cancers after infection.

At least some oncogenes products have the activity of protein kinases (Erikson *et al.* 1980; Radke and Martin 1980); however, the process through which their activity results in malignant transformation is not known. But before considering the problem of malignant transformation as caused by viral oncogenes, it is convenient to study further the relation existing between the genome of the cell and the viral genome.

As said above, there are indications that viral genomes are present in the tumour genome; the point arises then, are there sequences homologous to viral genomes in the cell before infection? Are there sequences homologous to oncogenes in the cellular genome?

Modern techniques of chemical genetics allow an answer to this question. Further, are the sequences—and then the products—of different viral oncogenes similar to each other?

The answers are quite surprising. The cDNA probes prepared from the *onc*-gene of some viruses hybridize with the oncogenes of different viruses. For example, the *src* oncogene of the avian sarcoma hybridizes stringently with the MuLV virus oncogene; this means that the oncogene sequences in viruses are highly conserved, and there may be a similarity of action of the different *onc*-genes.

It was also observed (Pulciani *et al.* 1982) that the probe from the viral oncogene hybridizes with DNA of the isolated cell, treated with restriction enzymes and blotted, *before viral infection*. This is a most surprising finding, because it means that the cell has also oncogene sequences. To distinguish these *onc*-genes from the viral *onc*-genes, it is now customary to write *v-onc* for viral oncogenes, and *c-onc* for their homologues in the cells. So, *v-src* has an homologous *c-src*, *v-abl* has its homologous cellular oncogene *c-abl* in the murine genome, as *v-myc* and *c-myc*. Hybridization shows that all these sequences are highly conserved both in viruses and in cells.

This raises the question of the evolutionary meaning of the conservation of *onc*-genes in so different organisms. It is not surprising that *v-onc* genes hybridize with human DNA; radioactive probes permit the localization of oncogenes also in human chromosomes.

The presence of *onc*-genes may be a general property of the cell.

7. THE ACTION OF ONCOGENES

One fundamental observation on the action of oncogenes was made simultaneously by Reddy *et al.* and Tabin *et al.* in 1982. They studied cells of the human bladder carcinoma, which can be cultivated *in vitro*.

Human bladder carcinomas possess an *onc*-gene which is related to the *v-onc* of murine sarcoma viruses, as shown by comparative analysis of their

sequences. The most common *v-onc* gene the of murine sarcoma is the *v-has* oncogene, cause of the Harvey sarcoma. Then, in the human bladder tumour there is an homologue of the *v-has* which was designated *c-has-1*.

In fact, there is an homologous oncogene *c-has-1* in *every* normal human cell; therefore, it was important to study the differences between the *c-has-1* in the bladder carcinoma and in the normal human cell; if the two oncogenes are exactly equal, then the oncogene itself is not the cause of cancer; if they are different, one may gain insight into the causes of malignant transformation. The difference of action between the normal allele and the "cancer" allele was demonstrated before any sequence study was initiated by transformation procedures. It is possible to isolate quantities of the *c-has-1* from normal cells and from bladder cancer cells; it was shown that the segment of DNA containing the normal allele has no transforming properties on a special cell line, NIH 3T3 mouse cell line, whereas the *c-has-1* from the bladder cancer does transform the cells to the equivalent of malignant state.

The final result was obtained through sequentation of the DNA in both the normal and the cancer determining *onc*-gene. It was found that the only difference in the sequence resides in a single base substitution at position 653 of the restriction fragment containing the oncogene. The normal allele has a G in that position, in a GGC triplet; the bladder cancer allele has a T in the same position, and the triplet becomes GTC. Then the glycine of the normal allele is in the point mutant substituted by a valine, and this is the only difference existing at the oncogene level.

The protein which is coded by the *c-has-1* is called p21, and has the function of a protein kinase. It is speculated that the change glycine to valine may alter the steric properties of the molecule, which affects the interaction of p21 with its cellular targets.

It can be concluded that the alteration of the oncogene product is the cause of malignancy, and that a single mutation is involved in the process. However, it was also observed (Chang *et al.* 1982) that high levels of the normal p21 protein cause transformation of NIH 3T3 cells. Then, malignancy may be attributed to a mutant oncogene product, or to an high level of the product of the normal oncogene; a high level may be achieved when the normal gene is translocated close to a "strong" promoter, namely transcriptionally very active.

One consideration which is important at this point, is that these results seem to indicate that the two mutations hypothesis may be false. One single mutation alters the product of *c-has-1*, and results in malignancy; possibly one mutation changes the rate of transcription of the normal allele of *c-has-1*, and the result is again malignant growth—the homologous of malignant growth observed *in vitro*, in NIH 3T3 cells. However, this cell line is used for its ability to grow and to take up foreign DNA: and it was argued that the 3T3 cell is already part way to becoming a cancer cell and for that reason may not provide the right assay for certain kinds of tumorigenic DNA. (Logan and Cairns 1982). We argue further that this possibility is in accordance with the hypothesis of the two mutations: if 3T3 mouse fibroblasts are already susceptible to transfor-

mation, this means that in their genome there is already one of the two mutations necessary for induction of malignancy.

The second mutation comes in with the foreign DNA. It would be overly speculative, at this stage, to advance which type of susceptibility is conferred to 3T3 cells by their genome; suffice it to say that the second mutation is capable, in this line, of inducing malignant growth.

8. THE LOCALIZATION OF ONC-GENES ON CHROMOSOMES

Further information on the primary cause of malignant transformation of cells has been acquired by the study of the location of specific oncogenes on human chromosomes. The techniques of location are now very powerful, and in general they make use of man-mammal cell lines which contain only one human chromosome. Probes of the *onc*-gene are prepared with the formidable techniques of chemical genetics, and hybridization with the DNA of the cells containing the single human chromosome are attempted. When hybridization is successful, the locus of the *onc*-gene is identified (see for example McBride *et al.* 1982). Then, the study of cancers associated with chromosomal aberrations can give relevant information on the origin of malignancy.

A case in point is the Philadelphia chromosome in chronic myelocytic leukemia (De Klein *et al.* 1982). It is known since a decade (Rowley 1973) that CML is associated with a translocation of part of chromosome 22 to chromosome 9; the deletion of the short arm of 22 is quite evident in karyotype analysis, and it was never considered that the translocation could be reciprocal, since under the optic microscope there was no evidence of transport of material from 9 to 22. Recently (Heisterkamp *et al.*, 1982) it was shown that an homologous of the *v-abl* oncogene is located on chromosome 9; namely, in man there is an oncogene in chromosome 9, a *c-abl*, which is homologous to the viral oncogene causing Murine leukemia, homologous then to the *c-abl* of mice.

De Klein and her coworkers have shown, with hybridation techniques, that in patients with CML having the Philadelphia chromosome, the *c-abl* oncogene is translocated from chromosome 9 to chromosome 22; this from the genetic viewpoint, only means that the translocation is reciprocal; material is reciprocally exchanged between 9 and 22, although in different quantities, which render optically visible only the translocation 22 to 9. A further interesting point was the observation that in patient with CML the *c-abl* probes do not hybridize any more with the DNA of 9; however, they hybridize now with the DNA of 22. Then, *the c-abl gene is involved in the translocation*; from its normal site on 9, it is translocated on a new site on 22.

This finding suggests a role for the human *c-abl* gene in the generation of CML. It is advanced that the chromosomal translocation associated with CML may lead to an increase in the level of expression of *c-abl*, with consequent malignancy, such as in the case of transformation of 3T3 with high quantities of the product from *c-has-1*. This is consistent with the fact that on chromosome

22 there are the loci for the production of lambda type chains of the antibody molecule. These loci are transcriptionally very active, and translocation of a *c-abl* segment near one of their promoters, would result in increased expression of the *c-abl* product.

Other indirect evidence that translocation of an oncogene near a transcriptionally active promoter might be a cause of malignancy comes from studies of Burkitt's lymphoma with probes from a mouse plasmacytoma oncogene, *c-myc*. This probe hybridizes with DNA of chromosome 8, locating the cellular oncogene in that chromosome (Forman and Rowley 1982). In Burkitt's lymphoma, an 8-14 translocation has been observed very frequently; other translocations specifically associated with the lymphoma are 8-2 and 8-22. Now, chromosome 14 contains the immunoglobulin heavy chain gene cluster, which is active in Burkitt's lymphoma cells; chromosome 2 contains the sites for the immunoglobulin kappa light chain genes, and chromosome 22, as said above, the sites for the immunoglobulin lambda light chains genes.

This suggests that the origin of Burkitt's lymphoma lies in the translocation of the human cellular oncogene *c-myc* to transcriptionally active sites; the product of *c-myc* is then produced in abnormally high quantities, and malignant transformation is a result of the increase of the specific product.

9. THE ORIGIN OF ONCOGENES

The evidence presented above shows that, in humans and other vertebrates, there are genes whose product, abnormal either in structure or quantity, causes cancer. The two mutations hypothesis is not weakened by this, but strengthened, since both mutations might take place one after the other when there are enough cancer cells for the second mutation to appear after the first has taken place; for example, when a tumour has the size of one cubic millimeter it would contain enough cells for the second mutation to occur, and this long before any clinical symptomatology becomes evident. This would also be consistent with the long phase of slow growth of some tumours before they become invasive.

The question which is posed by the identification of cellular oncogenes and of their viral counterparts, is the following. Where do oncogenes come from? Are there oncogenes which have no viral homologues, or most of them have? Are most tumours caused by two-step mutation in oncogenes, or is this episodic and valid for any structural locus? Is any gene potentially an oncogene?

It is possible to give, at this time, only fragmentary answers to part of these questions. First, the fact that oncogenes are not essential for viral reproduction, induces belief (Temin 1980) that they are originated by transduction of a segment of a host cell, near which the viral molecule was integrated. If so, there might be as many oncogenes as there are integration sites in a human genome. This would require investigation of the regions of homology which can exist

in a genome of one million kilobases, for a genome of ten kilobases. By analogy with the number of integration sites of F in *E. coli*, one might speculate that there are many possible integration sites, and ample possibility of transduction of segments which would at some stage be recognized as oncogenes, if they cause cancer in appropriate conditions; otherwise they might exist as transduced segments, but would never be recognized.

Secondly, the evolutionary conservation of some oncogenes between such different vertebrates as birds and mammals indicates that they may not be in such large number and of such variable effect as one would expect if any segment of the cell DNA might be transduced by the virus.

They seem an instance more of specialized transduction than of generalized transduction: to each viral strain its oncogene. Whatever the case, the increasing speed with which new discoveries are reported on the biology of tumours thanks to the development of new technologies in chemical genetics, holds promise that some beneficial fallout will involve the cancer patients in not too distant a future.

APPENDIX

List of Dominant, recessive, and sex-linked cancers in Mendelian Inheritance in Man, by V. McKusick, 5th Edition 2nd Printing 1979.

Dominant

10060-10795-10940-10980-11225-11440-11450-11455-11490-11835-12755-12950
13110-13260-13270-13280-13755-13780-13800-14160-14415-14470-14800-14850
15070-15080-15140-15141-15170-15270-15340-15560-15570-15610-15835-16155
16230-16230-16344-16640-16700-16720-16730-16800-17130-17140-15790-16500
16510-17520-17530-17450-17580-17645-18020-18224-18450-18660-19118-19160
19330-19440.

Recessive

20230-20657-20890-21090-21200-21450-21530-21540-21660-22640-22660-22765
22785-22860-23500-23600-24610-25450-25596-25670-25965-26035-26420-26480
26700-27330-27423-27780-27870

Sex-linked

30030-30040-30100-30150-30500-31060-31310.

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